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PREPARATION OF THE DOCUMENT

Since the last FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Expert Consultation on the Risks and Benefits of Fish Consumption was held in 2010, new evidence has become available in this arena, and the two organizations decided, in agreement with the Codex Committee on Fish and Fishery Products, to update the conclusions and recommendations of the previous consultation. The Norwegian Institute of Marine Research was commissioned to conduct a systematic literature review to inform the 2023 Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption, held in Rome. The report resulting from this expert consultation will be published as a separate document.

Esther Garrido Gamarro, of the Secretariat, coordinated the work, with support from Jogeir Toppe, Juliana De Oliveira Mota, Vittorio Fattori, Moez Sanaa, Markus Lipp, Molly Ahner and Angeliki Vlachou, also of the Secretariat. The document was edited by Dianne Berest. Layout was provided by Tomaso Lezzi.

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ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DHA	docosahexaenoic acid
dl-PCBs	dioxin-like polychlorinated biphenyls
EPIC	European Prospective Investigation into Cancer and Nutrition
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
FFQ	food frequency questionnaire
GDM	gestational diabetes mellitus
HOMA2-IR	homeostatic model assessments for insulin resistance
HOMA2-B	homeostatic model assessments for beta-cell function
HR	hazard ratio
I^2	measurement of heterogeneity
IQ	intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LCn3PUFA	long-chain n-3 polyunsaturated fatty acid
LOD	limit of detection
LOQ	limit of quantification
MI	myocardial infarction
N	number (of)
OCDD	octachlorodibenzodioxin
OHAT	Office of Health Assessment and Translation
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-p-dioxin
PCDD/F	polychlorinated dibenzo-p-dioxin and dibenzofuran

PCDF	polychlorinated dibenzofuran
PECOS	Population, exposure, comparison, outcomes and study designs
PICOS	Population, intervention, comparison, outcomes and study designs
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
RR	risk ratio
T2D	type 2 diabetes
TCDD	2,3,7,8-tetrachlorodiobenzo-p-dioxin
TEF	toxic equivalent factor
TEQ	toxic equivalent quotient
TWI	tolerable weekly intake
VKM	Norwegian Scientific Committee for Food and Environment
WCRF	World Cancer Research Fund
WHO	World Health Organization

EXECUTIVE SUMMARY

The report of the first Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption was published in 2010. Since then, new literature, data and information on the subject have become available. As such, FAO and WHO decided to generate a background report consisting of a comprehensive literature review, followed by an expert consultation, to update the report with new scientific evidence.

This background document aims to provide scientific evidence about the risks and benefits of fish consumption in order to update the 2010 Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. To provide new scientific evidence, five extensive literature reviews were conducted, focusing on the following five topics:

1. evidence of health benefits from fish consumption;
2. toxic effects of dioxins and dioxin-like polychlorinated biphenyls (dl-PCBs) (from studies published since 2010);
3. toxic effects of methylmercury (MeHg) (from studies published since 2010);
4. the role of selenium (Se) with regard to the health effects of MeHg;
5. occurrence data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products (from studies published since 2010).

The reviews followed a systematic approach, performing a systematic literature search and implementing elements from systematic literature reviews. A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets prespecified eligibility criteria to answer a specific research question. When conducting systematic reviews, systematic methods are used, aiming to minimize bias in order to produce more reliable findings to inform decision-making. In this background document, a combined method was applied integrating primary research, systematic reviews and other relevant, available risk and benefit assessments. In addition, the available literature was summarized. The PRISMA guidelines for searching, selecting and reporting on literature were followed during the research and preparation of this document.

1. EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION

To evaluate the evidence of health benefits from fish consumption, the literature reviewed comprised the report, Benefit and risk assessment of fish in the Norwegian diet, published by The Norwegian Scientific Committee for Food and Environment (VKM) in 2022, as well as literature (systematic reviews and original primary studies) included from a systematic literature search. The VKM report was based on an extensive systematic literature review evaluating the epidemiological evidence for associations between fish consumption and health outcomes.

A systematic literature search was performed in the databases PubMed, Web of Science and Cochrane Library. The initial search resulted in 39 092 records. After screening the titles and abstracts, 791 records were assessed in full text. Further, 127 records were quality assessed with risk-of-bias tools. Thus, the final review included 1 risk-and-benefits assessment (VKM, 2022), 22 systematic reviews, and 47 original primary studies. The literature reviewed was further categorized into the following health outcomes: allergy and immunology, birth and growth outcomes, bone health, cancer, cardiovascular diseases and outcomes, type 2 diabetes, neurodevelopment and neurological disorders, mortality, and overweight and obesity. A final weight of evidence was performed, using the criteria of the 2018 World Cancer Research Fund (WCRF) report, Judging the evidence, to grade the evidence for the different health outcomes into the categories: convincing (strong evidence); probable (strong evidence); limited, suggestive; limited, no conclusion; and substantial effect of risk unlikely (strong evidence).

2. TOXIC EFFECTS OF DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (FROM STUDIES PUBLISHED IN THE LAST TEN YEARS)

To evaluate the evidence of toxic effects of dioxins and dl-PCBs published in the last ten years, the literature consisted of the report, Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food, published by the European Food Safety Authority (EFSA, 2018) and literature (original primary studies) included from a systematic literature search.

The systematic literature search was performed in the databases PubMed and Web of Science. The initial search resulted in 2 770 records. After screening the titles and abstracts, 396 records were assessed in full text. Further, 81 records were quality assessed with risk-of-bias tools. Thus, the final review of the literature included one risk assessment (EFSA, 2018) and 20 original primary studies. The literature reviewed was further categorized into the following health outcomes: chloracne and other dermal effects, reproductive effects, female reproductive effects, birth outcomes, thyroid disease and thyroid hormones, type 2 diabetes and obesity, cardiovascular effects, hepatic disorders and digestive effects, effects in the immune system, effects in the nervous system, effects in teeth and bones, cancer, and other effects. A final weight of evidence was not performed, as only literature published after 2010 was included, and therefore it was not possible to give an overall grading of the available evidence.

3. TOXIC EFFECTS OF METHYLMERCURY (FROM STUDIES PUBLISHED IN THE LAST TEN YEARS)

To evaluate the evidence of toxic effects of MeHg published in the last ten years, the literature consisted of the EFSA 2012 MeHg report, Scientific Opinion on the risk for public health related to the presence of mercury and MeHg in food; the 2022 VKM report; and literature (original primary studies) included from a systematic literature search.

The systematic literature search was performed in the databases PubMed and Web of Science. The initial search resulted in 1 929 records. After screening the titles and abstracts, 396 records were assessed in full text. Further, 100 records were quality assessed with risk-of-bias tools. Thus, the final review included 2 risk assessments (EFSA, 2015 and VKM, 2022), 16 systematic reviews, and 20 original primary studies. The literature reviewed was further categorized into the following health outcomes: neurological outcomes, cardiovascular outcomes, growth, and other health outcomes. A final weight of evidence was not performed, as only literature published after 2010 was included, and thus it was not possible to give an overall grading of the available evidence.

4. THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF METHYLMERCURY

To evaluate the evidence of the role of Se with regard to the health effects of MeHg, the literature review included original primary studies identified from a systematic literature search.

The systematic literature search was performed in the databases PubMed and Web of Science. The initial search resulted in 1 154 records. After screening the titles and abstracts, 234 records were assessed in full text. Further, 47 records were quality assessed with risk-of-bias tools. Finally, 45 original human primary studies were included in the final literature review. The literature reviewed was further categorized into the following health outcomes: cardiovascular outcomes, oxidative stress, immune system, reproduction, thyroid hormones, birth outcomes, neurodevelopment and cognition, vision function, and motor function. A final weight of evidence using the report, Judging the evidence (WCRF, 2018), was performed, grading the evidence for the different health outcomes into the categories: convincing (strong evidence); probable (strong evidence); limited, suggestive; limited, no conclusion; or substantial effect of risk unlikely (strong evidence).

5. OCCURRENCE DATA FOR METHYLMERCURY, DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN FISHERY AND AQUACULTURE PRODUCTS (FROM STUDIES PUBLISHED IN THE LAST TEN YEARS)

To evaluate the data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products published in the last ten years, data were obtained from the WHO GEMS/Food database and the ESFA Chemical Monitoring database (both public databases) and from literature included from a systematic literature search.

A systematic literature search was performed in the database Web of Science. The initial search resulted in a total of 6 851 records. After screening the titles and abstracts, 2 306 records were assessed in full text. Further, 1 252 records were quality assessed. As a result, the final review of the literature included 554 original primary articles. Concentration data for total Hg, MeHg and/or dioxins and dl-PCBs were extracted from these articles, along with necessary metadata and compiled in an Excel spreadsheet. Further, data on concentrations of MeHg, dioxins and dl-PCBs obtained from the literature review and the data from the EFSA database, were treated and compiled separately.

BACKGROUND

At its thirty-eighth session, held in 2006, the Codex Committee on Food Additives and Contaminants asked the Codex Alimentarius Commission to seek scientific advice from FAO and WHO on the risks and benefits of fish consumption; specifically, to compare the health benefits of fish consumption with the risks associated with the contaminants MeHg and dioxins (defined here to include polychlorinated dibenzo-p-dioxins [PCDDs], polychlorinated dibenzofurans [PCDFs] and dioxin-like polychlorinated biphenyls [dl-PCBs]), which may be present in fish. The request was driven by growing public concern regarding the presence of chemical contaminants in fish and, at the same time, the increasing clarity of the multiple nutritional benefits of including fish in the diet. In response to the request, from 25 to 29 January 2010, FAO and WHO conducted the Expert Consultation on the Risks and Benefits of Fish Consumption to review data on the levels of nutrients and specific chemical contaminants (MeHg and dioxins) in a range of fish species and to review scientific literature covering the risks and benefits of fish consumption. The review considered the risks and benefits for specific endpoints, including sensitive groups of the population. The findings of the Expert Consultation were published in the Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption (FAO and WHO, 2010). Since then, new literature, data and information on the subject have become available. As such, FAO and WHO decided to conduct another comprehensive literature review and prepare a background document of the findings, in order to update the 2010 report with new scientific evidence.

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CHAPTER 1
INTRODUCTION

1.1 FISH AS FOOD

Global fishery and aquaculture production are at a record high, and the sector will play an increasingly important role in providing food and nutrition into the future (FAO, 2022). Global fish consumption has more than doubled in the last 50 years, and annual per capita consumption reached more than 20 kg in 2020 (FAO, 2022). In addition, fish is an important food source and a part of cultural food traditions of many people globally (FAO and WHO, 2010).

Unless otherwise stated, the term "fish" is here defined as finfish (vertebrates) and other seafood (aquatic invertebrates, including crustaceans, molluscs and echinoderms, most frequently consumed by humans), whether of marine or freshwater origin, farmed or wild (FAO, 2020). Aquatic mammals, reptiles, seaweed, algae and aquatic plants are considered outside the scope of this background document and, thus, are excluded from it (FAO, 2020). Furthermore, sustainability issues and environmental impacts are also considered outside the scope of this background document.

1.2 BENEFITS OF FISH CONSUMPTION

1.2.1 NUTRIENTS

Fish is dietary source of several important nutrients, including high-quality proteins, marine long-chain n-3 polyunsaturated fatty acids, or LC n-3 PUFAs (eicosapentaenoic acid and docosahexaenoic acid), vitamin A, vitamin D, vitamin B12, iodine, iron, selenium (Se), and zinc (Byrd *et al.*, 2021). The benefits of fish consumption have been related to the intake of these essential micronutrients and fatty acids, as consuming seafood can potentially reduce micronutrient deficiencies (Golden *et al.*, 2021). Globally, fish and seafood intake provides about 7 percent of all proteins and 17 percent of animal protein, and up to more than 50 percent of animal protein in several countries in Africa and Asia (FAO, 2022).

1.2.2 HEALTH BENEFITS

Until recently, most research on the health benefits of fish consumption has focused on the beneficial effects of proteins and marine LC n-3 PUFAs (FAO and WHO, 2010). In recent decades, however, the potential health benefits of micronutrients from fish consumption have received more attention (Golden *et al.*, 2021). Recent estimates propose that, globally, over half of preschool-aged children and two-thirds of women of reproductive age have micronutrient deficiencies, including deficiencies in vitamin A, iron, iodine and vitamin D (Stevens *et al.*, 2022). Micronutrient deficiencies increase the risk of morbidity and mortality worldwide (Micha *et al.*, 2020), and consumption of fish and seafood can potentially improve human health by supplying essential micronutrients (Golden *et al.*, 2021). Moreover, by replacing the intake of foods such as red and processed meats, fish consumption might further reduce the risk of diet-related non-communicable diseases (Golden *et al.*, 2021).

Previous risk assessments and guidelines for fish consumption have mostly pointed to the potential health benefits of fish consumption related to a reduced risk of cardiovascular disease and a lower risk of suboptimal neurodevelopment (FAO and WHO, 2010; EFSA, 2014a).

1.3 RISKS OF FISH CONSUMPTION

In addition to considering the health benefits of fish consumption, however, the fact that fish may contain undesirable components that may impact human health must also be considered. Many contaminants are ubiquitously present in the environment and may be present in fish and seafood, depending on factors such as geography and the age and trophic level of aquatic animals. Of particular concern are substances such as dioxins, dioxin-like polychlorinated biphenyls (dl-PCBs) and methylmercury (MeHg).

1.3.1 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

Dioxins and dl-PCBs are members of a group of compounds that are classified as persistent organic pollutants, as they are characterized by their persistence in the environment and their potential to bioaccumulate and biomagnify in the food chains. Dioxins and dl-PCBs are often grouped together due to their ability to bind to the aryl hydrocarbon receptor and, therefore, share similar toxicological properties. They are often considered together within the context of public health concerns (JECFA 2002, EFSA 2022).

1.3.1.1 Dioxins

Dioxins are a collective term for the chlorine-containing groups of polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Their diverse chemical structures depend on the number of chlorine atoms (1 to 8) and their position in the rings. There are 75 different PCDDs and 135

different PCDFs, also termed different "congeners" (EFSA, 2011). Dioxins enter the environment mainly as byproducts of industrial processes, but also from natural processes, such as volcanic eruptions and forest fires (Kanan *et al.*, 2018). Of the many PCDD and PCDF congeners, 17 of them (7 PCDDs and 10 PCDFs) are considered relevant to public health because of their persistence and toxic effects (Van den Berg *et al.*, 2006).

1.3.1.2 Dioxin-like polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are a group of organochlorine compounds, consisting of two compound benzene rings that are substituted with chlorine atoms. Their chemical structures depend on the number and positions of the chlorine atoms (between 1 and 10) at the two rings, which makes for 209 different compounds, or congeners (EFSA, 2011). Twelve of the PCB congeners have structures and toxicological properties that are similar to those of dioxins. These 12 congeners are therefore termed dioxin-like PCBs, or dl-PCBs. All PCBs are synthetic compounds that were produced for numerous industrial applications, until they were banned in the 1980s and scheduled to be phased out in most countries through the Stockholm Convention. Because of these regulations, the emissions of both dioxins and dl-PCBs have been reduced by more than 90 percent since 1987. However, due to their chemical stability, they are very persistent in the environment (Mozaffarian *et al.*, 2006).

1.3.1.3 Toxicity of dioxins and dioxin-like polychlorinated biphenyls

The potential negative health effects of dioxins and dl-PCBs include endocrine, immune, developmental, reproductive and carcinogenic effects (JECFA, 2002; EFSA, 2018). The mechanism of toxicity is proposed to be similar for all the congeners of dioxins and dl-PCBs; that is, through activating the aryl hydrocarbon receptor causing the same type of biochemical and adverse effects mediated by the aryl hydrocarbon receptor (JECFA, 2002; EFSA, 2018). The congeners differ in the number and position of their chlorine atoms, which affects the affinity of each congener to the aryl hydrocarbon receptor, leading to differences in their toxic potential. Because of the variation in toxicity, toxic equivalency factors (TEFs) were developed to express the toxicities of dioxins and dl-PCBs (Van den Berg *et al.*, 2006). The TEF values published by the World Health Organization (WHO) in 2005 and are given in **Table 1.1**.[1]

Among the congeners of dioxins and dl-PCBs, 2,3,7,8-tetrachlorodiobenzo-p-dioxin (TCDD) was defined as the most toxic congener and was assigned a TEF of 1. All other congeners were assigned TEF values based on their toxicity relative to that of TCDD. As dioxins and dl-PCBs can be present together, for instance in foods, the total dioxin-like toxicity of existing mixtures can be calculated by summing the products of each single congener's concentration and its corresponding TEF, resulting in toxic equivalent quotients (TEQ) (Van den Berg *et al.*, 2006).

[1] The 2005 TEF values set by WHO have recently been updated at an expert meeting held by WHO in October 2022. The outcome of this expert consultation was published in 2023, after the development of this background document (DeVito *et al.* 2024).

TABLE 1.1 **DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS WITH TOXICITY EQUIVALENCE FACTOR (TEF) SET BY THE WORLD HEALTH ORGANIZATION IN 2005**

COMPOUND	TEF
Polychlorinated dibenzo-p-dioxins (PCDDs) (n = 7)	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
Polychlorinated dibenzofurans (PCDFs) (n = 10)	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.0003
Dioxin-like polychlorinated biphenyls (dl-PCBs) (n = 12)	
Non-ortho PCBs (n = 4)	
PCB-77	0.0001
PCB-81	0.0003
PCB-126	0.1
PCB-169	0.03
Mono-ortho PCBs (n = 8)	
PCB-105	0.00003
PCB-114	0.00003
PCB-118	0.00003
PCB-123	0.00003
PCB-156	0.00003
PCB-157	0.00003
PCB-167	0.00003
PCB-189	0.00003

Notes: TEF: toxicity equivalence factor, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, PeCDD: pentachlorodibenzo-P-dioxin, HxCDD: hexachlorodibenzo-p-dioxin, HpCDD: heptachlorodibenzo-p-dioxin, OCDD: octachlorodibenzo-p-dioxin, TCDF: tetrachlorodibenzofuran, PeCDF: pentachlorodibenzofuran, HxCDF: hexachlorodibenzofuran, HpCDF: heptachlorodibenzofuran, PCB: polychlorinated biphenyls.
Source: Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A. and Haws, L. 2006. The 2005 World Health Organization re-evaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicological Sciences*, 93(2): 223-241.

1.3.1.4 Dioxins and dioxin-like polychlorinated biphenyls in the environment

Dioxins and dl-PCBs are found throughout the environment, but the compounds are lipid-soluble and therefore tend to accumulate in organisms, where the compounds are mainly bound to lipids. As dioxins biomagnify in the food chain, the highest concentrations are generally found in fatty tissues of top predators. Because of their chemical stability, once dioxins enter the human body, they last a long time and are stored in fat tissue. The half-life of dioxins in the human body has been estimated at 7 to 11 years (Kerger *et al.*, 2007).

1.3.1.5 Main food sources of dioxins and dioxin-like polychlorinated biphenyls

More than 90 percent of human exposure to dioxins and dl-PCBs is through food consumption (WHO, 2016). The highest concentrations are found in organisms located high up in the food chain, and particularly in fat of animal origin (VKM, 2022). The main food sources of dioxins and dl-PCBs are fish and seafood, meat, eggs, and milk and dairy products (EFSA, 2018).

1.3.1.6 Tolerable intakes of dioxins and dioxin-like polychlorinated biphenyls

In 2018, ESFA established a tolerable weekly intake (TWI) for dioxins and dioxin-like PCBs in food of 2 picograms per kg of body weight (EFSA, 2018). This new TWI is seven times lower than the previous TWI set in 2001 by the European Commission's former Scientific Committee on Food. According to EFSA, this updated TWI should protect against effects on semen quality, lower sex ratio of sons to daughters, higher levels of thyroid-stimulating hormone in newborns and developmental enamel defects on teeth.

1.3.2 METHYLMERCURY

Mercury (Hg) is a toxic non-essential element and metal that is naturally present in the earth's crust. It is distributed in the environment by both natural and anthropogenic processes, including volcanic eruptions, erosion, mining, coal incineration and other industrial processes. Hg cycles between the atmosphere, water, ocean, biota and land, where it undergoes complex transformations between the different forms of Hg (ATSDR, 2022). Humans are exposed to Hg during these biogeochemical cycles, and this may result in various health implications (ATSDR, 2022).

Depending on the chemical state, Hg toxicity and toxicokinetics vary. The chemical forms of Hg can be categorized into three groups; metallic or elemental Hg (Hg^0), inorganic Hg compounds (Hg_2^{2+} and Hg_2^{+}), and organic Hg compounds (EFSA, 2012; ATSDR, 2022). Organic Hg is combined with carbon covalently. Methylmercury (MeHg) is the most common form of organic Hg found in the environment, and the form of Hg of most concern, due to its toxicological properties (Guangliang *et al.*, 2012).

1.3.2.1 Main food sources

Humans are exposed to MeHg predominantly through fish and seafood consumption (Bradley *et al.*, 2017). In fish, 80 to 100 percent of total Hg in fish muscle is present in the form of MeHg, and 100 percent presence of MeHg is often assumed to account for a conservative approach in exposure estimates (EFSA, 2012; VKM, 2014). MeHg is primarily produced by methylation of inorganic Hg as a result of microbial activity of microorganisms in aquatic systems. MeHg content in fish and seafood species varies extensively and depends on a variety of factors including species, trophic level, size, age and diet (Sheehan *et al.*, 2014). MeHg accumulates in organisms and biomagnifies along the aquatic food chain, reaching the highest concentrations in animals at the highest trophic levels. Thus, long-lived predatory seafood species contain the highest concentrations of MeHg (National Research Council, 2000; Guangliang *et al.*, 2012).

1.3.2.2 Toxicity and health effects of methylmercury

All chemical forms of Hg are toxic to humans, although toxicity depends on several factors including the chemical form of Hg, exposure route, dose, age at exposure and duration of exposure (Berlin *et al.*, 2014). The toxic effects of Hg affect several body compartments and studies have shown adverse effects on the central and peripheral nervous system, kidneys, cardiovascular system, liver, gastrointestinal system and immune system (Berlin *et al.*, 2014). However, the primary targets of MeHg toxicity are the brain and the central nervous system (Antunes dos Santos *et al.*, 2016).

1.3.2.3 Tolerable intakes

In 2003, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) established a provisional TWI for MeHg of 1.6 µg/kg of body weight (FAO/WHO, 2004). In 2012, EFSA established a TWI for MeHg of 1.3 µg/kg of body weight (EFSA, 2012). Both JECFA's provisional TWI and ESFA's TWI are based on the most sensitive toxicological endpoint, which was considered to be neurodevelopmental outcomes after prenatal exposure to MeHg.

1.3.3 SELENIUM AND METHYLMERCURY

While fish and seafood consumption is the main source of MeHg exposure (EFSA, 2012), fish and seafood are also rich in micronutrients, including vitamins and minerals. In particular, fish and seafood are major sources of selenium (Se).

The most sensitive toxicological endpoints for MeHg toxicity were proposed to be brain damage in developing foetus and young children (FAO and WHO, 2004; EFSA, 2012). Therefore, concern has been raised for populations with high exposure to MeHg. However, the epidemiological studies investigating populations with moderate exposure to MeHg from fish consumption in pregnancy and neurodevelopmental outcomes in offspring have shown conflicting results,

reporting both negative and null effects of increased MeHg exposure (Grandjean *et al.*, 1997: Crump *et al.*, 1998; Davidson *et al.*, 1998; Myers *et al.*, 2003; Strain *et al.*, 2012; van Wijngaarden *et al.*, 2013b). One proposed explanation of the results showing no adverse effect of increased MeHg exposure from fish consumption, was counteraction by the high levels of Se in fish, as Se may have a protective effect against MeHg toxicity (Cuvin-Aralar *et al.*, 1991; Chapman *et al.*, 2000; Raymond *et al.*, 2004).

Selenium is an essential trace element, the main function of which, in the human body, is as part of enzymes such as glutathione peroxidase, which has an important role in protecting against oxidative stress, and in the enzyme iodothyrodine 5'-deiodinase, which is important for the metabolism of the thyroid hormones (EFSA, 2014b). EFSA has set a dietary reference value for Se of 70 µg/day for adults and an additional 15 µg for lactating women (EFSA, 2014b). However, EFSA did not consider the possible protective effect of Se on MeHg toxicity in this dietary reference value. An upper limit for Se intake was proposed at 255 µg/day, and it is assumed that no consumers with a normal diet will exceed this (EFSA, 2023).

The proposed protective effect of Se against MeHg toxicity was claimed to be achieved by influencing the transport, bioavailability, speciation and detoxification processes (Raymond *et al.*, 2004). Several animal studies suggest that Se can reduce MeHg toxicity when both are simultaneously present in the diet, particularly in seafood (Stillings *et al.*, 1974; Ohi *et al.* 1980; Bjerregaard *et al.*, 2012; Mellingen *et al.*, 2022).

The molecular basis for this proposed effect is the very strong binding between Se and Hg – one million times stronger that the binding between Hg and sulphur. This binding might be part of the basis both for the toxic effects of MeHg and the protective effect of Se (Timmerman *et al.*, 2021). Se and Hg may form complexes in blood and, thereby, decrease the availability of both. MeHg is proposed to interfere with or block the function of enzymes containing Se, and extra dietary Se can mitigate this blocking. Additionally, direct binding of Se and Hg in nodules is proposed as a mechanism to inactivate MeHg. This will normally require demethylation of MeHg to inorganic Hg, as shown to occur in mammals with very high levels of both Hg and Se, such as the bottlenose dolphin (Marumoto *et al.*, 2022). To ensure Se sufficiency for its essential functions, Se requirements may therefore increase with MeHg exposure.

Though mechanistic *in vitro* studies and animal studies have shown potential effects of Se against MeHg toxicity, very few human studies have been conducted on this question.

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CHAPTER 2
METHODS

To provide new scientific evidence, five extensive literature reviews were conducted focusing on the following topics:

> evidence of health benefits from fish consumption;
> toxic effects of dioxins and dl-PCBs (published in the last ten years);
> toxic effects of MeHg (published in the last ten years);
> the role of Se with regard to the health effects of MeHg;
> occurrence data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products (published in the last ten years).

The reviews followed a systematic approach, including a systematic literature search and elements from systematic literature reviews. A systematic literature review attempts to identify, appraise and synthesize all the empirical evidence that meets prespecified eligibility criteria to answer a specific research question (Cochrane Library, 2023). When conducting systematic reviews, systematic methods are selected, aiming to minimize bias and produce more reliable findings to inform decision-making (Cochrane Library, 2023). The following steps are generally followed in a systematic review (Page *et al.*, 2021):

1. determination of the scope and research question;
2. definition of inclusion and exclusion criteria;
3. development of a literature search strategy;
4. performance of literature search in relevant databases;
5. selection of the literature by screening of titles and abstracts;
6. selection of the literature by screening of full texts;
7. quality assessment of the selected literature;
8. extraction of data and results from the selected literature;
9. synthesizing and summarizing of evidence from the selected literature.

Generally, systematic reviews include the primary research that is available (Clarke, 2011), although some reviews also summarize the available systematic reviews (Aromataris *et al.*, 2015). The literature review presented here uses a combined method, integrating primary research, systematic reviews, and other

relevant risk and benefit assessments. In addition to reviewing the literature, the literature was summarized. The review was conducted according to the PRISMA guidelines for searching, selecting and reporting on literature (Page *et al.*, 2021).

2.1 METHODS FOR THE REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"

The objective of this literature review was to evaluate the evidence of health benefits from fish consumption. The review included a systematic literature search, quality assessment of the literature, summarizing the available literature, and weighing the evidence.

In June 2022, the Norwegian Scientific Committee for Food and Environment published the report, Benefit and risk assessment of fish in the Norwegian diet (VKM, 2022). The report included a systematic literature review (including both systematic reviews and primary articles) of fish consumption and relevant health outcomes. The report was included in this literature review as it was considered sufficiently comprehensive for the evaluation of evidence of health benefits from fish consumption. In addition to selecting this report, a comprehensive literature search was performed. The following sections provide a comprehensive description of the VKM report, followed by a description of the methods of the literature search and further steps.

2.1.1 2022 VKM REPORT: BENEFIT-AND-RISK ASSESSMENT OF FISH IN THE NORWEGIAN DIET

The Norwegian Scientific Committee for Food and Environment (VKM) carries out independent risk assessments for the Norwegian Food Safety Authority (Mattilsynet) and the Norwegian Environment Agency (Miljødirektoratet). The VKM comprises independent experts who conduct independent risk assessments.

In 2022, the VKM published the report, Benefit and risk assessment of fish in the Norwegian diet.[2] The report was based on an extensive systematic literature review conducted to evaluate the epidemiological evidence for associations between fish consumption and health outcomes. The review covered both original primary studies and systematic reviews. The health outcomes included were: cardiovascular disease (CVD); congenital heart disease (CHD); myocardial infarction; stroke; heart failure; heart fibrillation; venous thrombosis; neurodevelopment in children; mental disorders in children (such as autism spectrum disorder [ASD] and attention deficit hyperactivity disorder [ADHD]); cognition and cognitive decline in adults (including Alzheimer's disease and dementia); depression in adults; type 2 diabetes (T2D); weight/overweight in children and adults; bone health; birth outcomes (such as preterm birth, small-for-gestational-age, low birth weight, birth weight

[2] A protocol for the methodology of the report was published in 2020 after a public consultation, and the work was conducted according to the protocol (VKM, 2020).

[continuous], birth length and head circumference [continuous]); asthma and allergy (especially in children); multiple sclerosis; rheumatoid arthritis; vaccine response and semen quality/male fertility.

The systematic literature review followed the established guidelines for performing systematic reviews (PRISMA or JBI) for searching, selecting and reporting on the literature. The review, performed in the databases Medline, Embase and PsycINFO, included a systematic literature search, including the search string for all the health outcomes. The search resulted in 27 182 papers (26 384 primary studies and 798 systematic reviews, after removal of duplicates).

These papers were further screened by two blinded reviewers, using predefined inclusion and exclusion criteria. After screening the papers, 409 papers (346 primary studies and 63 systematic reviews) were included for quality assessment using risk-of-bias tools. Based on quality assessment, 100 papers (76 primary studies and 24 systematic reviews) were excluded, leaving 309 papers (270 primary studies and 39 systematic reviews) included in the review for data extraction. In addition, pooled estimates were calculated from the primary studies included. This entailed calculating a summary risk ratio (RR) with 95 percent confidence interval (CI) for binary disease outcomes in relation to the highest versus lowest fish intake. The pooled estimates (summary RR) were further compared to previous meta-analyses that were included from the literature search. Finally, the weight of evidence was based on the criteria from the World Cancer Research Fund (WCRF).

The literature search and inclusion and exclusion criteria were based on the work of the VKM in their 2022 report, which was graded with the quality-assessment tool AMSTAR-2 as "high quality" (Appendix 3, **Table A3.35**) and was therefore considered sufficiently comprehensive to answer the research question "evidence of health benefits of fish consumption".

As the literature search string used in the 2022 VKM report focused on Norway, for this background report, the search string was extended to a global setting including all fish and seafood species according to the major species produced in aquaculture and marine capture production (FAO, 2020).

2.1.2 LITERATURE SEARCH STRATEGY

The search strategy was developed using a population, intervention, comparison, outcome and study designs, or PICOS, table (**Table 2.1**) for the research question "What is the evidence of health benefits from fish consumption?".

TABLE 2.1 **POPULATION, INTERVENTION, COMPARISON, OUTCOMES AND STUDY DESIGN TABLE FOR THE LITERATURE SEARCH ON "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**

POPULATION	INTERVENTION/ EXPOSURE	COMPARISON	HEALTH OUTCOMES	STUDY DESIGNS
General population[1] Including both sexes and all ages (foetuses, infants, children, adolescents, adults).	Fish consumption The term "fish" is here defined as finfish (vertebrates) and other seafood (aquatic invertebrates, including crustaceans, molluscs and echinoderms), whether of marine or freshwater origin, farmed or wild.	No consumption or lower fish consumption	> Allergy and immunology > Birth and growth outcomes > Bone health > Cancer > Cardiovascular disease > Neurodevelopment and neurological disorders > Mortality > Obesity	Systematic reviews > Meta-analysis > Cochrane reviews > Systematic reports/ reviews without a meta-analysis > Umbrella reviews > Randomized controlled trials Non-randomized intervention trials Prospective cohort studies

Note: [1]The following conditions will also be considered part of the general population: type 2 diabetes, overweight and obesity, musculoskeletal disorders, malnutrition and nutritional deficiencies.

2.1.2.1 Population

The target population of the literature search is the general population, including both sexes, foetuses and infants, children, adolescents and adults.

2.1.2.2 Intervention/exposure

The intervention is in term of fish consumption. The term "fish" is here defined as finfish (vertebrates) and other seafood (aquatic invertebrates, including crustaceans, molluscs and echinoderms), whether of marine or freshwater origin, farmed or wild. Marine mammals and algae, as well as sustainability issues and environmental impacts, are considered outside the scope of the report.

2.1.2.3 Comparison

The group of participants with fish consumption are compared to a group with no fish consumption or lower fish consumption.

2.1.2.4 Health outcomes

Table 2.2 lists the categories of health outcomes defined to investigate the evidence of the health benefits of fish consumption. The health outcomes were selected based on established knowledge about fish and seafood consumption and health outcomes relevant to nutrients for which fish and seafood are good sources.

TABLE 2.2 **CATEGORIES OF HEALTH OUTCOMES INCLUDED IN THE LITERATURE SEARCH ON "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**

HEALTH OUTCOME	DEFINITION
Allergy and immunology	Allergy, asthma/wheezing, eczema, multiple sclerosis, allergic rhinitis, rheumatoid arthritis, inflammation, immunodeficiency
Birth and growth outcomes	Birth weight, premature birth, small for gestational age
Bone health	Osteoporosis, osteopenia, rickets, osteomalacia, bone density, bone resorption, demineralization, vitamin D deficiency
Cancer	Cancer or tumours
Cardiovascular diseases and outcomes (CVD)	Heart or cardiac diseases, failure, event, arrest, infarct Atherosclerosis, stenosis, restenosis Ischemia, thromboses, thromboembolism, tachycardia, arrythmia, fibrillation Stroke, cardiac death, transient ischemic attack Brain haemorrhage, brain infarct
Dental health	Dental or teeth malformation, enamel changes and defects
Type 2 diabetes	Type 2 diabetes
Neurodevelopment and neurological disorders	Child development, cognitive function, neurodevelopment, intelligence quotient, attention deficit hyperactivity disorder (ADHD), attention deficit disorder (ADD), Asperger, schizophrenia, Alzheimer's, Parkinson's, depression
Mortality	Mortality, death, death rate
Overweight and obesity	Overweight or obesity defined by body mass index (BMI)

2.1.2.5 Study designs

The study designs and types of articles included systematic reviews (meta-analysis, Cochrane reviews, systematic reviews and umbrella reviews). For primary studies, randomized controlled trials (RCTs) and prospective cohort studies were included.

2.1.3 LITERATURE SEARCH

The literature search was performed on 29 Nov. to 3 Dec. 2021, in the databases PubMed, Web of Science and Cochrane Library. The search strategy for each database is given in Appendix 3 (Table A3.1).

The search terms included a combination of the following:

> *fish and seafood*: other typical words for fish and seafood, specific fish and seafood species;
> *study type*: systematic reviews, meta-analyses, umbrella reviews, RCTs, trials, prospective cohort studies;
> *dietary intake*: specification that the literature investigated consumption, eating or intake of fish and seafood;
> *health outcomes*: relevant health outcomes included in literature search.

In Web of Science the literature search was performed under the field "topic search" which included search words within title, abstract, author keyword and keywords

plus. In PubMed, the literature search was performed including "all fields". In Cochrane Library, the literature search was performed under the field of "Title Abstract Keyword".

All records identified in the searches from each of the databases were imported into the reference manager program EndNote. Duplicates were removed in EndNote by comparing articles with similar "title" and "authors".

2.1.4 SELECTION OF ARTICLES FROM THE LITERATURE SEARCH

Title and abstract screening of articles from the literature search was performed blind by two reviewers using Rayyan, a web-based tool for selecting studies in systematic reviews (Ouzzani *et al.*, 2016). The selection of articles was based on predefined inclusion and exclusion criteria (see **Table 2.3**), which were developed based on the research question and a PICOS diagram. Full-text articles were retrieved when the information given in the title or abstract seemed to fulfil the inclusion criteria. After screening the articles by title and abstract, the blinding was removed, and the two reviewers discussed any conflicting decisions regarding the papers that were included and excluded.

The articles selected via abstract and title screening were further reviewed in full text according to the same inclusion and exclusion criteria.

To avoid reporting duplicate publications, the systematic reviews and primary studies that were included in the 2022 VKM report were excluded for further assessment in the literature search. Furthermore, the primary studies that were already included in the systematic reviews included in the literature search, were also excluded to avoid duplicate reporting of publications.

2.1.5 QUALITY ASSESSMENT (RISK OF BIAS)

2.1.5.1 Systematic reviews

All the systematic reviews that fulfilled the inclusion criteria were quality-assessed using AMSTAR 2 (Shea *et al.*, 2017). AMSTAR 2 is a tool used to assess the methodological quality of systematic reviews and meta-analyses, which consists of 16 questions (see Appendix 2, Table A2.1). Each systematic review was quality-assessed independently by two reviewers, after which they discussed their findings and determined which reviews would be included. If the two reviewers were unable to agree on the inclusion or exclusion of a systematic review, a third member in the review team helped make a final determination.

TABLE 2.3 **INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH ON "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION"**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION

> Studies investigating fish consumption in relation to one or more health outcomes defined in the literature search strategy
> Study design:
  > systematic reviews: meta-analysis (from systematic reviews), Cochrane reviews, systematic reports/reviews without meta-analysis, umbrella reviews
  > randomized controlled trials
  > non-randomized intervention trials
  > prospective cohort studies
> Population:
  > general population, including both sexes and all ages (foetuses, infants, children, adolescents and adults).
  > The following conditions will also be considered as part of the general population: type 2 diabetes, obesity, musculoskeletal disorders, malnutrition and nutritional deficiencies, and nutritional deficiency diseases (goitre, osteoporosis, rickets, osteomalacia, anaemia).
	> Studies investigating fish consumption without any relation to any of the health outcomes defined in the literature search strategy
	> Studies investigating exposure to LCn3PUFAs or dietary supplements only
	> Dietary pattern studies
	> Studies investigating contaminants: PCBs, POPs, metals
	> Study design:
	  > retrospective cohort studies
	  > case-control studies
	  > cross-sectional studies
	  > animal studies
	  > in vitro studies
	  > non-systematic reviews (e.g. narrative reviews and scoping reviews).
	  > systematic reviews including only results from retrospective cohort studies, case-control studies, cross-sectional studies, animal studies or in vitro studies.
	> Population: Specific patient groups (exceptions are specified in the inclusion criteria).
	> Non-English-language articles
	> Publication types: book chapters, case stories, letters to the editor, posters, abstracts

AMSTAR 2 is not intended to generate an overall score, but rather to indicate an overall level of confidence in the results of the review, as follows:

- **high (zero or one non-critical weakness):** The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.
- **moderate (more than one non-critical weakness):** The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
- **low (one critical flaw with or without non-critical weaknesses):** The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.
- **critically low (more than one critical flaw with or without non-critical weaknesses):** The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Papers graded "high" or "moderate" were included, while papers graded "low" or "critically low" were excluded for further assessment.

2.1.5.2 Primary studies

All the primary studies that fulfilled the inclusion criteria were quality assessed for risk of bias. This assessment was performed using the quality-assessment tools developed for Nordic Nutrition Recommendations (NNR, 2014), which were further adapted for the VKM report. These tools were chosen as they were appropriate for nutritional studies assessing fish consumption as the exposure with different health outcomes. Specific tools for RCTs and prospective cohort studies were used in this case. All the questions included in the quality-assessment tools for RCTs and prospective cohort studies are given in Appendix 2, **Table A2.2** and **Table A2.3**. The quality-assessment tool for RCTs and trials consists of 6 domains and 23 questions. The quality-assessment tool for prospective cohort studies consists of 7 domains and 22 questions. Each primary study was quality assessed independently by two reviewers, after which they discussed and determined if the study was to be included or not. If the two reviewers were unable to agree, a third member of the review team was called in to assist in making a final decision. A prespecified Excel template, including all the questions used, was completed by each reviewer when conducting the quality assessment of each systematic review. Based on the answer to each question, the primary study was graded as A (high quality), B (moderate quality) or C (low quality) (VKM, 2022):

> **A (high quality):** The results from studies that have an acceptably low level of bias are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a comprehensive study design; clear description of the participants, setting, interventions, and control group(s); appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; less than 30 percent dropout (depending on the length of the study, see the quality-assessment tool for RCTs in Appendix 2) or over 50 percent participation rate for prospective cohort studies; clear reporting of dropouts; and no obvious bias. Where appropriate, studies must provide a valid estimation of food intake/nutrient exposure, from dietary assessments and/or biomarkers with a reasonable range of measurement error, and justification for approaches to control for confounding in the design and analyses.

> **B (moderate quality):** Studies may have some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A". They have some deficiencies, but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

> **C (low quality):** Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis or reporting; there are large amounts of missing information, or discrepancies in reporting.

Papers graded A or B were included, while papers graded C (low quality) were excluded for further assessment.

2.1.6 EXTRACTION OF DATA FROM THE INCLUDED LITERATURE

Relevant prespecified data were extracted from the systematic reviews and primary studies selected and recorded in premade data-extraction forms. The data extraction was performed by one person, and the extracted data was double-checked by another person.

2.1.6.1 From systematic reviews

The data extracted from the systematic reviews included:

- reference details: reference, year, title;
- outcome: main outcome and specific outcome groups;
- population: type of population and number of participants;
- study information: study design and number of studies included;
- information regarding fish intake;
- overall results: including results from meta-analysis, if applicable;
- overall conclusion.

2.1.6.2 From primary studies

The data extracted from the primary studies reviewed included:

- reference details: reference, trial or study name, geography, year of sampling;
- study information: study type, study duration and follow-up time;
- participants: number of participants, age (years) at exposure assessment, sex;
- measurements and intake of fish consumption;
- for RCTs and trials: information regarding intervention, duration, dose and control group;
- outcome: measurement of outcome and type of outcome;
- overall results;
- overall conclusion.

2.1.7 SUMMARY OF THE LITERATURE REVIEWED

The results from the 2022 VKM report, the systematic reviews and primary studies were summarized according to each health outcome. For the 2022 VKM report, this included summarizing the literature included in their report, the effect of fish consumption on the specific health outcome, and the final weight of evidence. From the systematic reviews and primary studies from the literature search, the extracted data from the data extraction tables were summarized with the most relevant information for each health outcome.

2.1.8 WEIGHT OF EVIDENCE OF THE LITERATURE

In the final weight of evidence of the literature reviewed, the weight of evidence for the specific health outcomes in the 2022 VKM report was compared with that of the systematic reviews and primary studies from the literature search, and a final weight of evidence was computed. The 2022 VKM report used the weight-of-evidence scale of the WCRF (2018a), where evidence is graded as "convincing (strong evidence)", "probable (strong evidence)", "limited, suggestive", "limited, no conclusion", or "substantial effect of risk unlikely (strong evidence)". **Table 2.4** provides the criteria for each WCRF weight-of-evidence grading. (The outcome "cancer" is replaced with "outcome" as several health outcomes were included here).

TABLE 2.4 **CRITERIA OF THE WORLD CANCER RESEARCH FUND FOR WEIGHING THE EVIDENCE**

WEIGHT-OF-EVIDENCE GRADING	DESCRIPTION
CONVINCING (STRONG EVIDENCE)	Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce risk of an outcome. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All the following are generally required: > evidence from more than one study type; > evidence from at least two independent cohort studies; > no substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect; > good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias; > presence of a plausible biological gradient ("dose-response") in the association. Such a gradient needs not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly. > Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant health outcomes.
PROBABLE (STRONG EVIDENCE)	Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of an outcome. All the following criteria are generally required: > evidence from at least two independent cohort studies, or at least five case-control studies; > no substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect; > good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias; > evidence for biological plausibility.
LIMITED — SUGGESTIVE	Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad, and includes associations where the evidence falls only slightly below that required to infer a probably causal association through those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification. All the following criteria are generally required: > evidence from at least two independent cohort studies or at least five case-control studies; > the direction of effect is generally consistent though some unexplained heterogeneity may be present; > evidence for biological plausibility.

TABLE 2.4 CRITERIA OF THE WORLD CANCER RESEARCH FUND FOR WEIGHING THE EVIDENCE (cont.)

WEIGHT-OF-EVIDENCE GRADING	DESCRIPTION
LIMITED — NO CONCLUSION	Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded "limited — no conclusion" for several reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders), or by any combination of these factors. When an exposure is graded "limited — no conclusion", this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of an outcome. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on an outcome risk, this exposure will be judged "substantial effect of risk unlikely".
SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)	Evidence is strong enough to support a judgement that a particular food, nutrient or physical activity exposure is unlikely to have a substantial causal relation to cancer outcomes. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All the following criteria are generally required: > evidence from more than one study type; > evidence from at least two independent cohort studies; > summary estimate of effect close to 1.0 for comparison of high versus low exposure categories; > no substantial unexplained heterogeneity within or between study types or in different populations; > good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure; confounding and selection bias. > absence of a demonstrable biological gradient ("dose-response"); > absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant outcomes.

Source: WCRF (World Cancer Research Fund). 2018. *Judging the evidence. Continuous Update Project Expert Report 2018.* https://www.wcrf.org/wp-content/uploads/2021/02/judging-the-evidence.pdf.

2.2 METHODS FOR THE REVIEW "TOXIC EFFECTS OF DIOXINS AND DL- POLYCHLORINATED BIPHENYLS"

The objective of the review was to evaluate new data (published after the 2010 FAO/WHO report on the risks and benefits of fish consumption) on toxic effects of dioxins for all population groups. This was conducted through a systematic search, quality assessment and the summarizing of the available literature on this topic.

2.2.1 LITERATURE SEARCH STRATEGY

Dioxins have previously been risk assessed by different authorities. The most recent assessment was conducted by EFSA in June 2018, with the results set forth in the report, Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food (EFSA, 2018). The assessment was conducted through a comprehensive systematic literature search, including studies published between 1 July 1998 and 5 July 2016. This report was evaluated for use as a starting

point in the current evaluation, using the quality-assessment tool for systematic reviews, AMSTAR 2 (see Section 2.1.5.1). The AMSTAR 2 score was "high" (judgement given in Appendix 4, **Table A4.6**), and, as such, the EFSA report was used as a basis for the years 2010 to 2016. In addition, the extensive literature search protocol and search strategy developed by EFSA (Vedrine *et al.*, 2018), was used and updated for the years 2016 to 2022. To avoid duplicate reporting of publications, only studies published from 5 July 2016 onwards were included in the further search. The search covered literature published since 2010 and was based on the following PECOS table (**Table 2.5**), aiming to identify and characterize the toxic effects of dioxins and dl-PCBs in all human population groups.

TABLE 2.5 **POPULATION, EXPOSURE, COMPARISON, OUTCOMES AND STUDY DESIGNS (PECOS) TABLE FOR THE LITERATURE SEARCH ON "TOXIC EFFECT OF DIOXINS AND dl-PCBs"**

POPULATION	INTERVENTION/ EXPOSURE	COMPARISON	HEALTH OUTCOMES	STUDY DESIGNS
General population, all population groups Including both sexes, all ages (foetuses, infants, children, adolescents, and adults) in all countries	Exposure of dioxins and dl-PCBs	Lower exposure of dioxins	> Toxic and adverse effects on human health (any health outcome or endpoint)	Cohort studies Case-control studies Cross-sectional studies Systematic reviews and meta-analyses

Note: dl-PCB: dioxin-like polychlorinated biphenyl

2.2.1.1 Population

The target population of the literature search is the general population, including all population groups, both sexes and all ages (foetuses, infants, children, adolescents and adults) in all countries.

2.2.1.2 Exposure

The intervention or exposure is dioxin exposure. This includes all routes of exposure (dietary, dermal, inhalation and transplacental exposure). Studies were included if dioxins were measured in human tissues (including by bioassays) or if the total dietary exposure to the following target compounds was estimated:

> 17 polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) and 12 dl-PCBs
> 17 PCDD/Fs
> 12 dl-PCBs
> 17 PCDD/Fs plus non-ortho PCBs, at least one PCB being PCB-126
> TCDD (when dominating the TEQs, as in the Seveso incident) or any of the individual target congeners that contribute to a substantial part of the TEQs.

2.2.1.3 Comparison

The group of participants with exposure to dioxins was compared to a group with lower exposure to dioxins.

2.2.1.4 Outcomes

Toxic and adverse effects on human health (any health outcome or endpoint) were included.

2.2.1.5 Study designs

Human studies of cohort, case-control and cross-sectional studies were included. Studies with any duration and any number of subjects were included. Also, systematic reviews and meta-analyses were included.

2.2.2 LITERATURE SEARCH

The literature search was performed on 13 December 2021. The searches were performed in two databases, namely PubMed and Web of Science Core Collection, focusing on literature published since 2010. The search strategy for each database is provided in Appendix 4, Table A4.1 and Table A4.2.

The search terms included a combination of the following:

- *dioxins:* TCDD, dioxin, PCB, PCDD and PCDF;
- *population:* human, women, men, children;
- *outcome:* adverse effect or health outcome and dioxins measures in human tissues and waste products;
- *study design:* specific study designs included.

In Web of Science, the literature search was performed under the field "topic search", which included search words within title, abstract, author keyword and keywords plus. In PubMed, the literature search included search words within title and abstract. The literature searches were restricted to type of publication, human studies, language (English), and date of publication, in accordance with the literature search criteria (**Table 2.5**).

All identified records from the searches in each of the databases were imported into the reference manager program, EndNote. Duplicates were removed in EndNote by comparing articles with similar "title" and "authors".

2.2.3 SELECTION OF STUDIES FROM THE LITERATURE SEARCH

The studies included from the literature search were further assessed by screening the titles and abstracts. This was performed independently by two reviewers using Rayyan, a web-based tool for selecting studies in systematic reviews (Ouzzani *et al.*, 2016). Study selection was based on the predefined inclusion and exclusion criteria (**Table 2.6**), which were developed based on the research question and a

PECOS table. Full-text articles were retrieved when the information given in the title or abstract seemed to fulfil the inclusion criteria. After screening the papers by title and abstract, the blinding was removed, and the two reviewers discussed any conflicting decisions regarding studies that were included or excluded. The studies selected via abstract and title screening were further reviewed in full text according to the same inclusion and exclusion criteria.

TABLE 2.6 **INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH ON "TOXIC EFFECTS OF DIOXINS AND dl-PCBs"**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION
> Studies investigating exposure to dioxins in relation to one or more health outcomes in a human population > Studies including all routes of exposure (dietary, dermal, inhalation, transplacental) > Studies where dioxins were measured in human tissues (including by bioassays), or studies in which the total dietary exposure to the following target compounds was estimated: > - 17 PCDD/Fs and 12 dl-PCBs > - 17 PCDD/Fs > - 12 dl-PCBs > - 17 PCDD/Fs plus non-ortho PCBs, at least one PCB being PCB-126 > - TCDD (when dominates the TEQs, as in the Seveso incident) or any of the individual target congeners that dominates the TEQs > Study designs: > systematic reviews > randomized controlled trials > non-randomized intervention trials > cohort studies > case-control studies > cross-sectional studies > case series/case reports > Population: > general population, all population groups > both sexes, all ages (foetuses, infants, children, adolescents, and adults) in all countries > Published from 5 July 2016 onwards	> Studies on mono-ortho PCBs only > Studies on non-dioxin-like PCBs (indicator) > Studies on mixtures in which the contribution from the target compounds does not allow the calculation of TEQs. > Studies on gene expression or drug metabolizing activity or levels only > Study design: > animal studies > in vitro studies > other reviews (narrative reviews) > Publication types: expert opinions, case studies, editorials, letters to editors, PhD theses, abstracts, conference proceedings > Non-English-language articles

Note: dl-PCB: PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans, PCB: polychlorinated biphenyl, dl-PCB: dioxin-like polychlorinated biphenyl, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, TEQ: toxic equivalent quotient.

The systematic reviews retrieved in full text from the literature search included only a few relevant primary studies not already included in EFSA, 2018 (that is, published after 2016). Therefore, all the systematic reviews were excluded, except the EFSA 2018 Dioxin report (the excluded systematic reviews are listed in Appendix 4, **Table A4.3**). Primary studies published after 2016 were included for individual quality assessment.

2.2.4 QUALITY ASSESSMENT (RISK OF BIAS)

2.2.4.1 Systematic reviews

The risk assessment report of dioxins and dl-PCBs from EFSA 2018 was quality assessed using the quality-assessment tool for systematic reviews, AMSTAR 2. More information regarding the AMSTAR 2 tool is provided in Section 2.1.5.1 and in Appendix 2, **Table A2.1**.

2.2.4.2 Primary studies

All the studies that fulfilled the inclusion criteria were quality assessed using the Risk of Bias Rating Tool for Human and Animal studies of the US National Toxicology Program's Office of Health Assessment and Translation (OHAT) (Appendix 2, **Table A2.4**) (Rooney *et al.*, 2014; OHAT, 2015; OHAT, 2019). The OHAT tool, which was also used in the EFSA (2018) report on dioxins and dl-PCBs in feed and food, consists of 11 different questions or domains, where each question is applicable to specific study designs. The tool can be used for the following study designs:

> experimental animal;
> human controlled trial (randomized controlled trials and non-randomized experimental studies);
> cohort studies;
> case-control studies;
> cross-sectional studies;
> case series/reports.

For cohort, case-control and cross-sectional studies and case series or reports, seven questions are applicable; while for experimental animal studies, nine questions are applicable. The questions are grouped under six types of bias (confounding, selection, performance, attrition/exclusion, detection and selective reporting). Each risk-of-bias question is given a score based on a four-point scale, where the reviewer chooses between four different options, based on the quality of the study (**Table 2.7**):

> (++): Definitely low risk of bias
> (+): Probably low risk of bias
> (-) or (not reports [NR]): Probably high risk of bias
> (--): Definitely high risk of bias.

TABLE 2.7 **RISK-OF-BIAS CATEGORIES**

RISK-OF-BIAS RATING		EXPLANATION
(++)	Definitely low risk of bias	There is direct evidence of low risk-of-bias practices.
(+)	Probably low risk of bias	There is indirect evidence of low risk-of-bias practices OR it is deemed that deviations from low risk-of-bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias.
(-) NR	Probably high risk of bias/not reported	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g. not reported [NR]) provided about relevant risk-of-bias practices.
(- -)	Definitely high risk of bias	There is direct evidence of high risk-of-bias practices.
NA	Not applicable	Not relevant for this study.

Some of the risk-of-bias questions were considered key questions (Appendix 2, **Table A2.4**). The individual bias rating for each question was then combined by an algorithm and translated into an overall tier for each study (**Table 2.8** and **Table 2.8**) (OHAT 2019).

TABLE 2.8 **OVERALL RISK-OF-BIAS JUDGMENT**

TIER (TOTAL SCORE)	CRITERIA FOR CLASSIFICATION
1 (low risk of bias)	All key questions are scored (+) or (++) AND (+) or (++) for more than half the non-key questions
2 (moderate risk of bias)	All combinations not falling under tier 1 or 3
3 (high risk of bias)	All key questions are scored (- -) or (-) AND (- -) or (-) for more than half the non-key questions

Each paper was quality assessed independently by two reviewers using OHAT, after which the reviewers discussed their assessments and agreed on a final decision for each paper. If the two reviewers could not agree on a final decision, a third member of the review team was included to help make a final determination. A prespecified Excel template, including all the bias questions, was completed by each reviewer when conducting the quality assessment of each paper. Only Tier 1-rated articles were considered for data extraction and summarizing.

2.2.5 EXTRACTION OF DATA FROM THE LITERATURE

For the extraction of data from the primary studies included, a modified version of the EFSA extraction template was used (EFSA, 2018), including the following information:

- study or trial name;
- number of participants;
- funding source;
- study design and time frame;
- sex, age, ethnicity and socioeconomic variables;
- geography;
- compounds of dioxins or dl-PCBs measures, type of tissues measured, validation

of the method;

- levels measured in human tissue or estimated dietary intake;
- outcome measured (health category and specific outcomes measured) and method used to measure health outcome;
- confounders assessed;
- measures of effect between exposure and outcome (including statistical test and treatment of variables);
- dose–response effect, if applicable.

2.2.6 SUMMARIZATION OF THE INCLUDED LITERATURE

As previously described, the risk assessment by EFSA (2018) was used as a basis for summarizing the available literature. Thus, the summaries consist of a short summary of the findings and conclusions by EFSA, supplemented with a brief description of the studies identified through the present systematic literature search.

All studies deemed Tier 1 quality according to the risk-of-bias assessment were within the endpoint health categories suggested by EFSA. As such, this report summarizes the result according to the categories used by EFSA in their 2018 report: chloracne and other dermal effects, reproductive effects (including male reproductive effects, female reproductive effects and birth outcomes), thyroid disease and thyroid hormones, T2D and obesity, cardiovascular effects, hepatic disorders and digestive effects, effects on the immune system, effects on the nervous system, effects on teeth and bones, cancer and other effects.

A weight-of-evidence approach was not given as the review of "Toxic effects of dioxins and dl-PCBs" only included literature published after 2010. As such, it was not possible to compute an overall grading of the available evidence.

2.3 METHODS FOR THE REVIEW "TOXIC EFFECTS OF MeHg"

The objective of the review was to evaluate new data (published after the 2010 FAO/WHO report on the risks and benefits of fish consumption) on the toxic effects of MeHg for all population groups. The evaluation was conducted through a systematic search, quality assessment, and summarizing of the available literature.

2.3.1 LITERATURE SEARCH STRATEGY

The search strategy was developed using a PECOS table (Table 2.9) aiming to identify and characterize toxic effects of MeHg in all human population groups, focusing on literature published since 2010.

TABLE 2.9 **POPULATION, EXPOSURE, COMPARISON, OUTCOMES AND STUDY DESIGNS (PECOS) TABLE FOR THE LITERATURE SEARCH ON "TOXIC EFFECTS OF MeHg"**

POPULATION	EXPOSURE	COMPARISON	OUTCOMES	STUDY DESIGNS
General population, all population groups Including both sexes, all ages (foetuses, infants, children, adolescents, and adults), and pregnant and lactating women, in all countries	Exposure to MeHg	Reference groups assumed to have a lower exposure to MeHg than exposed groups	Toxic and adverse effects on human health (any health outcome) are included.	Cohort studies Case-control studies Cross-sectional studies Randomized controlled trials or non-randomized trials Systematic reviews Meta-analysis (if included in a systematic review)

2.3.1.1 Population

The target population of the literature search was the general population, including all population groups, both sexes, all ages (foetuses, infants, children, adolescents and adults), and pregnant and lactating women, in all countries (if reported in English).

2.3.1.2 Exposure

The intervention or exposure is in terms of MeHg exposure from ingestion (dietary intake) or transplacental exposure. As the focus was on studies on MeHg exposure from fish consumption, the review excluded studies targeting occupational or environmental Hg only and studies assessing dermal absorption or inhalation of MeHg.

2.3.1.3 Comparison

Participants with MeHg exposure were compared to individuals with lower MeHg exposure.

2.3.1.4 Outcomes

Toxic and adverse effects on human health (any outcome) were included.

2.3.1.5 Study designs

Human RCTs or trials; cohort, case-control and cross-sectional studies; systematic reviews and meta-analyses were included. Any study duration and any number of subjects in the studies were included.

2.3.2 LITERATURE SEARCH

The literature search for individual primary studies was performed on 15 December 2021. The literature search was performed in two databases, namely PubMed and Web of Science Core Collection, focusing on literature published since 2010.

The search strategy for each database is given in Appendix 5, **Table A5.1** and **Table A5.2**.

The search terms included a combination of the following:

> MeHg: methylmercury, MeHg, methyl-Hg, CH3Hg;

> *study type*: specified study design in the inclusion criteria: cohort studies, case-control studies, cross-sectional studies

In Web of Science, the literature search was performed under the field "topic search", which included search words within title, abstract, author keyword and keywords plus. In PubMed, the literature search included search words within title and abstract.

All identified records from the searches in each of the databases were imported into the reference manager program, EndNote (version 20), and duplicate entries were removed comparing articles with similar "title" and "authors".

2.3.2.1 Systematic reviews

The search terms used for systematic reviews were identical to those used for finding relevant primary studies. This literature search was also limited to papers published since 2010. The search strategy for the updated literature search is given in Appendix 5, **Table A5.1**.

2.3.3 SELECTION OF STUDIES FROM THE LITERATURE SEARCH

The studies included from the literature search were further assessed by screening the titles and abstracts. This was performed independently by two reviewers using Rayyan, a web-based tool for selecting studies in systematic reviews (Ouzzani *et al.*, 2016). Studies were selected based on the predefined inclusion and exclusion criteria (**Table 2.10**), which were developed based on the research questions and the information provided in the PECOS diagram (**Table 2.9**). After screening the papers by title and abstract, blinding in Rayyan was removed, and the two reviewers discussed with a third reviewer any conflicting decisions regarding the included or excluded papers. Subsequently, full texts of the records that fulfilled the inclusion criteria based on the initial screening were retrieved. The full-text records were further reviewed in detail according to the same inclusion and exclusion criteria before proceeding to quality assessment.

TABLE 2.10 **INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH ON "TOXIC EFFECTS OF MeHg"**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION

> Studies investigating MeHg exposure in relation to one or more health outcomes in a human population
> Ingestion (dietary) or transplacental exposure of MeHg
> Study designs:
  > systematic reviews
  > randomized controlled trials
  > non-randomized intervention trials
  > cohort studies
  > case-control studies
  > cross-sectional studies
> Population:
  > general population, all population groups
  > both sexes, all ages (foetuses, infants, children, adolescents and adults), and pregnant and lactating women, in all countries.
> Published from 1 January 2010 onwards
	> Studies on mercury (Hg) only (unless the study specifically described Hg exposure in relation to seafood or fish intake)
	> Studies including populations exposed to Hg in working environments (e.g. miners, dentists)
	> Studies including populations from contaminated areas (mines, factories) unless data on MeHg exposure was provided and seafood/fish as exposure source was specifically named
	> Studies in which only levels of Hg or MeHg were measured in human tissues and adverse health effects were not considered OR if health effects were reported but tissue or Hg concentration was not measured in blood/hair/toenails
	> Dermal absorption or inhalation of mercury
	> Studies where MeHg is only a confounding or stratifying variable
	> Studies on gene expression or drug metabolizing activity/ levels only
	> Comparison with existing health-based guidance values (HBGV) only
	> Study designs:
	  > animal studies
	  > in vitro studies
	  > case reports
	  > qualitative studies
	  > other reviews (narrative reviews)
	> Publication types: Expert opinions, case studies, editorials, letters to editors, PhD theses, abstracts, conference proceedings
	> Non-English-language articles

As both systematic reviews and primary studies were included in the literature review, there was some overlap between the primary studies identified in our literature search and the primary studies included in the systematic reviews that were identified in the literature search. To avoid overlap and double reporting of the primary studies, primary studies from the literature search that were already included in one of the systematic reviews were excluded from the review. Primary studies that were excluded for this reason are listed in Appendix 5 (Table A5.5). Subsequently, systematic reviews and original primary studies (not included in earlier reviews) were subjected to quality assessment with risk of bias.

2.3.4 QUALITY ASSESSMENT (RISK OF BIAS)

2.3.4.1 Systematic reviews

All systematic reviews that fulfilled the inclusion criteria were quality assessed using AMSTAR 2 (Shea *et al.*, 2017). Information regarding the quality-assessment tool AMSTAR 2 is provided in Section 2.1.5.1 and in Appendix 2 (**Table A2.1**).

2.3.4.2 Primary studies

All primary studies that fulfilled the inclusion criteria (and were not already included in systematic reviews assigned an AMSTAR 2 rating of *high* or *medium*) were quality assessed using the quality-assessment tool OHAT Risk of Bias Rating Tool. Information regarding the quality-assessment tool is given in Section **2.2.4.2** and in Appendix 2 (**Table A2.4**). Only studies graded Tier 1 were included for further assessment.

2.3.5 EXTRACTION OF DATA FROM THE INCLUDED LITERATURE

Relevant prespecified data were extracted from the systematic reviews and primary studies included in the review, into premade data-extraction forms. The extracted data was double-checked by a different person than the person who extracted the data.

2.3.5.1 Systematic reviews

The data extracted from the systematic reviews included:

> reference details: reference, year, title;
> outcome: main outcome and specific outcome groups;
> population: type of population and number of participants included;
> study information: study design and number of studies included;
> information regarding MeHg/Hg measurements and MeHg/Hg levels;[3]
> overall results: including results from meta-analysis if applicable;
> overall conclusion.

2.3.5.2 Primary studies

The data extracted from the primary studies included:

> reference details: reference, trial or study name, geography, year of sampling;
> study information: study design, study duration and follow-up time;
> participants: type of population, number of participants in the study, age (years) at exposure assessment, sex;

[3] Most studies measured Hg, not specifically MeHg. Measurement of Hg is used as a proxy of MeHg exposure.

- measurements (type of specimen, analytical method) and levels of Hg;
- measurement of fish intake;
- outcome: measurement of outcome and type of outcome assessed; specific outcome and overall outcome measured;
- overall results;
- overall conclusion.

2.3.6 SUMMARIZATION OF THE LITERATURE

The systematic reviews and primary studies from the literature search covered a diverse range of health outcomes associated with exposure to MeHg. These were grouped into four primary domains, namely (i) neurological outcomes, (ii) cardiovascular outcomes, (iii) growth, and (iv) other outcomes. Narrative summaries were prepared for each systematic review and primary study, organized into these same four domains.

In addition to the findings extracted from the systematic reviews and primary studies, the main findings of two reports – Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food (EFSA, 2012) and Benefit and risk assessment of fish in the Norwegian diet (VKM, 2022) – were provided for the respective health outcomes. Both reports included reviews of literature related to the health effects of MeHg exposure. In their 2012 report, ESFA considered original primary studies only (original primary studies published between 2004 and 2012), while, in their 2022 report, VKM included a review of systematic reviews published since 2012.

A weight-of-evidence approach was not given, as the review of "Toxic effects of MeHg" only included literature published after 2010, and as such it was not possible to compute an overall grading of the available evidence.

2.4 METHODS FOR THE REVIEW "THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF MeHg"

The objective of the review was to evaluate the role of Se with regard to the health effects of MeHg. The evaluation was conducted through a systematic search, a quality assessment, and by summarizing the available literature and weighing the evidence.

2.4.1 LITERATURE SEARCH STRATEGY

The search strategy was developed based on the research question "What is the role of Se with regard to the health effects of MeHg?". The search strategy, defined in a PICOS table, is set forth in **Table 2.11**. Studies investigating the role of Se on MeHg health effects were included.

As few human studies have assessed the role of Se with regard to the health effects of MeHg, it was decided to include both human and animal studies (mammalian models systems) in the literature search. The animal studies included from the literature search were only used as background information for mechanistic and biologically plausible evidence in the context of the human studies included. Only the human studies were quality assessed (assessment of risk of bias) and systematically weighed for evidence.

TABLE 2.11 **POPULATION, INTERVENTION, COMPARISON, OUTCOMES AND STUDY DESIGNS TABLE FOR LITERATURE SEARCH ON "THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF MeHg"**

POPULATION	INTERVENTION/ EXPOSURE	COMPARISON	OUTCOMES	STUDY DESIGNS
Human studies: > General population, including both sexes and all ages (foetuses, infants, children, adolescents and adults). > Patient groups Animal studies: > Mammalian model systems, including rodents (rats, mice, guinea pigs), dogs and monkeys	Effects and measurement of Se on MeHg health effects.	No exposure to Se or lower exposure to Se	Health outcomes related to adverse effects of MeHg exposure or toxicity	Human studies: > randomized controlled trials > non-randomized intervention trials > cohort studies > case-control studies > cross-sectional studies Animal studies (including trials with Se and MeHg exposure from ingestion (dietary intake)

2.4.2 LITERATURE SEARCH

The literature search was performed on 13 December 2021. The literature search was performed in two databases, namely, PubMed and Web of Science Core Collection, with no restrictions regarding when the studies were conducted. The search strategy for each database is given in Appendix 5, **Table A5.1**.

The search terms included a combination of the following:

> *selenium*: selenium or HgSe;
> MeHg: methylmercury, MeHg, CH3Hg;
> *exposure and outcome*: health, benefits, effect, toxic, intervention, uptake, accumulation, excretion, clearance, response, exposure, stressor, interaction;
> *type of population and study group*: human, mammal, patient, rat, mouse, rodent, guinea pig, dog, monkey, men, man, women, woman, child, infants, toddler, infant, foetus.

All identified records from the searches in each of the databases were imported into the reference manager program, EndNote (version 20). Duplicates were further removed in EndNote by comparing articles with similar "title" and "authors".

2.4.3 SELECTION OF STUDIES FROM THE LITERATURE SEARCH

The studies included from the literature search were further assessed by screening the titles and abstracts. This was performed independently by two reviewers using Rayyan, a web-based tool for selecting studies in systematic reviews (Ouzzani *et al.*, 2016). The selection of studies was based on the predefined inclusion and exclusion criteria (**Table 2.12**), which were developed based on the research questions and the information provided in the PICOS table (**Table 2.11**). After screening the papers by title and abstract, blinding in Rayyan was removed, and the two reviewers discussed with a third reviewer any conflicting decisions regarding the inclusion or exclusion of papers. Subsequently, full texts of the records that fulfilled the inclusion criteria based on the initial screening were retrieved. The full-text records were further reviewed in detail according to the same inclusion and exclusion criteria before proceeding to quality assessment.

TABLE 2.12 **INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH ON "THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF MeHg"**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION

> Studies investigating the role of selenium with regard to the health effects of MeHg.
  > Measured health outcome (e.g. neurodevelopment, intelligence quotient [IQ], sperm quality, cardiovascular disease)
> Measured concentrations of Hg/MeHg and Se (e.g. in blood, serum, plasma, hair, nails, cord blood) or estimated dietary intake of Hg/MeHg and Se
> Population:
  > Human studies:
  » general population, including both sexes and all ages (foetuses, infants, children, adolescents and adults).
  » patient groups
  > Animal studies:
  » mammalian model systems, including rodents (rats, mice, guinea pigs), dogs and monkeys.
> Study designs:
  > Human studies:
  » randomized controlled trials
  » non-randomized intervention trials
  » cohort studies
  » case-control studies
  » cross-sectional studies
  » case studies/reports
  > Animal studies (including trials with Se and MeHg exposure from ingestion [dietary intake])
	> Studies conducted on invertebrates
	> In vitro studies
	> Measurement only of concentrations of Hg and Se in animals or humans, and not related to health effects of Hg/MeHg
	> Studies only measuring indirect health effects (e.g. demethylation of MeHg)
	> Studies in which the effect of Se was not assessed separately but in combination with other covariates or confounders.

2.4.4 QUALITY ASSESSMENT (RISK OF BIAS)

All studies that fulfilled the inclusion criteria were quality-assessed using the OHAT quality-assessment tool. Information regarding the OHAT quality-assessment tool is provided in Section **2.2.4.2** and Appendix 2, **Table A2.4**. Only studies graded Tier 1 or Tier 2 were included for further assessment.

2.4.5 EXTRACTION OF DATA FROM THE LITERATURE

Relevant prespecified data were extracted from the included studies into premade data-extraction forms in Excel. The data included:

> reference details: reference, trial or study name, geography, year of sampling;
> study information: study type, study duration and follow-up time;
> participants: number of participants in the study, age (years) at exposure assessment, sex;
> measurements and levels of Hg/MeHg exposure;
> measurements and levels of Se exposure;
> measurements of health outcomes;
> overall results: the role of Se with regard to the health effects of MeHg;
> overall conclusion.

The data extraction was performed by one person, and the extracted data was double checked by another person.

2.4.6 SUMMARIZATION OF THE LITERATURE INCLUDED

The studies included from the literature search covered a diverse range of health outcomes where Se and MeHg exposure were measured. These were grouped into different categories of health outcomes, namely:

> cardiovascular;
> oxidative stress;
> immune system;
> reproduction;
> thyroid hormones;
> birth;
> neurodevelopment and cognition;
> vision function;
> motor function.

The studies included for each health outcome were summarized together. In addition, the animal studies were summarized together with the relevant health outcomes, though the animal studies were not included in the weight of evidence.

2.4.7 WEIGHT OF EVIDENCE OF THE LITERATURE

For a final grading of the available literature, the weight-of-evidence approach was used, following the guidelines from the WCRF (2018a), where the evidence is graded "convincing (strong evidence)", "probable (strong evidence)", "limited, suggestive", "limited, no conclusion", or "substantial effect of risk unlikely (strong evidence)". Information regarding the tool used for weighing of evidence is given in Section 2.1.8.

2.5 METHODS FOR THE REVIEW "OCCURRENCE DATA FOR MeHg, DIOXINS AND dl-PCBs"

The objective of the review was to evaluate and collect new data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products published in the last ten years (2011 to 2021). The data were obtained by conducting a systematic literature search in the database Web of Science and by extracting data from public databases (WHO's GEMS/Food database and EFSA's Chemical Monitoring database).

2.5.1 LITERATURE SEARCH STRATEGY

The search strategy was developed according to the objective of the systematic review. Inclusion and exclusion criteria are given in **Table 2.13**.

For occurrence data on MeHg, analysed data of MeHg or total Hg were included. The objective was to include data on MeHg; however, studies analysing MeHg are relatively rare, and total Hg is often used as a proxy for MeHg. Therefore, data on total Hg were also included.

For occurrence data on dioxins and dl-PCBs, data were included if results were reported for either: all 29 congeners, all 17 dioxin-congeners, or all 12 dl-PCBs. Concentration data could only be included if they were reported as upper-bound TEQ values (WHO, 2005), or in a form that could be transformed to upper-bound TEQ values (**Table 2.13**).

2.5.2 LITERATURE SEARCH

Specific literature searches were conducted for Hg or MeHg and for dioxins on 22 November 2021. The literature search was performed in the database Web of Science. The search strategy is given in Appendix 7, **Table A7.1** and **Table A7.2**. The search terms included a combination of the following:

- *contaminant measured:*
  - Hg OR mercury OR MeHg OR Me-Hg OR "methyl Hg" OR "methyl-Hg" OR "methylmercury" OR "methyl-mercury"
  - dioxin* OR furan* OR PCDD* OR PCDF* OR "polychlorinated dibenzodioxin*" OR "polychlorinated dibenzofuran*" OR TEQ;

TABLE 2.13 **INCLUSION AND EXCLUSION CRITERIA FOR THE LITERATURE SEARCH ON "THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF MeHg"**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION
> Types of species included: > finfish (vertebrates) and shellfish (aquatic invertebrates); > marine and freshwater origin; > farmed and wild; > raw, unprocessed samples; > edible part analysed: finfish: muscle or whole fish; shellfish: muscle meat, soft tissue, whole body, or edible parts; > individual or composite samples; > concentrations given on fresh-weight basis and, if not, fresh weight; concentrations must be possible to calculate based on dry-weight concentrations and dry-matter content or lipid-weight concentrations and fat content. > Occurrence data (analysed data) of: > MeHg or Hg; > dioxins (polychlorinated dibenzodioxins and polychlorinated dibenzofurans) and dioxin-like PCBs (non-ortho and mono-ortho PCBs). Analysed either all 29 congeners, or all 17 dioxin-congeners, or all 12 dl-PCBs. Concentration data must be reported as upper-bound TEQ-values (WHO, 2005), or in a form that can be transformed to upper-bound TEQ-values. > Data from samples collected in 2011 or later > Data must include names of species, which part(s) of the animal were analysed, and from which geographical area the species were sampled > The data had to be analysed in accredited laboratories, or by a method validated by performance testing (e.g. proficiency testing or use of appropriate reference material).	> Type of samples excluded: > marine mammals and algae; > data from feeding trials or exposure studies; > processed samples; > data where the name of the species or genus is not given; > data on dry-weight or fat-weight basis, where it was not possible to recalculate to fresh-weight concentrations. > Sampling year before 2011 or year of sampling not provided > Data where quality control of the analytical method was not appropriately described.

Notes: PCB: polychlorinated biphenyl, TEQ: toxic equivalent quotient, WHO: World Health Organization

> *fish and seafood species:* several typical words for fish and seafood, specific fish and seafood species;

> measurement of contaminant: concentration* OR level* OR measure* OR amount* OR value* OR content* OR determin*.

In Web of Science, the literature search was performed with the complete search string within the search fields title (TI), abstract (AB), and author keyword (AK). The literature searches were restricted by type of publication (excluding review articles, proceedings papers, meeting abstracts, corrections, editorial materials, letters, retracted publications and news items), language (including only publications in English), and date of publication (1 January 2011 through 31 December 2021).

All identified records from the Web of Science searches were imported into the reference manager program, EndNote. Duplicates were removed in EndNote by comparing articles with similar "title" and "authors".

2.5.3 SELECTION OF STUDIES FROM THE LITERATURE SEARCH

Screening of titles and abstracts was performed blind by two reviewers using Rayyan, a web-based tool for selecting studies in systematic reviews (Ouzzani *et al.*, 2016). The selection of studies was based on predefined inclusion and exclusion criteria (**Table 2.13**), which were developed based on the research question. Full-text articles were included when the information given in the title or abstract seemed to fulfil the inclusion criteria. After screening the articles by title and abstract, the blinding was removed, and the two reviewers discussed any conflicting decisions regarding studies to be included or excluded, consulting a third reviewer as needed. When consensus was reached on all the studies, full-text articles were retrieved for all included studies. The full-text articles were further reviewed according to the inclusion and exclusion criteria.

2.5.4 QUALITY ASSESSMENT

For the quality assessment, a quality-assessment template was prepared using questions adapted from a quality-assessment system used by the European Food Information Resource (Oseredczuk *et al.*, 2009). Using this template, the articles were assessed according to questions in six different categories, as shown in **Table 2.14**.

Each question was answered with "yes", "no" or "n.a." (not applicable). Only articles that met all the required criteria for inclusion (that is, for which the answer to all strictly required questions was "yes") were included. Questions marked by an asterisk in Table 2.14 were not considered strictly required, and articles could be included even if the answer was "no" for these two questions.

Because only few articles reported data for dioxins and dl-PCBs, slightly less strict criteria were used for inclusion of such articles. Specifically, for articles reporting data for dioxins and dl-PCBs, the following three criteria were modified, as follows:

- *Sampling year missing*: accepted if the article was published after 2015 (assuming sampling year 2011 or later for publications after 2015).
- *Data given on dry-weight, and dry-matter (or moisture) content not provided*: Accepted. In such cases, an approximate dry-matter content of 25 percent for both finfish and shellfish was used for calculating wet-weight results.
- *Analytical method validation not described*: accepted if the method was described and considered appropriate, even if information about method validation (quality assessment/quality control) was missing.

The Excel template of the quality assessment is given in Appendix 7 (**Table A7.3**), together with the results of the screening and quality assessment for all full-text articles.

TABLE 2.14 **QUESTIONS FOR QUALITY ASSESSMENT OF ARTICLES, ADAPTED FROM THE EUROPEAN FOOD INFORMATION RESOURCE**

1. Food description
> Was year of capture provided? > Was the food source or main ingredient provided? Species Latin name > Was the part of animal provided? > Was analysed portion described and is it clear if food was analysed with or without inedible portion? > Was the extent of heat treatment/other processing provided? > Was information on geographic origin of the food provided? > If results given on dry weight: Was the moisture content of the sample measured and the result provided? > If dioxin results given on lipid weight only, was fat content provided?
2. Component identification
> Is the component described unambiguously? > Is the unit unequivocal? > Is the matrix unit unequivocal?
3. Sampling plan
> Was the number of primary samples provided?
4. Number of analytical samples
> Was the number of analytical samples provided?
5. Sample handling
> Were the samples homogenized? *
6. Analytical method and performance
> Were analytical sample replicates tested? * > Was the laboratory accredited for this method? (Stop here if the answer is yes, if no answer next questions). > Was the analytical method used in the source appropriate? Was the method validated by one or more of the following: > Was the method validated by an in-house validation study? > Was the method validated by performance testing (PT schemes, proficiency testing)? > Was the method validated by a collaborative study? > Was the method validated using an appropriate reference material (analyte, concentration, matrix)? > Was the method validated by a recovery study leading to a relative standard deviation ≤ 20 percent?

Note: Questions marked by an asterisk (*) were not considered strictly required, and the article could be included even if the answer was "no" for these two questions.
Source: Oseredczuk, M., Salvini, S., Roe, M. & Moller, A. 2009. *EuroFIR Workpackage 1.3., Task group 4. Guidelines for Quality Index Attribution to original data from scientific literature or reports for EuroFIR data interchange.* https://www.eurofir.org/wp-admin/wp-content/uploads/Deliverables/EuroFIR_Quality_Index_Guidelines.pdf. Accessed 26th October 2022.

2.5.5 EXTRACTION OF DATA

For the articles included, the concentrations and metadata were extracted and compiled in an Excel data sheet (Appendix 7, **Table A7.4**). The data retrieved included: year(s) of sampling, geographic origin, species identification, subgroup (finfish/shellfish), tissue (fillet, whole fish, muscle, soft tissue, edible parts), wild/farmed, sampling method (field sampling, purchased from fishermen or market), habitat (river, lake, ocean or estuary), number of primary and analytical samples, sample type (individual or pooled), matrix unit (wet weight or dry weight), mean value, median value, minimum value and maximum value. Where the results were given in dry weight, results for dry-matter content were also included. None of the articles included had data given on the basis of lipid weight.

2.5.6 DATA FROM PUBLIC DATABASES

FAO and EFSA were contacted on 26 October 2021 to request access to data on total Hg, MeHg, dioxins and dl-PCBs in seafood from 2011 onwards. Data on Hg in food (including seafood) were received from EFSA on 21 June and 14 October 2022, and data on dioxins and dl-PCBs in food were received on 24 August and 11 November 2022. Via FAO/WHO, access was granted to GEMS/Food data on Hg, MeHg, dioxins and dl-PCBs in seafood. Data on Hg and MeHg were accessed 15 September 2022, and data on dioxins and dl-PCBs were accessed 28 September 2022.

2.5.6.1 Extraction of relevant data from European Food Safety Authority datasets

The data from EFSA were assessed using the exclusion and inclusion criteria shown in **Table 2.15**.

TABLE 2.15 **INCLUSION AND EXCLUSION CRITERIA FOR DATA, FROM THE EUROPEAN FOOD SAFETY AUTHORITY DATABASE**

CRITERIA FOR INCLUSION	CRITERIA FOR EXCLUSION

> Type of samples included:
  > finfish and shellfish;
  > marine and freshwater origin;
  > farmed and wild;
  > raw, unprocessed samples;
  > edible part analysed: finfish (muscle meat); shellfish (edible parts);
  > individual or composite samples.
> Occurrence data (analysed data) of:
  > MeHg or total Hg;
  > dioxins (polychlorinated dibenzodioxins and polychlorinated dibenzofurans) and dioxin-like PCBs (non-ortho and mono-ortho PCBs); analysed either all 29 congeners, or all 17 dioxin-congeners, or all 12 dl-PCBs; concentration data reported as raw data that can be transformed to upper-bound TEQ-values;
  > concentrations given on fresh-weight basis and if not, fresh-weight concentrations must be possible to calculate based on dry-weight concentrations and dry-matter content or lipid-weight concentrations and fat content.
> Data from samples collected in the year 2011 or later
> Data including name of species or group of species and information about geographical sampling area.
	> Type of samples excluded:
	  > non-seafood;
	  > fish liver, fish roe, fish offal, fish oil, meal from fish or mollusc (feed), fish oils, other seafood products for feed;
	  > processed or preserved products (dried, canned, marinated/pickled, smoked, etc.);
	  > samples where name of species was not given or sample description was too general (e.g. fish meat, marine fish, molluscs, crustaceans);
	  > samples analysed for inorganic mercury only;
	  > samples missing information about whether data were given on fresh-weight or lipid-weight basis and samples where it was not possible to recalculate fresh-weight values (fat content missing);
	  > samples analysed for dioxins or dioxin-like PCBs, for which less than 17 dioxin-congeners or less than 12 dl-PCBs were reported;
	> Sampling year before 2011.

Notes: PCB: polychlorinated biphenyl, dl-PCB: dioxin-like polychlorinated biphenyl, TEQ: toxic equivalent quotient.

2.5.6.2 Processing of data included from the European Food Safety Authority dataset

Samples where results were given on fat-weight basis were converted to fresh weight using the fat content of the sample.

Most data for dioxins and dl-PCBs in the EFSA dataset were reported as raw concentrations, and only a small subset of the samples also had concentrations reported as upper-bound TEQ-values for sum dioxins and dl-PCBs. For consistency, the individual raw congener concentrations were used for all samples. TEQ values for individual congeners were calculated using the WHO 2005 TEF values for each congener (Van den Berg *et al.*, 2006). Upper-bound sums of 17 dioxins and furans (sum dioxin), 12 dl-PCBs (sum dl-PCB) and all 29 dioxins and dl-PCBs (sum dioxin and dl-PCB) were calculated using limit of quantification (LOQ) values (or limit of detection [LOD] values when LOQ value was not given) for congeners with concentrations below the LOQ (or LOD). Three samples of blue mussel, three samples of Atlantic salmon, one sample of Japanese seabass, one sample of sea bream, and one sample of trout with very high concentrations of upper-bound sum dioxins were considered outliers and excluded from the dataset because the data showed that the high concentrations were caused by incorrectly reported (much too high) LOQ values for the dioxin congeners. The results for these samples originated from a single laboratory in a single year.

Three samples (blue whiting, clams, shrimps and prawns) were excluded from the dataset because of extreme values of LOQ for total Hg (10–70 mg/kg). These extreme LOQ values may have been reported with an erroneous unit of measurement (µg/kg values reported as mg/kg).

The EFSA dataset contained information about geographic origin either as a description of marine area, inland water area or country of origin for all included samples. This information was used to assign the samples to specific major fishing areas as classified by FAO (FAO-areas). In cases where a specific FAO area could not be assigned (for instance, because the geographic information was given in very broad terms or the country of origin was bordered by more than one FAO area), the samples were categorized as unspecified (for example, “Pacific Ocean, unspecified” or “France, unspecified”).

The samples were categorized as inland or marine based on the geographic information given. In cases where the exact geographic location was unclear, the samples were categorized as inland or marine when sample descriptions elsewhere in the dataset indicated “freshwater fish” or “marine fish”, respectively. Where no such information was found, the samples were categorized as “unspecified”. Most of the samples originated from marine waters, and it is probable that most of the “unspecified” samples were from marine waters rather than from inland waters. As such, data for samples from marine and unspecified waters were combined in the final tables.

In order to categorize samples as wild or farmed, finfish/shellfish species information and information about sampling point (SAMPPOINT_ID) given in the EFSA dataset was used. Samples with SAMPPOINT_ID given as "Aquaculture", "Breeding", "Farm", "Hatchery", "Rearing of animals" or "Slaughterhouse" were categorized as farmed finfish/shellfish, while samples with SAMPPOINT_ID given as "Fishery activities", "Fishing", "Fishing and processing", "Game handling establishment", "Hunting" or "Natural habitat" were categorized as wild finfish/shellfish. In addition, some finfish species or species groups which are generally known not to be used in aquaculture were categorized as wild fish. Many of the remaining samples were, however, sampled at border-control posts; from distribution, wholesale or retail sale; during processing activities or storage; in restaurants or in other parts of the value chain, giving no information indicating whether the samples were from wild or farmed finfish/shellfish. These samples were categorized as "unspecified", except for some samples where information about the origin of the samples from aquaculture were found in other parts of the dataset. Most of the samples were from wild finfish/shellfish, and most of the unspecified samples are thus likely to be wild finfish/shellfish. Data for wild and "unspecified" samples were, therefore, combined in the final results.

The dataset with all the included samples from EFSA is given in Appendix 7, **Table A7.5**.

2.5.6.3 Extraction of relevant data from the Global Environment Monitoring System/Food datasets of the World Health Organization

Relevant data from the GEMS/Food datasets were extracted after removal of the following types of samples:

- samples collected before 2011;
- samples of processed products (such as breaded haddock and raw breaded squid rings) or samples where the food state (FoodStateName) was unknown;
- samples where the sample description was too general (for instance, fish muscles);
- samples from marine mammals;
- samples analysed for inorganic Hg only.

After removal of the samples according to these exclusion criteria, there were no samples left to include from the GEMS/Food dataset on dioxins and dl-PCBs. For the GEMS/Food dataset on Hg and MeHg, 5 826 samples were included, 5 304 samples were analysed for total Hg and 522 samples were analysed for MeHg. The dataset contained very little information about the geographic origin of the samples, and only three different region codes ("PAHO", "SEARO" and "WPRO") were given in the dataset. In the WHO region Codelist, "SEARO" and "WPRO" were found to be acronyms for Southeast Asia Region and Western Pacific Region, respectively, whereas the region code "PAHO" was not listed in

the WHO region Codelist. Since the geographic origin of the samples was given only within these very wide geographical regions, it was not possible to assign the samples to their respective FAO areas. Information needed to categorize the samples as farmed or wild was also missing in the dataset. Because of these limitations, and because this dataset contained a relatively small number of samples compared to the data from the literature review and the EFSA database, these data were not processed further in this study. The dataset with all the included samples is, however, available in Appendix 7, **Table A7.6**.

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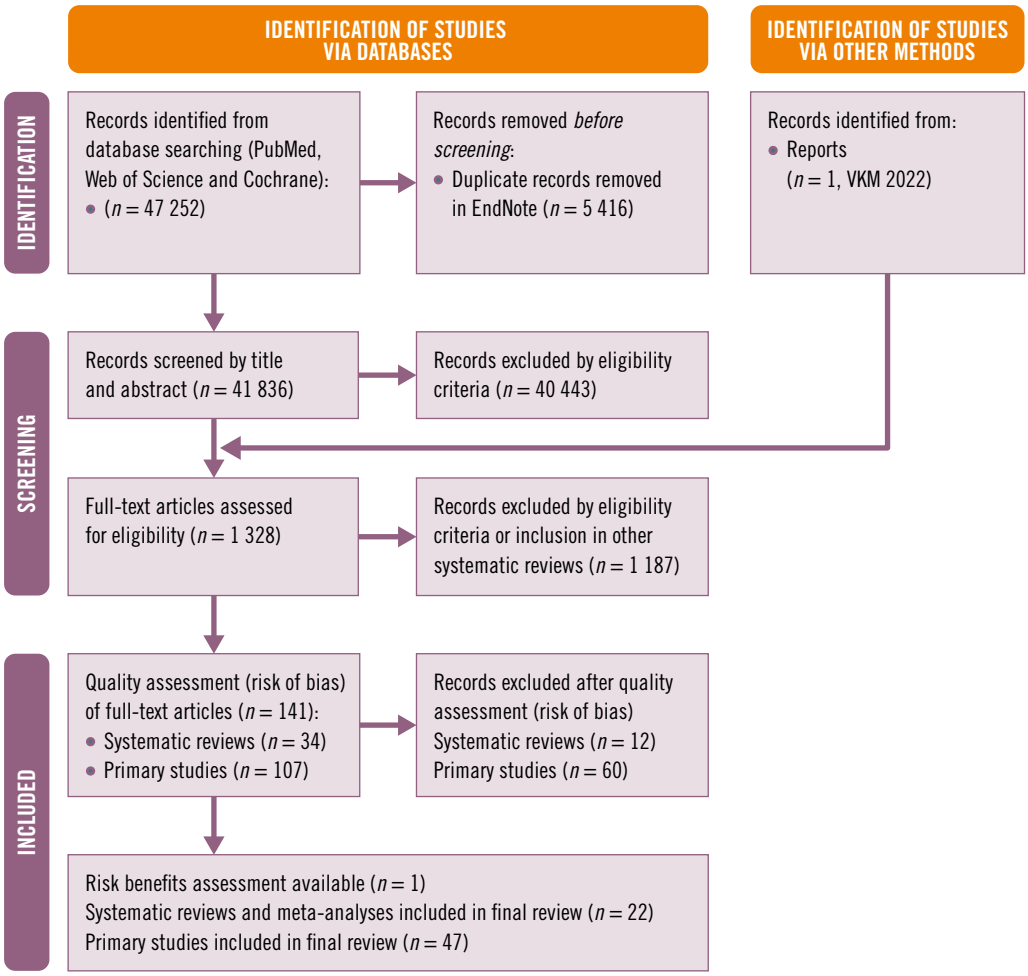
CHAPTER 3
RESULTS AND SUMMARIZATION OF THE LITERATURE REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"

3.1 LITERATURE SEARCH AND QUALITY ASSESSMENT

Literature searches for the systematic review on the "Evidence of health benefits from fish consumption" were performed in the databases PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. A literature search was performed for each category of health outcomes that were defined (**Table 2.2**). **Figure 3.1** provides a flow diagram of the results from the literature searches regarding all the themes in "Evidence of health benefits from fish consumption". The literature searches resulted in 39 092 records. Of these, 5 401 duplicate records were removed, leaving 33 691 records that were assessed via title and abstract screening in Rayyan. Based on title and abstract screening, 32 895 records were excluded, and 791 records were assessed in full text. In the full-text assessment, 665 records were excluded for further assessment based on criteria, and 127 records (one risk/benefits assessment [the 2022 VKM report], 32 systematic reviews and 94 primary studies) were quality assessed with risk-of-bias tools. As a result, 12 systematic reviews and 60 primary studies were excluded owing to the low quality of the studies. Thus, the final review included one risk/benefits assessment (the 2022 VKM assessment), 22 systematic reviews and 47 primary studies. The results from the literature search for each theme of health outcomes are given in **Table 3.1** and further summarized in the following paragraphs.

FIGURE 3.1. **FLOW DIAGRAM FOR THE REVIEW ON THE "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**



Source: The figure was prepared based on Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L. *et al.* 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71

TABLE 3.1 **RESULTS OF THE LITERATURE SEARCH ON "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**

HEALTH OUTCOME	1. TOTAL HITS (WEB OF SCIENCE, PUBMED, COCHRANE)	2. NUMBER OF DUPLICATES REMOVED IN ENDNOTE BEFORE SCREENING	3. DUPLICATE RECORDS REMOVED DURING ABSTRACT SCREENING IN RAYYAN	4. TOTAL RECORDS SCREENED IN RAYYAN (1–[2+3])	5. RECORDS EXCLUDED BASED ON CRITERIA DURING ABSTRACT SCREENING IN RAYYAN	6.RECORDS SOUGHT FOR FULL-TEXT SCREENING
Allergy and immunology	5 136	551	113	4 472	4 314	158
Birth and growth outcomes	5 973	369	5	5 599	5 564	35
Bone health	693	86	14	593	549	44
Cancer	3 831	710	82	3 039	2 998	41
Cardiovascular disease	3 717	426	58	3 233	3 067	166
Dental health	19	2	0	17	17	0
Type 2 diabetes	2 223	290	173	1 760	1 700	60
Neurodevelopment and neurological disorders	8 612	1 277	4	7 331	7 214	117
Mortality	3 793	583	59	3 151	3 026	125
Overweight and obesity	5 095	534	65	4 496	4 458	38
Total number of records	**39 092**	**4 828**	**573**	**33 691**	**32 902**	**784**

3.1.1 ALLERGY AND IMMUNOLOGY

Literature searches for the theme "Allergy and immunology" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 5 136 records. Before screening, 608 duplicates were removed in EndNote and 113 duplicates were removed in Rayyan. Thus, 4 472 records were screened by title and abstract, using the online screening tool Rayyan. As a result of this assessment, based on inclusion and exclusion criteria, 4 314 records were excluded. Thus, 158 records were assessed for full-text screening. Of these, 16 records were systematic reviews and 142 records were primary studies.

3.1.1.1 Systematic reviews

Sixteen reviews were assessed in full-text after title and abstract screening. Of these, two reviews were excluded, based on inclusion and exclusion criteria, and six reviews were excluded as they were already assessed in the risk/benefits assessment in the 2022 VKM report (see list of excluded reviews in Appendix 3, **Table A3.2**). Thus, eight systematic reviews were assessed for risk of bias using the tool AMSTAR 2, according to the overall confidence in the results of the systematic review. One review was graded "high" confidence, four were graded "moderate" confidence, one was graded "low" confidence, and two were graded "critically low" confidence (judgement and references given in Appendix 3, **Table A3.20**). The reviews graded "low" or "critically low" were excluded. As such, after the risk-of-bias assessment, five systematic reviews were included for further assessment in this review (Pattison *et al.*, 2004; Di Giuseppe *et al.*, 2014; Netting *et al.*, 2014; Ierodiakonou *et al.*, 2016; and Venter *et al.*, 2020).

3.1.1.2 Primary studies

After the title and abstract screening, 142 primary studies remained and were assessed in full text. Of these, 78 primary studies were excluded, based on inclusion and exclusion criteria, and 42 primary studies were excluded as they were already assessed in one of the systematic reviews included in this review (see list of excluded primary studies in Appendix 3, **Table A3.3**). Thus, 22 primary studies were quality assessed with the risk-of-bias tool. All 22 primary studies were graded "C (low quality)" with the risk-of-bias tool and therefore were excluded for further assessment (Appendix 3, **Table A3.21**).

3.1.2 BIRTH AND GROWTH OUTCOMES

Literature searches for the theme "Birth and growth" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 5 973 records. Before screening, 369 duplicates were removed in EndNote and 5 duplicates were removed in Rayyan. Thus, 5 599 records were assessed in title and abstract screening using the online screening tool, Rayyan. As a result of this screening, and based on inclusion and

exclusion criteria, 5 564 records were excluded in Rayyan. Thus, 35 records remained and were assessed in full text. Of these, one record was a systematic review, and 34 records were primary studies.

3.1.2.1 Systematic reviews

One review was assessed in full text after title and abstract screening. This review, by Hibben *et al.* (2019), was also excluded in this screening, based on inclusion and exclusion criteria (Appendix 3, **Table A3.4**).

3.1.2.2 Primary studies

After the title and abstract screening, 34 primary studies were assessed in full text. Of these, 11 were excluded based on inclusion and exclusion criteria and 20 were excluded as they were already assessed in one of the systematic reviews included (see list of excluded primary studies in Appendix 3, **Table A3.5**). Thus, three primary studies were quality assessed with the risk-of-bias tool. Two studies were graded "B (moderate quality)", while one study was graded "C (low quality)" (see Appendix 3, **Table A3.22**). The study graded "C" was excluded, leaving two primary studies, which were included for further assessment in this review (Oken *et al.*, 2004; Zhao *et al.*, 2022).

3.1.3 BONE HEALTH

Literature searches for the theme "Bone health" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 693 records. Before screening, 86 duplicates were removed in EndNote and 14 duplicates were removed in Rayyan. Thus, 593 records were assessed through title and abstract screening, using the online screening tool, Rayyan. In the title and abstract screening, 549 records were excluded based on inclusion and exclusion criteria. Thus, 44 records were assessed in full-text screening. Of these, 7 records were systematic reviews and 37 records were primary studies.

3.1.3.1 Systematic reviews

Seven reviews were assessed in full text after the title and abstract screening. Of these, five were excluded based on inclusion and exclusion criteria and two were excluded as they were already assessed in the 2022 VKM risk/benefit assessment (see list of excluded reviews in Appendix 3, **Table A3.6**). Thus, no systematic reviews were further quality assessed with risk of bias or included for further assessment in this review.

3.1.3.2 Primary studies

After the title and abstract screening, 37 primary studies were assessed in full text. Of these, 17 were excluded based on inclusion and exclusion criteria and nine were excluded as they were already assessed in one of the systematic reviews included

(see list of excluded primary studies in Appendix 3, **Table A3.7**). Thus, 11 primary studies were quality assessed with the risk-of-bias tool. Four studies were graded "B (moderate quality)", while seven were graded "C (low quality)" (Appendix 3, **Table A3.23**). The study graded "C" was excluded for further assessment, leaving four primary studies that were included for further assessment in this review (Hirota *et al.*, 2005; Lucey *et al.*, 2008; Thacher *et al.*, 2015 and Tong *et al.*, 2020).

3.1.4 CANCER

Literature searches for the theme "Cancer" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 3 831 records. Before screening, 710 duplicates were removed in EndNote and 82 duplicates were removed in Rayyan. Thus, 3 039 records were assessed through title and abstract screening, using the online screening tool, Rayyan. As a result, 2 998 records were excluded in Rayyan, based on inclusion and exclusion criteria. Thus, 41 records were assessed through full-text screening. Of these, 21 were systematic reviews and 20 were primary studies.

3.1.4.1 Systematic reviews

After the title and abstract screening, 21 reviews were assessed in full text. Of these, 18 were excluded based on inclusion and exclusion criteria (see list of excluded reviews in Appendix 3, **Table A3.8**). Thus, three systematic reviews were assessed for risk-of-bias, using the tool AMSTAR 2 according to the overall confidence in the results of the systematic review. Two reviews were graded "high" confidence, and one was graded "moderate" confidence (judgement and references given in Appendix 3, **Table A3.24**). Thus, all the three systematic reviews were included for further assessment in this review (Jayedi *et al.*; 2020, Kazemi *et al.*, 2021 and Gao *et al.*, 2022).

3.1.4.2 Primary studies

After the title and abstract screening, 20 primary studies were assessed in full text. Of these, eight were excluded based on inclusion and exclusion criteria and two were excluded as they were already assessed in one of the systematic reviews included in this review (see list of excluded primary studies in Appendix 3, **Table A3.9**). Thus, ten primary studies were quality assessed with the risk-of-bias tool. All ten studies were graded "B (moderate quality)" (Appendix 3, **Table A3.25**), and, as such, ten primary studies were included for further assessment in this review (Etemadi *et al.*, 2018; Outzen *et al.*; 2018, Ma *et al.*, 2019; Aglago *et al.*, 2020; Bradbury *et al.*, 2020; Cai *et al.*, 2020; Makiuchi *et al.*, 2020; Zamani *et al.*, 2020; Dianatinasab *et al.*, 2021 and Hermans *et al.*, 2021).

3.1.5 CARDIOVASCULAR DISEASES AND OUTCOMES

Literature searches for the theme "Cardiovascular diseases and outcomes" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 3 717 records. Before screening, 426 duplicates were removed in EndNote and 58 were removed in Rayyan. Thus, 3 233 records were assessed through title and abstract screening using the online screening tool, Rayyan. In this screening, based on inclusion and exclusion criteria, 3 067 records were excluded, leaving 166 records, which were assessed in full text. Of these, 16 were systematic reviews, and 150 were primary studies.

3.1.5.1 Systematic reviews

After the title and abstract screening, 16 reviews were assessed in full text. Of these, 13 reviews were excluded based on inclusion and exclusion criteria (see list of excluded reviews in Appendix 3, **Table A3.10**). Thus, three systematic reviews were assessed for risk of bias, using the tool AMSTAR 2, according to the overall confidence in the results of the systematic review. Two reviews were graded "moderate" confidence, and one was graded "critically low" confidence (judgement and references given in Appendix 3, **Table A3.26**). The review graded "critically low" was excluded, leaving two systematic reviews, which were included for further assessment in this review (Mente *et al.*, 2009 and Chowdhury *et al.*, 2012).

3.1.5.2 Primary studies

After the title and abstract screening, 150 primary studies were assessed in full text. Of these, 57 primary studies were excluded based on inclusion and exclusion criteria and 83 were excluded as they were already assessed in one of the systematic reviews included (see list of excluded primary studies in Appendix 3, **Table A3.11**). Thus, ten primary studies were quality assessed with the risk-of-bias tool. All ten studies were graded "B (moderate quality)" (Appendix 3, **Table A3.27**) and, as such, all ten were included for further assessment in this review (Frost *et al.*, 2005; Matheson *et al.*, 2009; Lajous *et al.*, 2013; Gammelmark *et al.*, 2016; Venø *et al.*, 2018; Lasota *et al.*, 2019; Tong *et al.*, 2019; Acosta *et al.*, 2021; Petermann-Rocha *et al.*, 2021 and Zhong *et al.*, 2021).

3.1.6 TYPE 2 DIABETES

Literature searches for the theme "Type 2 diabetes" (T2D) were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 2 223 records. Before screening, 290 duplicates were removed in EndNote and 173 duplicates were removed in Rayyan. Thus, 1 760 records were assessed through title and abstract screening, using the online screening tool, Rayyan. In this screening, 1 700 records were excluded based on inclusion and exclusion criteria. Thus, 60 records remained for full-text screening. Of these, 19 were systematic reviews and 41 were primary studies.

3.1.6.1 Systematic reviews

After the title and abstract screening, 19 reviews were assessed in full text. Of these, six were excluded based on inclusion and exclusion criteria and four were excluded as they were already assessed in the 2022 VKM risk/benefit assessment (see list of excluded reviews in Appendix 3, **Table A3.12**). Thus, nine systematic reviews were assessed for risk of bias, using AMSTAR 2, according to the overall confidence in the results of the systematic review. Five reviews were graded "high" confidence, two were graded "moderate" confidence, and two were graded "critically low" confidence (judgement and references given in Appendix 3, **Table A3.28**). The reviews graded "critically low" were excluded, leaving seven systematic reviews, which were included for further assessment in this review (Wallin *et al.*, 2012; Wu *et al.*, 2012; Xun *et al.*, 2012; Zheng *et al.*, 2012; Zhou *et al.*, 2012; Zhang *et al.*, 2013 and Muley *et al.*, 2014).

3.1.6.2 Primary studies

After the title and abstract screening, 41 primary studies were assessed in full text. Of these, 24 were excluded based on inclusion and exclusion criteria and 16 were excluded as they were already assessed in one of the systematic reviews already included (see list of excluded primary studies in Appendix 3, **Table A3.13**). Thus, one primary study was quality assessed with the risk-of-bias tool and this was graded as "B (moderate quality)" (Appendix 3, **Table A3.29**). After the risk-of-bias assessment, only this primary study was included for further assessment in this review (Chen *et al.*, 2020).

3.1.7 NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS

Literature searches for the theme "Neurodevelopment and neurological disorders" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 8 612 records. Before screening, 1 277 duplicates were removed in EndNote and 4 duplicates were removed in Rayyan. Thus, 7 331 records were assessed through title and abstract screening, using the online screening tool, Rayyan. As a result of this screening, 7 214 records were excluded in Rayyan based on inclusion and exclusion criteria. Thus, 117 records were assessed in full text. Of these, 23 were systematic reviews, and 94 were primary studies.

3.1.7.1 Systematic reviews

After the title and abstract screening, 23 reviews were assessed in full text. Of these, nine were excluded based on inclusion and exclusion criteria and 11 were excluded as they were already assessed in the 2022 VKM risk/benefit assessment (see list of excluded reviews in Appendix 3, **Table A3.14**). Thus, three systematic reviews were assessed for risk of bias with the tool AMSTAR 2, according to the overall confidence in the results of the systematic review. Two reviews were graded "low" confidence,

and one was graded "critically low" confidence (judgement and references given in Appendix 3, **Table A3.30**). The reviews graded "low" or "critically low" were excluded, and as such, none of the systematic reviews were included for further assessment in this review.

3.1.7.2 Primary studies

After the title and abstract screening, 94 primary studies were assessed in full text. Of these, 22 primary studies were excluded based on inclusion and exclusion criteria and 58 were excluded as they were already assessed in one of the systematic reviews included (see list of excluded primary studies in Appendix 3, **Table A3.15**). Thus, 14 primary studies were quality assessed with the risk-of-bias tool. Two studies were graded "B (moderate quality)", while ten were graded "C (low quality)" (Appendix 3, **Table A3.31**). The studies graded "C" were excluded for further assessment, leaving two primary studies to be further assessed in this review (Mesirow *et al.*, 2017 and Al-Ghannami *et al.*, 2019).

3.1.8 MORTALITY

Literature searches for the theme "Mortality" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 3 793 records. Before screening, 583 duplicates were removed in EndNote and 59 duplicates were removed in Rayyan. Thus, 3 151 records were assessed through title and abstract screening, using the online screening tool, Rayyan. After this screening, 3 026 records were excluded in Rayyan based on inclusion and exclusion criteria, leaving 125 records for full-text screening. Of these, 24 were systematic reviews and 101 were primary studies.

3.1.8.1 Systematic reviews

After the title and abstract screening, 24 reviews were assessed in full text. Of these, eight were excluded based on inclusion and exclusion criteria and 11 were excluded as they were already assessed in the 2022 VKM risk/benefit assessment (see list of excluded reviews in Appendix 3, **Table A3.16**). Thus, five systematic reviews were assessed for risk of bias using AMSTAR 2, according to the overall confidence in the results. Three reviews were graded "moderate" confidence, and two were graded "low" confidence (judgement and references given in Appendix 3, **Table A3.31**). The reviews graded "low" were excluded, and three systematic reviews remained for further assessment in this review (He *et al.*, 2004; Geelen *et al.*, 2007 and Szymanski *et al.*, 2010).

3.1.8.2 Primary studies

After the title and abstract screening, 101 primary studies were assessed in full text. Of these, 40 were excluded based on inclusion and exclusion criteria and 45 were excluded as they were already assessed in one of the systematic reviews included

in this review (see list of excluded primary studies in Appendix 3, **Table A3.17**). Thus, 16 primary studies were quality assessed using the risk-of-bias tool. Five studies were graded "B (moderate quality)", while 11 studies were graded "C (low quality)" (Appendix 3, **Table A3.33**). The studies graded as "C" were excluded for further assessment, leaving five primary studies for further assessment in this review (Walda *et al.*, 2002; Iso *et al.*, 2006; Streppel *et al.*, 2008; Pertiwi *et al.*, 2021 and Sun *et al.*, 2021).

3.1.9 OVERWEIGHT AND OBESITY

Literature searches for the theme "Overweight and obesity" were performed in PubMed, EMBASE and Cochrane, with no lower limit for the year of publication. The literature searches resulted in 5 095 records. Before screening, 534 duplicates were removed in EndNote and 65 were removed in Rayyan. Thus, 4 496 records were assessed through title and abstract screening, using the online screening tool, Rayyan. As a result of this screening, 4 458 records were excluded in Rayyan based on inclusion and exclusion criteria, leaving 38 records to be assessed in full text: 3 systematic reviews and 35 primary studies.

3.1.9.1 Systematic reviews

After the title and abstract screening, three reviews were assessed in full text. One review was excluded based on inclusion and exclusion criteria, and two reviews were excluded as they were already assessed in the 2022 VKM risk/benefit assessment (see list of excluded reviews in Appendix 3, **Table A3.18**). Thus, no systematic reviews were further quality assessed with risk-of-bias tools or included for further assessment in this review.

3.1.9.2 Primary studies

After the title and abstract screening, 35 primary studies were assessed in full text. Of these, 20 primary studies were excluded based on inclusion and exclusion criteria and 8 were excluded as they were already assessed in one of the systematic reviews included (see list of excluded primary studies in Appendix 3, **Table A3.19**). Thus, seven primary studies were quality assessed with the risk-of-bias tool. Three studies were graded "B (moderate quality)", while four studies were graded "C (low quality)" (see Appendix 3, **Table A3.34**). The studies graded "C" were excluded for further assessment, leaving three primary studies that were included for further assessment in this review (Smith *et al.*, 2015; Tørris *et al.*, 2017 and Beulen *et al.*, 2018).

3.2 RESULTS AND SUMMARIZATION OF THE INCLUDED LITERATURE

For each health outcome, the results of the review "Evidence of health benefits from fish consumption" are divided into the following sections: i) summary from the 2022 VKM report; ii) summary from the systematic reviews included from the literature search; and iii) summary from the primary studies included from the literature search. Moreover, for each health outcome, an overall summary of all the literature included – the 2022 VKM report, the systematic reviews and the primary studies – was made. Finally, a final weight-of-evidence analysis was performed for each health outcome (summary provided in Section **3.3**). An overview of the literature included in the final weight of evidence for each health outcome is given in Appendix 3, **Table A3.35**.

3.2.1 ALLERGY AND IMMUNOLOGY

The literature included in the theme "Allergy and immunology" includes results from the 2022 VKM report, and five systematic reviews from the literature search. No original primary studies were included from the literature search for this theme.

3.2.1.1 Summary of the findings on "Allergy and immunology" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

The 2022 VKM report, Benefit and risk assessment of fish in the Norwegian diet, summarized the evidence of an association between fish consumption and the outcomes of "allergic rhinitis", "allergic sensitization in children", "asthma in children", "eczema in children", "multiple sclerosis", and "rheumatoid arthritis".

3.2.1.1.1 Allergic rhinitis in children

3.2.1.1.1.1 Description of the studies included

The 2022 VKM report includes two systematic reviews and one pooled analysis investigating the association between fish intake and allergic rhinitis in children as an outcome. The associations of fish intake during pregnancy and allergic rhinitis reported in the pooled analysis by Stratakis *et al.* (2017) (RR = 1.01, 95% CI: 0.99, 1.03) and in the systematic reviews by Malmir *et al.* (2021) (RR = 0.91, 95% CI: 0.75, 1.09) and by Zhang *et al.* (2017) (RR = 0.95, 95% CI: 0.62-1.45), were not statistically significant. The systematic review by Zhang *et al.* (2017) also included the outcome of early introduction of fish and risk of allergic rhinitis in children, finding a reduced risk with higher fish intake (RR = 0.54, 95% CI: 0.36, 0.81).

The VKM report included five original primary studies, including one pooled analysis, with allergic rhinitis in children or adolescents as an outcome in relation to either maternal or child fish intake. All studies had a prospective observational design (birth cohort, or cohort based on intervention study) with rhinitis or rhino conjunctivitis as the outcome. The body of evidence on allergic rhinitis consisted of European studies and one US cohort. Most of the included studies reported no associations between fish consumption and risk of allergic rhinitis.

3.2.1.1.1.2 Conclusion, weight of evidence

The evidence that maternal fish intake during pregnancy affects the risk of rhinitis in the offspring was graded "limited, no conclusion" since no overall statistically significant differences were found in one pooled analysis and two meta-analyses, and no clear dose-response relationship was found.

The evidence that child fish intake in the first year protects against allergic rhinitis was graded "limited, no conclusion". The conclusion was based on one meta-analysis and three primary studies on early fish introduction.

3.2.1.1.2 Allergic sensitization in children

3.2.1.1.2.1 Description of the studies included

The 2022 VKM assessment included four primary studies regarding allergic sensitization in children in relation to fish intake by mothers during pregnancy (two studies) or child intake (two studies). All four studies included were European birth cohort studies. Sensitization was diagnosed as high serum immunoglobulin (Ig) E to any food or inhalant allergen, or as a positive skin prick test (SPT) at ages 2 to 8 years.

The VKM report also included two systematic reviews on maternal fish intake in pregnancy and risk of allergic sensitization.

The four primary studies and two systematic reviews were used to evaluate the evidence for an association of fish intake with the development of allergic sensitization in children.

3.2.1.1.2.2 Conclusion, weight of evidence

The evidence that maternal fish intake during pregnancy affects the risk of allergic sensitization to food or inhalant allergens was graded "limited, no conclusion" by VKM.

The evidence that child fish intake protects against sensitization was also graded "limited, no conclusion".

3.2.1.1.3 Asthma in children

3.2.1.1.3.1 Description of the studies included

The VKM assessment included eight primary studies, three with results on pregnancy intake, two on intake during lactation, and five on intake in children. All studies were prospective observational studies (birth cohort, nested case-control, or cohort based on intervention study). The body of evidence on asthma consisted of European studies and one US cohort. All studies included total fish intake. From the primary studies included, VKM calculated summary RR. No significant association of maternal intake during pregnancy and asthma in school-age children was reported by VKM (RR = 1.16, 95% CI: 0.88, 1.54). Further, no conclusions can be drawn regarding a differential effect of fatty and lean fish intake during pregnancy.

VKM also mentioned three meta-analyses of maternal intake and infant intake of fish and risk of child asthma.

The evidence of an association between fish intake in the lactation period (two studies) and risk of asthma was also too limited to make any conclusion.

The evidence of an association between fish intake in infancy and risk of asthma was also limited. Further, the results showed no association or protective association between fish intake and asthma in the first year of life.

3.2.1.1.3.2 Conclusion, weight of evidence

The evidence indicating effects of maternal fish intake during pregnancy on the risk of asthma in the offspring was graded "limited, no conclusion". The conclusion was based on no statistically significant findings in one pooled analysis, two meta-analyses, and a summary analysis conducted by VKM, as no clear dose–response relationship was found.

No conclusion could be drawn for an association between child fish intake and asthma since studies remain limited with inconsistent results of fish intake and the outcome.

3.2.1.1.4 Fish intake and eczema in children

3.2.1.1.4.1 Description of the studies included

The VKM assessment included two meta-analyses covering maternal intake (high–low) of fish during pregnancy and infant intake of fish and the risk of child eczema. The VKM assessment included nine primary studies with eczema in children as the outcome, one with results on pre-pregnancy intake, seven on pregnancy intake, one on intake during lactation, and three on intake in children. One study was a community-based lifestyle intervention with a control cohort, while eight studies were cohorts.

The primary studies had a skewed geographic distribution, with one study from Asia (Japan) and nine studies from Europe (France, Germany, the Kingdom of the Netherlands, Norway, Poland, Spain, Scotland and Sweden).

Two meta-analyses of maternal intake of fish during pregnancy and risk of child eczema mentioned in the VKM report found borderline statistically significant associations on the protective side. Analysis of the combined meta-analyses and primary studies by VKM showed weak association. Furthermore, no conclusions could be drawn regarding a differential effect of fatty and lean fish.

Prospective studies of fish intake in children and the risk of eczema were reported by VKM. Associations were protective for intake in the first year of life, but not later.

3.2.1.1.4.2 Conclusion, weight of evidence

The evidence that maternal fish consumption during pregnancy reduces the risk of eczema was graded "limited, suggestive". Evidence on fish intake in the lactation period and risk of eczema (one study) was too limited for a conclusion.

No conclusions could be drawn for the effects of fatty fish or lean fish due to limited evidence.

The evidence that fish intake in infants reduces the risk of eczema was graded "limited, suggestive". Protective associations were found for intake in the first year of life, but not later. Associations with eczema at 8 and 12 years of age were attenuated when restricted to analyses of children without early symptoms of allergic disease (one study), suggesting an influence of disease-related modification of exposure.

3.2.1.1.5 Fish intake and multiple sclerosis

3.2.1.1.5.1 Description of the studies included

The VKM assessment included two primary studies (case control) with occurrence of multiple sclerosis as the outcome. The studies overlapped partially as they used data from the Swedish Epidemiological Investigation of Multiple Sclerosis (EIMS) study.

The VKM assessment also included one meta-analysis (based on case-control studies) on fish intake and the risk of multiple sclerosis.

VKM did not calculate a summary RR based on the two identified studies as they partially overlapped. The overall results from the primary studies showed higher risk among those with the lowest intake. This applied to both fatty and lean fish, when analysed separately. The association with multiple sclerosis was found independent of vitamin D status (mediation analysis).

In one meta-analysis (Rezaeizadeh *et al.*, 2020), increased intake of fish was associated with a significantly decreased risk of multiple sclerosis (RR = 0.77, 95% CI: 0.64, 0.92).

3.2.1.1.5.2 Conclusion, weight of evidence

A protective association between fish intake and the risk of multiple sclerosis was graded "limited, suggestive" by VKM due to uncertain mechanisms and the evidence base consisting of case-control studies only.

3.2.1.1.6 Rheumatoid arthritis

3.2.1.1.6.1 Description of the studies included

The VKM assessment included one systematic review and six primary studies (two case-control and four prospective cohort studies) that included the outcome of rheumatoid arthritis incidence.

The primary studies were performed in Denmark, France, Greece, Sweden and the United States of America.

The systematic review included in the VKM report (which included 5 cohort and 5 case-control studies) showed a significant 11 percent lower risk of rheumatoid arthritis among those with high versus low intake of fish, but not when limited to

cohort studies. Stronger associations were found in case-control studies.

In three primary cohort studies, the summary RR from the three cohort studies showed no statistically significant association.

3.2.1.1.6.2 Conclusion, weight of evidence

The evidence was graded "limited, suggestive" for a protective effect of fish consumption on the risk of rheumatoid arthritis.

3.2.1.2 Summary of the findings on "Allergy and immunology" in the systematic reviews included from the literature search

Five systematic reviews were included from the literature search on the theme "Allergy and immunology". Similar to the outcomes reported in the 2022 VKM report, the outcomes of the systematic reviews were summarized and analysed in the following categories:

> allergic rhinitis: two systematic reviews assessing the association with maternal fish intake or early fish introduction in children;
> allergic sensitization in children: one systematic review describing the association between early fish introduction and the outcome in children;
> asthma in children: two systematic reviews describing the association between maternal fish intake and the outcome in children;
> eczema in children: two systematic reviews describing the association between maternal fish intake and the outcome in children;
> multiple sclerosis: no further systematic reviews identified;
> rheumatoid arthritis: two systematic reviews assessing the association between fish intake and the risk of rheumatoid arthritis.

The summary of the results from the systematic reviews assessed are summarized in **Table 3.2**. The primary studies included in the systematic reviews were mainly prospective cohort studies or randomized controlled trials. In three systematic reviews (Pattison *et al.*, 2004; Netting *et al.*, 2014 and Venter *et al.*, 2020), data were summarized narratively and not pooled for meta-analysis. In two systematic reviews (Di Giuseppe *et al.*, 2014 and Ierodiakonou *et al.*, 2016), the outcomes were reviewed through meta-analysis. The results from the systematic reviews are summarized in the following sections according to the outcomes.

3.2.1.2.1 Allergic rhinitis in children

Two systematic reviews (Ierodiakonou *et al.*, 2016 and Venter *et al.*, 2020) estimating the association between maternal fish intake or early fish introduction and allergic rhinitis were included. A description of these systematic reviews, including main outcome, population, type of studies and overall results, is provided in **Table 3.2**. One systematic review (Ierodiakonou *et al.*, 2016) included four prospective cohort studies for estimating the association between early dietary introduction of fish and allergic rhinitis. The other study (Venter *et al.*, 2020) included two observational

studies of maternal fish intake in association with allergic rhinitis. Fish and seafood intake was assessed based on different quantitative food frequency questionnaires.

In the maternal fish intake analysis of Venter *et al.*, 2020, heterogeneity was found between studies. Fatty fish were associated with reduced risk of allergic rhinitis in one study, while, in the other study, all fish were associated with increased risk of allergic rhinitis.

The meta-analysis described by Ierodiakonou *et al.*, 2016 found a protective association between early dietary introduction of fish and allergic rhinitis, based on four prospective cohort studies.

3.2.1.2.2 Allergic sensitization in children

One systematic review (Ierodiakonou *et al.*, 2016) describes the association between early fish introduction and the risk of allergic sensitization. **Table 3.2** summarizes this systematic review, including the main outcome, population, type of studies included and overall results. The study included five prospective cohort studies on children with fish introduced into their diet in the first year of age. There was low- to very low-certainty evidence that early fish introduction was associated with reduced allergic sensitization from the five prospective cohort studies combined.

3.2.1.2.3 Asthma in children

Two systematic reviews (Netting *et al.*, 2014 and Venter *et al.*, 2020) describing the association between maternal fish intake and asthma in children were included. Netting *et al.* (2014) combined six studies, including one randomized control study, one retrospective cohort study and four prospective cohort studies. Venter *et al.* (2020) included one randomized control, two observational studies of maternal fish intake in association with asthma in children less than three years of age and four observational studies of maternal fish intake in association with asthma in children at age three years and above. Different quantitative food frequency questionnaires were commonly used to derive fish intake.

Netting *et al.* (2014) did not pool data for meta-analysis. Most studies showed no association between maternal food intake and asthma or wheezing in children.

In one RCT included in Venter *et al.* (2020), maternal fish was not associated with asthma or wheezing in children. In most of the observational studies included, reduced offspring asthma (in children less than three years of age) was associated with higher intake of total fish and fatty fish. For children three years of age and above, higher maternal intake of fatty fish in pregnancy was associated with reduced offspring asthma/wheezing outcomes in the observational studies. In contrast, higher intake of fish sticks was associated with an increased offspring risk of asthma/wheezing in the observational studies.

3.2.1.2.4 Eczema in children

Two systematic reviews (Netting *et al.*, 2014 and Venter *et al.*, 2020) were found to describe an association between maternal fish intake and eczema. **Table 3.2** summarizes the systematic reviews, including main outcome, population, type of studies included and overall results. Venter *et al.* (2020) included four randomized controlled trials, consisting of one study with salmon and three studies with fish oil. The authors also included four observational studies. Netting *et al.* (2014) included ten studies: one randomized control, one retrospective cohort and eight prospective cohort studies. Maternal dietary intake was obtained from different quantitative food intake frequency questionnaires.

The data in both systematic reviews were summarized narratively and not pooled for meta-analysis. From the combined studies described by (Venter *et al.*, 2020), effect of fish consumption during pregnancy on eczema was unclear among the studies. Similarly, most studies showed no association between maternal food intake and allergy outcomes as described by (Netting *et al.*, 2014).

3.2.1.2.5 Multiple sclerosis

No systematic reviews were identified for the outcome multiple sclerosis.

3.2.1.2.6 Rheumatoid arthritis

Two systematic reviews (Pattison *et al.*, 2004 and Di Giuseppe *et al.*, 2014) describing the association between fish intake and rheumatoid arthritis were included (see **Table 3.2**). In one systematic review, described by Pattison *et al.* (2004), eight case-control and six prospective cohort studies were included, but only two studies reported an association between rheumatoid arthritis onset and fish consumption. Studies were hospital-based (inpatients and outpatients) or population-based. Fish intake was obtained from food frequency questionnaires. The other study described by Di Giuseppe *et al.* (2014) showed a dose–response meta-analysis to evaluate fish consumption and the risk of rheumatoid arthritis, including four case-control and three prospective cohort studies. Participants were hospital-based or population-based. Fish consumption was expressed as servings per week.

In one systematic review, reported by Pattison *et al.* (2004) the results could not be pooled due to the heterogeneity of the study designs. A protective effect of higher consumption of fish on the risk of rheumatoid arthritis was reported by Pattison *et al.* (2004), however, the review included a small number of studies, with variation in study design. In the meta-analysis conducted by Di Giuseppe *et al.* (2014), the results showed a decreased risk of developing rheumatoid arthritis for each one serving of fish per week (RR = 0.96, 95% CI: 0.91, 1.01).

TABLE 3.2 **RESULTS FROM THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH ON "ALLERGY AND IMMUNOLOGY"**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Lerodiakonou *et al.*, 2016 Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis	Early fish introduction in infancy and risk of allergic sensitization	Introduction of fish in infancy and followed up during childhood n = 14 193 Studies from Finland, Germany and Sweden	n = 5, prospective cohort studies	Fish introduction before age 6 to 9 months. Fish intake measured by questionnaires.	Meta-analysis: Risk of sensitization to any allergen: OR = 0.75, 95% CI: 0.64, 0.88. Meta-analysis: Risk of sensitization to any food: OR = 0.52, 95% CI: 0.37, 0.73.	There was low to very low certainty evidence that early fish introduction could reduce the risk of allergic sensitization in children.	Moderate
	Early fish introduction in infancy and risk of allergic rhinitis	Introduction of fish in infancy and followed-up during childhood n = 12 781 Studies from Finland, Norway and Sweden	n = 4, prospective cohort studies.	Fish introduction before age 6 to 12 months Fish intake measured by questionnaires.	Meta-analysis: Risk of allergic rhinitis at age ≤4 y: OR = 0.59, 95% CI: 0.4, 0.87. Meta-analysis: Risk of allergic rhinitis at age 5–14 y: OR = 0.68, 95% CI: 0.47, 0.98.	There was some evidence that early introduction of fish could reduce the risk of allergic rhinitis in children.	
Venter *et al.*, 2020 Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology	Maternal fish intake during pregnancy and risk of asthma/wheezing in children	Children of age <3 y as an outcome	n = 2, observational studies	Semi-quantitative food frequency questionnaires	Higher intake of fish and fatty fish were associated with reduced offspring asthma/wheezing in the observational studies.	The effects of maternal fish consumption in pregnancy and the effects on child outcomes of asthma, allergy and eczema are unclear and no firm conclusion could be drawn.	Moderate
		Children of age of 3 y or above as an outcome.	n = 4, observational studies		Higher intake of fatty fish was associated with reduced offspring asthma/wheezing outcomes in the included observational studies. Higher intake of fish sticks was associated with an increased offspring risk of asthma/wheezing in the observational studies.		
	Maternal fish intake during pregnancy and risk of allergic rhinitis in children	Children from 18 months to 7 years (study 1), and 3 years to 8 years (study 2).	n = 2, observational studies		Fatty fish were associated with reduced risk of allergic rhinitis while all fish (unspecified type) were associated with increased risk of allergic rhinitis. However, heterogeneity was found between studies.		
	Maternal fish intake during pregnancy and risk of eczema in children	Children from 6 months onwards	n = 4, observational studies		In one study, intake of fatty fish and shellfish was positively associated with offspring risk of eczema; while in the other four studies, maternal intake of fish was associated with a reduced risk of developing atopic dermatitis.		

TABLE 3.2 **RESULTS FROM THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH ON "ALLERGY AND IMMUNOLOGY" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Netting *et al.*, 2014 Does maternal diet during pregnancy and lactation affect outcomes in offspring? A systematic review of food-based approaches	Maternal fish intake in pregnancy and risk of eczema in children	>40 000 children	n = 10 studies: n = 1 RCT n= 1 retrospective cohort study n = 8 prospective cohort studies	Maternal fish intake in pregnancy	The studies investigated the outcome of eczema for different age groups: *3 months to 1 year:* One study found no clear link between eczema in children and how much fish their mothers ate during pregnancy. Two studies found that daily consumption of about 30 g of fish by their mothers during pregnancy and increased consumption (daily versus less frequently) showed protective effects against eczema. However, no adjustments of the results for potential confounders were applied in these studies. *2 years to less than 3 years:* In one study, when mothers consumed around 30 grams of fish daily during pregnancy or ate fish more frequently (every day compared to less often), their children had a lower risk of eczema. However, these studies did not consider other factors that might affect the results. *5 years:* In a study involving 5-year-old children, if mothers ate fish at least once a week during pregnancy, their children had a reduced risk of eczema.	The findings suggest that there might be a connection between maternal fish consumption during pregnancy and a lower risk of eczema in children. However, the results vary between studies and age groups, and some studies didn't account for other factors that could influence the outcomes.	Moderate
	Maternal fish intake in pregnancy and risk of asthma/wheezing in children		n = 5 studies: n = 1 RCT n = 4 prospective cohort studies	Maternal fish intake in pregnancy	The results from the studies were not consistent across the board. Some studies found a potential protective effect of maternal fish intake on the risk of asthma and wheezing in children, suggesting that higher fish consumption during pregnancy might be associated with a lower risk of these respiratory issues. However, other studies did not find a significant association.	Overall, while there were indications of a potential protective effect of maternal fish consumption during pregnancy against the risk of asthma and wheezing in children, the results were not consistent across all studies.	

TABLE 3.2 **RESULTS FROM THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH ON "ALLERGY AND IMMUNOLOGY" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Pattison et al., 2004 The role of diet in susceptibility to rheumatoid arthritis: a systematic review	Investigating a possible effect of individual components of diet and the development of rheumatoid arthritis (RA)	One study: Hospital-based inpatients and outpatients (n = 168 patients vs n = 137 controls) men and women aged 24-89 y. One study: Population-based, female participants aged 15–64 y (n = 324 cases vs. 1 243 controls)	n = 2 case-control studies	Food frequency questionnaires	Two studies reported association between rheumatoid arthritis onset and fish consumption. In one study, the association was significant only for high consumption of broiled or baked fish (≥ 2 servings/ week), and a stronger effect was seen in seropositive compared to seronegative cases.	Protective effect of higher consumption of fish on the risk of rheumatoid arthritis was reported. However, it was inconclusive due to the small number of studies available and due to variation in study design.	Moderate
Di Giuseppe et al., 2014 Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis	Association between fish consumption and risk of rheumatoid arthritis (RA)	Studies were from Denmark, Greece, Sweden and the United States. n = 174 701 included in analyses with n = 3 346 cases with rheumatoid arthritis	n = 7 studies: 4 case-control studies 3 prospective cohort studies	FFQs (fish consumption was expressed as servings per week)	For each one serving per week increment in fish consumption, the RR (95% CI) of RA was 0.96 (0.91, 1.01). The risk of RA was 20 to 24 percent lower for 1 to 3 servings per week of fish (RR (95% CI) = 0.76 (0.57, 1.02) as compared to no consumption.	Results from the meta-analysis showed an inverse (but not significant) association between fish consumption and RA.	Moderate

Note: n: numbers, OR: odds ratio, CI: confidence interval, FFQ: food frequency questionnaire, RCT: randomized controlled trial, RR: risk ratio, RA: rheumatoid arthritis

3.2.1.3 Final weight of evidence for "Allergy and immunology"

A final weight of evidence for the outcome "Allergy and immunology" was based on the 2022 VKM report and the systematic literature search. An overview of the total amount of literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

3.2.1.3.1 Allergic rhinitis in children

The evidence for associations of maternal fish intake and early fish introduction with child rhinitis are based on the 2022 VKM report, two systematic reviews and three primary studies.

In the maternal fish intake analysis described by the systematic review (Venter *et al.*, 2020), heterogeneity was found between studies. In addition, associations between fish intake during pregnancy and allergic rhinitis assessed by VKM were not statistically significant. The evidence that maternal total, fatty and lean fish intake during pregnancy affect the risk of rhinitis in the offspring was therefore graded "limited, no conclusion".

There was lower-certainty evidence that early fish introduction was associated with reduced allergic rhinitis from the meta-analysis by (Ierodiakonou *et al.*, 2016). In the VKM report, very limited data was found to describe protective associations of infant fish intake and allergic rhinitis. Only intake in the first year of life was associated with a reduced risk of rhinitis in one of two studies, while intake at later ages (2 to 8 years) was not included by VKM. The evidence that child fish intake in the first year protects against rhinitis is therefore graded "limited, no conclusion".

3.2.1.3.2 Allergic sensitization in children

The evidence that maternal fish intake during pregnancy affects the risk of allergic sensitization to food or inhalant allergens is graded "limited, no conclusion" based on two primary studies and two systematic reviews included in the VKM assessment.

The evidence that child fish intake protects against sensitization was also graded "limited, no conclusion". This evidence was based on two studies included in the VKM assessment and one systematic review included from the literature search.

3.2.1.3.3 Asthma in children

The evidence indicating effects of maternal fish intake during pregnancy on the risk of asthma in the offspring was graded "limited, no conclusion". This conclusion was based on no significant findings in the two systematic reviews included from the literature search and two meta-analyses included in the VKM report.

No conclusion could be drawn for an association between child fish intake and asthma, and the evidence was graded "limited, no conclusion". This was based on limited primary studies with inconsistent results of fish intake and outcomes reported in the VKM report.

3.2.1.3.4 Eczema in children

In the VKM report, the evidence that maternal fish consumption during pregnancy reduced the risk of eczema was graded "limited, suggestive". This was based on two meta-analyses that found borderline associations on the protective side (Malmir *et al.*, 2021: RR=0.93, 0.84-1.03 and Zhang *et al.*, 2017: RR=0.84, 0.69-1.01). Maternal fish consumption was not associated with eczema in the offspring in a recent meta-analysis by Malmir *et al.* (2021). However, in a dose–response meta-analysis Malmir *et al.* found that maternal fish consumption during pregnancy was weakly associated with a lower risk of eczema.

Further, according to the two systematic reviews (Netting *et al.*, 2014 and Venter *et al.*, 2020) from the systematic literature search, the effect of fish consumption during pregnancy on eczema is unclear. Those reviews showed no association between maternal food intake and allergy outcomes. However, such studies were not pooled for meta-analysis. Venter *et al.* found inconsistency of direction of effect. Thus, the evidence from the studies was not sufficient to identify any protective effect from maternal fish consumption during pregnancy on the risk of eczema. As such, the final weight of evidence that maternal fish consumption during pregnancy reduces the risk of eczema was graded "limited, no conclusion".

The evidence that fish intake in infants reduces the risk of eczema was graded "limited, suggestive" based on the primary studies assessed by VKM. Protective associations were found for intake in the first year of life, but not later.

3.2.1.3.5 Multiple sclerosis

Based on the assessment by VKM, a protective association of fish intake with the risk of multiple sclerosis was graded "limited, suggestive" due to uncertain mechanisms and the evidence base consisting of case-control studies only.

3.2.1.3.6 Rheumatoid arthritis

With regard to an association between fish consumption and rheumatoid arthritis, VKM identified six studies and one meta-analysis, including a dose-response analysis. In the meta-analysis identified by VKM, based on case-control and cohort studies, total fish intake was associated with reduced risk of rheumatoid arthritis; but the association was not statistically significant when only including cohort studies. Furthermore, VKM's summary RR was not statistically significant for cohort studies. A protective effect of higher consumption of fish on the risk of rheumatoid arthritis was reported by one systematic review (Pattison *et al.*, 2004); however, the review included a small number of studies and there were variations in the study design. The results of the meta-analysis by Di Giuseppe *et al.* (2014), based on four case-control and three prospective cohort studies, showed an inverse association between fish consumption and rheumatoid arthritis.

Evidence was too limited to conclude on the association between the intake of fish and rheumatoid arthritis. Thus, the evidence was graded "limited, no conclusion" for a protective effect of fish consumption on the risk of rheumatoid arthritis.

3.2.2 BIRTH AND GROWTH OUTCOMES

The literature included on the theme "Birth and growth outcomes" includes results from the 2022 VKM report, and two original primary studies from the literature search. No systematic reviews were included from the literature search.

3.2.2.1 Summary of the findings on "Birth and growth outcomes" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

In the 2022 VKM report, Benefit and risk assessment of fish in the Norwegian diet, the authors summarized the evidence of an association between maternal fish consumption in pregnancy and the outcomes of "preterm birth", "small for gestational age", "birth weight", "birth length", "birth head circumferences" and "low and high birth weight".

3.2.2.1.1 Preterm birth

3.2.2.1.1.1 Description of the studies included

The VKM assessment included 1 systematic review and meta-analysis (Zhao *et al.*, 2021) which included 11 observational studies (prospective cohort and case-control studies) (n = 36 391 participants) investigating the association between maternal fish consumption in pregnancy and the risk of preterm birth. In the systematic review, the summary odds ratio (OR) (95% CI) of highest versus lowest intake of total fish showed no clear effect of fish consumption: 0.90 (0.72, 1.14). Though in linear analyses (including 7 cohort studies and 4 675 participants), a dose–response increment of consumption of 45 g fish/day was associated with a 16 percent lower risk of preterm birth (summary OR = 0.84, 95% CI: 0.71, 1.01). No clear effects were found for lean or for fatty fish intake in the meta-analysis by Zhao *et al.*, 2021.

The VKM assessment included 11 original primary studies (10 single studies and 1 pooled analysis) that investigated the association between maternal fish consumption and the risk of preterm birth (< gestational week 37). All studies were prospective birth cohorts, except for two – a case-control study and a retrospective cohort study. VKM calculated a summary RR of the primary studies in relation to the highest versus lowest intake of total fish, which showed a direction of a protective effect of fish consumption (RR = 0.89, 95% CI: 0.77, 1.04), but with significant heterogeneity ($P_{heterogeneity}$ = 0.001). VKM also calculated a summary RR for the studies, separating intake into lean (n = 3 cohort studies) and fatty fish (n = 4 cohort studies), though no clear effects were found (lean fish: RR = 0.83, 95% CI: 0.64, 1.08, $P_{heterogeneity}$ = 0.44); fatty fish: RR = 0.89, 95% CI: 0.70, 1.13, $P_{heterogeneity}$ = 0.29).

3.2.2.1.1.2 Conclusion, weight of evidence

In the final weight of evidence, the VKM gave more weight to the dose–response results included. Because of the evidence for biological plausibility and a dose–response association, the evidence of a protective effect of maternal total fish intake in pregnancy on the risk of preterm birth was graded "probable". No conclusions could be drawn for fatty or lean fish intake, and these outcomes were graded "limited, no conclusion".

3.2.2.1.2 Small for gestational age

3.2.2.1.2.1 Description of the studies included

The VKM assessment included one systematic review and meta-analysis (Zhao *et al.*, 2021), which included nine observational studies (prospective cohort studies and case-control studies) (n = 2 146 participants) investigating the association between maternal fish consumption in pregnancy and risk of being small for gestational age. In the systematic review, the summary OR (95% CI) of highest versus lowest intake of total fish showed no clear effect of fish consumption: 0.79 (0.59, 1.06) (including 11 cohort studies and 2 146 participants). Though in linear analyses (including 7 cohort studies and 1 360 participants) a dose-response increment of 45 g/day of fish consumption was associated with a 16 percent lower risk of being born small for gestational age (summary OR = 0.84, 95% CI: 0.71, 0.98 $P_{heterogeneity}$ = 0.04). No clear effects were found on lean or fatty fish intake in the meta-analysis.

The VKM assessment included nine original primary studies (eight single studies and one pooled analysis) that investigated the association between maternal fish consumption and the risk of being born small for gestational age. Five of the studies were birth cohorts, while four were case-control studies. VKM calculated a summary RR of the studies in relation to the highest versus lowest intake of total fish which, showed no clear effect of fish consumption (RR = 1.02, 95% CI: 0.80, 1.30), with significant heterogeneity ($P_{heterogeneity}$ = 0.02). VKM also calculated a summary RR for the effect of intake prior to pregnancy, which showed a protective effect of total fish consumption (n = 3 case-control studies, summary RR = 0.73, 95% CI: 0.61, 0.88, $P_{heterogeneity}$ = 0.38).

No clear effects were found on lean or fatty fish intake in the studies included in the 2022 VKM assessment.

3.2.2.1.2.2 Conclusion, weight of evidence

Based on the results from the systematic review and the calculated summary RR for fish consumption prior to pregnancy, there was some evidence that maternal fish intake could protect against being born small for gestational age. The evidence of the association between a protective effect of maternal total fish consumption and the risk of small for gestational age was therefore graded "limited, suggestive". No conclusions could be drawn for fatty or lean fish intake, and these outcomes were graded "limited, no conclusion".

3.2.2.1.3 Birth weight

3.2.2.1.3.1 Description of the studies included

The VKM assessment included 13 original primary studies (12 single studies and 1 pooled analysis) that investigated the association between maternal fish intake in pregnancy and birth weight as a continuous variable. All studies were prospective birth cohorts. VKM did not calculate a summary RR of high versus low intake because of the large heterogeneity between the studies. Of the single studies, the

comparison of the association between the highest fish consumption group and birth weight versus that of the lowest fish consumption group was rather unclear. In the pooled analysis study (including 13 European cohort studies), a 15.2 g increase in birth weight in the highest versus the lowest intake of fish categories was reported.

3.2.2.1.3.2 Conclusion, weight of evidence

The evidence that maternal total, fatty and lean fish intake in pregnancy increases birth weight was graded "limited, suggestive (positive association)" by VKM.

3.2.2.1.4 Low and high birth weight

3.2.2.1.4.1 Description of the studies included

The VKM assessment included one systematic review and meta-analysis (Zhao *et al.*, 2021), which included 11 observational studies (birth cohorts) (n = 26 823 participants) investigating the association between maternal fish consumption in pregnancy and risk of low birth weight. In the systematic review, the summary OR (95% CI) of highest versus lowest intake of total fish showed a protective effect of fish consumption: 0.78 (0.61, 1.00). In addition, VKM included a linear analysis (including 7 cohort studies and 869 participants) where a dose–response increment of 45 g/day fish consumption was associated with a 35 percent lower risk of low birth weight (summary OR = 0.65, 95% CI: 0.47, 0.90, $P_{heterogeneity}$ = 0.04). The meta-analysis found no clear effects on lean and fatty fish intake.

The VKM assessment included ten original primary studies (nine single studies and one pooled analysis) that investigated the association between maternal fish consumption and risk of low and high birth weight. All studies were prospective birth cohorts. VKM calculated a summary RR of the studies in relation to the highest versus lowest intake of total fish, which showed a direction of a protective effect of fish consumption, although this was not statistically significant (RR = 0.86, 95% CI: 0.66, 1.13, $P_{heterogeneity}$ = 0.15). No conclusions could be drawn from the studies regarding fatty or lean fish intake.

The outcome "high birth weight" was only assessed in the pooled analyses by Leventakou *et al.*, 2014. They found a small increase in the risk of high birth weight with the highest versus lowest total intake of fish. The effects of lean and fatty fish were similar (measured on a continuous scale).

3.2.2.1.4.2 Conclusion, weight of evidence

In the final weight of evidence, the VKM assessment gave more weight to the dose–response results included. Because of the evidence for biological plausibility and a dose–response association, the evidence of a protective effect of maternal total fish intake in pregnancy on the risk of low birth weight was graded "probable". No conclusions could be drawn for fatty or lean fish intake, and these outcomes were graded "limited, no conclusion".

In the final judgement by the VKM assessment, the evidence that maternal total, fatty and lean fish consumption in pregnancy increased the risk of high birth weight was graded "limited, suggestive".

3.2.2.1.5 Birth length and head circumference

3.2.2.1.5.1 Description of the studies included

The VKM assessment included seven primary studies that investigated the association between maternal total fish intake in pregnancy and birth length and head circumference (one study only included birth length). Five of the studies included were prospective birth cohorts, one was a cohort-based community trial, and one was a retrospective cohort study. Six studies were conducted in Europe, while one was conducted in the United States. All studies presented estimates of total fish consumption, except for one study that presented intake of canned tuna. Five studies also presented intake of subcategories of lean and fatty fish.

VKM did not calculate a summary RR of high versus low intake because of the large heterogeneity between the studies. For intake of total fish in pregnancy and the relation to birth length, one study reported increased birth length in the highest intake category compared to the lowest, while the rest of the studies reported no association. For total fish intake in pregnancy and the relation to head circumference, two studies reported larger, and one study reported smaller head circumference in the highest compared to the lowest intake category, while the rest of the studies reported no association. For lean and fatty fish intake, the studies reported no clear association with either birth length or head circumference.

3.2.2.1.5.2 Conclusion, weight of evidence

The current evidence of an association between maternal total fish intake in pregnancy and birth length did not support an association, and the evidence was concluded to be "limited, suggestive (no association)". For head circumference, the evidence was inconsistent and was graded "limited, no conclusion". No conclusions could be drawn for fatty or lean fish intake, and these outcomes were graded "limited, no conclusion" for both birth length and head circumference.

3.2.2.2 Summary of the findings on "Birth and growth outcomes" in primary studies included in the literature search

3.2.2.2.1 Description of the primary studies

Two primary studies were included from the literature search in the "Birth and growth outcomes" category. **Table 3.3** gives an overview of the results from the two studies, including author, title, study type, study population, measurement of fish and seafood consumption, measurement of outcome, overall results and overall conclusion. Both studies are prospective cohort studies. In the study by Oken *et al.*, 2004, participants were enrolled from 1999 to 2002 in Project Viva in Massachusetts, in the United States, to collect data on gestational diet, pregnancy outcomes and offspring health. The study by Zhao *et al.*, 2022 was a prospective analysis of data from the Tongji Birth cohort in Wuhan, China from 2018 to 2021.

3.2.2.2.2 Description of study population

The study by Oken *et al.* included 2 109 women. The women's ethnicity reflected the diversity of the source population, including 16 percent Black, 7 percent Hispanic, and 6 percent Asian American subjects, ranging from 14 to 44 years of age.

The study by Zhao *et al.* included 2 149 pregnant women aged 18 to 45 years at baseline, but the analysis in the present study includes data from 1 701 mother–infant pairs.

3.2.2.2.3 Description of fish consumption

In Oken *et al.*, a semiquantitative FFQ, including intake of "canned tuna fish", "shrimp, lobster, scallops, clams", "dark meat fish, e.g., mackerel, salmon, sardines, bluefish, swordfish"; and "other fish, e.g., cod, haddock, halibut" was used to evaluate the maternal diet in relation to the outcomes.

Dietary intake was assessed through face-to-face interviews using a modified version of a semiquantitative FFQ in the study by Zhao *et al.* The modified FFQ consisted of 74 food items, including 4 fish items (saltwater fish, freshwater fish, prawn and crabs, and molluscs).

3.2.2.2.4 Results from the primary studies included

In the study by Oken *et al.*, the frequency of fish consumption during pregnancy showed a trend towards an inverse association with birth weight and foetal growth and was not associated with length of gestation. One unadjusted analysis, an increase in first-trimester fish consumption from less than one serving per month to more than two servings per week, was associated with a decrease in birth weight from 3 487 g to 3 452 g. After multivariable adjustment, there was still a suggestion of an inverse association between frequency of fish intake and foetal growth, although this relation was statistically significant only during the first trimester.

In the study by Zhao *et al.*, higher intake of freshwater fish during pregnancy showed a reduced risk of newborns born small for gestational age. The association also remained significant after adjusting for relevant confounders. No significant associations were observed between total fish, saltwater fish and shellfish intake and risk of newborns born small for gestational age.

TABLE 3.3 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "BIRTH AND GROWTH OUTCOMES"

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Zhao *et al.*, 2022 Tongji Birth cohort Wuhan, China	2018 to 2021 Cohort study More than 13th or less than 28th week of gestation until birth → 29 to 14 weeks	n = 2 149 pregnant women n = 1 701 mother–infant pairs were included in this analysis Cases (n = 1 701) Maternal age, years, median (IQR) 28.7 (26.8–30.8) Sex of infant, male, n (percent) = 895 (52.6)	Dietary intake including fish consumption was assessed through face-to-face interviews using a modified version of a semiquantitative FFQ. The four fish items were saltwater fish, freshwater fish, prawns and crabs, and molluscs. Prawns and crabs and molluscs were combined into one category, collectively called shellfish. Total fish, g/day, median (IQR) 23.9 (10.9-43.6) Freshwater fish, g/day, median (IQR) 12.1 (4.3-26.4) Saltwater fish, g/day, median (IQR) 0 (0-3.6) Shellfish, g/day, median (IQR) 5.0 (1.3-11.3)	Neonatal characteristics were obtained from hospital obstetric records, including gestational age, sex of the infant, and birth weight. Newborns were classified as SGA if their birth weight was below the 10th percentile of the gestational age distribution of the Chinese population.	From the lowest to highest quintiles of freshwater fish intake, the crude ORs for SGA were: Q1: reference Q2: 0.63 (95 % CI: 0.35, 1.11) Q3: 0.75 (95 % CI: 0.43, 1.31) Q4: 0.50 (95 % CI: 0.26, 0.93) Q5: 0.64 (95 % CI 0.35, 1.13) P for trend = 0.206). No significant associations were observed between total fish, saltwater fish, and shellfish intake and risk of SGA.	B	The study found supportive evidence that moderate intake of freshwater fish in mid-pregnancy is related to a lower risk of SGA in Chinese pregnant women.

TABLE 3.3 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "BIRTH AND GROWTH OUTCOMES" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Oken *et al.*, 2004 Project Viva	1999 to 2002 Birth cohort From mean gestational age 10.6 weeks until birth	n = 2 128 pregnant women who delivered a live infant n = 2 109 (99 percent) completed at least one dietary questionnaire, n = 1 797 1st trimester n = 1 663 2nd trimester n = 2 070 3rd trimester Maternal age ranged from 14 years to 44 years.	Semiquantitative food frequency questionnaires including intake of "canned tuna fish (3–4 oz.)" (1 oz. = 28.3g); "shrimp, lobster, scallops, clams (1 serving)"; "dark meat fish, e.g., mackerel, salmon, sardines, bluefish, swordfish (3–5 oz.)"; and "other fish, e.g., cod, haddock, halibut (3–5 oz.)." The lowest group reported consuming none/<1 serving of seafood per month; the remaining subjects were divided into tertiles, with the highest intake group, more than two servings per week, used as the referent.	Birth weight in grams was obtained from the hospital medical record Length of gestation in days was calculated by subtracting the date of the last menstrual period from the date of delivery. Birth weight for gestational age was determined by using as a reference a combined 1999–2000 US natality data set. This method adjusts for gestational age and provides a normal z value measuring distance of the birth weight from the median for a given gestational age.	On unadjusted analysis, an increase in first-trimester fish consumption from less than one serving per month to more than two servings per week was associated with a decrease in z value from 0.22 to 0.16 and a decrease in birth weight from 3 487 g to 3 452 g. After multivariable adjustment, there was still a suggestion of an inverse association between frequency of fish intake and foetal growth, although this relation was statistically significant at the conventional standard of $P < 0.05$ for only the first trimester. No indication of a relation with length of gestation. No association of seafood intake with the dichotomous outcomes low birth weight, small for gestational age, and preterm delivery.	B	Frequency of fish consumption during pregnancy showed a trend towards an inverse association with birth weight and foetal growth but was not associated with length of gestation.

Notes: All studies are prospective cohort studies. Q: quartile, IQR: interquartile range, SGA: small for gestational age, OR: odds ratio, FFQ: food frequency questionnaire, CI: confidence interval.

3.2.2.3 Final weight of evidence for "Birth and growth outcomes"

A final weight of evidence for the theme "Birth and growth outcomes" was based on the 2022 VKM report and the systematic literature search. An overview of the literature included in the final weight of evidence is provided in Appendix 3, **Table A3.35**.

The summary of the final weight of evidence for "Birth and growth outcomes" was based on the judgement from the 2022 VKM report and the two original primary studies included. The inclusion of the primary studies did not change the conclusion of the 2022 VKM report.

Thus, the final weight of evidence for the association between maternal total fish consumption in pregnancy is graded:

> preterm birth: "Probable (protective)";
> small for gestational age: "Limited, suggestive (protective)";
> birth weight (continuous scale): "Limited, suggestive (positive association)";
> low birth weight: "Probable (protective)";
> high birth weight: "Limited, suggestive (positive association)";
> birth length: "Limited, no conclusion";
> head circumference: "Limited, no conclusion".

For maternal lean and fatty fish intake in pregnancy, all outcomes were graded "limited, no conclusion", except for birth weight (continuous scale), which was graded "limited, suggestive (positive association)", and risk of high birth weight, which was graded "limited, suggestive (positive association).

3.2.3 BONE HEALTH

The literature included in the theme "Bone health" includes results from the 2022 VKM report and four original primary studies originating from the literature search. No systematic reviews were included.

3.2.3.1 Summary of the findings on "Bone health" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

The 2022 VKM assessment included eight primary studies (one case-control study and seven prospective cohort studies), which included the outcomes of hip fracture, bone mineral density in the femoral neck, or total hip. The study populations were from Asia, Europe and the United States. VKM calculated a summary RR from four of the prospective cohort studies for incident hip fracture in relation to the highest versus lowest intake of total fish. This result suggested that a high intake of fish, compared to a lower intake of fish, may lower the RR of hip fracture (RR = 0.70, 95 % CI: 0.55, 0.88).

VKM also included one systematic review (Sadeghi *et al.*, 2019) that investigated the effects of total fish intake on the risk of hip fractures. The meta-analysis in Sadeghi *et al.* suggested a borderline significant protective effect of total fish intake.

In conclusion, from the VKM report, the evidence that high total fish consumption may lower the risk of hip fractures was graded "limited, suggestive". No conclusion could be drawn for fatty fish or lean fish as only one study was included.

3.2.3.2 Summary of the findings on "Bone health" in primary studies included in the literature search

3.2.3.2.1 Description of the primary studies included

Four primary studies were included under the category "bone health". A description of the studies, including study name, design, time period, study population, intake of fish consumption and overall results, can be found in **Table 3.4** and **Table 3.5**. Two of the primary studies were RCTs (Lucey *et al.*, 2008 and Tong *et al.*, 2020) and two were prospective cohort studies (Hirota *et al.*, 2005 and Thacher *et al.*, 2015).

3.2.3.2.2 Description of study population

One RCT included 276 adult men and women from 20 to 40 years of age (Lucey *et al.*, 2008), while the other included 96 children under the age of 5 years with calcium deficiency rickets (Thacher *et al.*, 2015). One of the prospective cohort studies was conducted on children (n = 548), with a follow-up time of 5 years (Hiorta *et al.*, 2005), while the other was conducted among adults (n = 54 898) and lasted from 1993 until 2016 (Tong *et al.*, 2020).

3.2.3.2.3 Description of fish consumption

In the RCTs, one intervened with ground fish, using limestone in the second study arm (Thacher *et al.*, 2015), while the other study had salmon, fish oil and cod as interventions (Lucey *et al.*, 2008). In Hirota *et al.*, questionnaires and interviews regarding several food groups, including fish and small fish, were applied and carried out among the participants; while in Tong *et al.*, questionnaires were used to classify participants into fish eaters, meat eaters, vegetarians and vegans.

3.2.3.2.4 Results from the primary studies

3.2.3.2.4.1 Calcium deficiency rickets

In the Thacher *et al.* study conducted with children with calcium-deficiency rickets, treatment with calcium as either ground fish or limestone for 6 months healed rickets in the majority of the children. There was no control group in this study.

3.2.3.2.4.2 Bone turnover and bone loss

In the RCT by Lucey *et al.*, different interventions with fish and fish oil were examined for attenuation of bone turnover and bone loss in overweight adults on a weight-loss diet. The inclusion of fish (salmon or cod) or fish oil in the diet was unable to attenuate the effect of weight loss on bone turnover. No significant differences were seen in the different bone turnover biomarkers between the different intervention groups.

3.2.3.2.4.3 Bone status

The study by Hirota *et al.* on Japanese adolescent girls and boys found that annual increase in bone status in girls aged 10 or 11 years was associated positively with increased intake of fish, fruit, vegetables, soybeans and milk products and associated negatively with preference for meat. They conclude that increased intake of fish could improve bone status (Hirota *et al.*, 2005). Japanese traditionally eat the whole body of small fish, which contains more calcium, vitamin D, magnesium and proteins, compared to fish filet, which may be the reason for the beneficial effect on bone status.

3.2.3.2.4.4 Hip fracture

In the European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford study conducted by Tong *et al.*, fish eaters, vegans and vegetarians were compared to meat eaters. The researchers found that fish eaters had a higher risk of hip fractures compared with meat eaters. These risk differences were likely partially due to their lower body mass index (BMI), and possibly to lower intake of calcium and protein.

TABLE 3.4 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (INTERVENTION STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "BONE HEALTH" FOR "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION"

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY YEAR OF SAMPLING	STUDY TYPE STUDY DURATION AND FOLLOW-UP TIME	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) AT EXPOSURE ASSESSMENT SEX (PERCENT, MEN)	MEASUREMENT AND INTAKE OF FISH AND SEAFOOD CONSUMPTION AT BASELINE	INTERVENTION AND CONTROL GROUP INFORMATION REGARDING INTERVENTION, DURATION, DOSE	MEASUREMENT OF OUTCOME	OVERALL RESULTS	RISK OF BIAS
Lucey *et al.*, 2008 SEAFOODplus YOUNG study Iceland, Spain and Ireland 2004-2005	Randomized controlled trial 8 weeks	n = 276 men and women 20–40 years 43 percent men	At baseline, seafood intake was assessed by a validated food frequency questionnaire (FFQ). Dietary intake was assessed by 2-day weighed food records before baseline (habitual diet).	Intervention: Participants were randomly assigned to 1 of 4 groups: Group 1: control (sunflower oil), Group 2: 150 g cod 3 times/week for 8 weeks, Group 3: 150 g salmon 3 times/week for 8 weeks, Group 4: 3 g fish oil /day for 8 weeks. Control: Sunflower oil, 6 capsules per day.	Serum osteocalcin and bone-specific alkaline phosphatase were measured. Serum C-terminal telopeptide of type I collagen was measured. Urinary N-telopeptides of type I collagen was measured.	No significant differences were seen in the different bone turnover biomarkers between the different intervention groups.	B
Thacher *et al.*, 2015 Nigeria 1998–2000	Randomized trial 14 or 24 weeks	n = 96 children Age: Group 1 limestone: median (p25–p75) 28 (19–42) months. Group 2, ground fish: median (p25–p75) 42 (27–59) months. Sex: male/female ratio, Limestone group: 16/29, Ground fish group: 23/28	Breastfeeding history, usual dairy product intake, were assessed.	Ground fish: 10 g twice/day for 14 weeks. Limestone: 1.75 g twice daily for 24 weeks. No control group.	Radiographic score, assessed by radiographic healing was defined as achieving a score of 1.5 or less on a 10-point scale.	Of the 88 children who completed the study, 29 (66 percent) in the ground fish group and 24 (55 percent) in the limestone group achieved the primary outcome of a radiographic score of 1.5 or less within 6 months (P = 0.39). The mean radiographic score improved from 6.2 ± 2.4 to 1.8 ± 2.2 in the ground fish group and from 6.3 ± 2.2 to 2.1 ± 2.4 in the limestone group ($P = 0.68$ for group comparison).	B

TABLE 3.5 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "BONE HEALTH"

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY TYPE YEAR OF SAMPLING, STUDY DURATION AND FOLLOW-UP TIME	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	MEASUREMENT AND INTAKE OF FISH AND SEAFOOD CONSUMPTION	MEASUREMENT OF OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Hirota *et al.*, 2005 Japan	Prospective cohort study 1995–1999 Follow-up time: 5 years	n = 548 262 girls + 286 boys Age: 10–15 years Girls: mean (SD) 12.4±1.6 Boys: 12.3±1.5 Sex: 52.2 percent men	Questionnaires and interviews regarding dairy consumption determined how often subjects consumed any type of milk, cheese or yogurt. Inquiries were also made about other traditional sources of calcium, such as soybeans, curdled soy protein (tofu), fermented soy (Natto), green leafy vegetables, other vegetables, seaweeds, fish, and small fish. Intake (frequency, times or dishes/week) mean (SD): Girls - of fish: 3.4 (1.7) Girls - of small fish: 2.0 (1.5) Boys - of fish: 3.4 (1.7) Boys - of small fish: 2.4 (2.0) ($p<0.05$ more than girls)	Bone measurement Bone status of the os calcis was measured with quantitative ultrasound (QUS) using the Achilles A1000 ultrasonometer. Achilles measures SOS (speed of sound in meters per second), and BUA (broad-band ultrasound attenuation in decibels per megahertz), a measure of frequency-dependent attenuation of the ultrasound wave passing through the heel. Stiffness index (SI), a variable derived from a combination of SOS and BUA, was calculated by the analysis software according to the equation: 0.67 BUA + 0.28 SOS) 420.	Associated factors with the initial bone status of 10- and 11-year-olds: Girls (n = 114): Intake of small fish: Pearson's correlation coefficient: r = 0.22; P = 0.024 Boys (n = 112): no association same test (Table 4). Associated factors with yearly change of bone status from age from 10–11 years to 11–12 years: Girls (n = 114); Increased fish intake was positively associated with bone status. Pearson's correlation coefficient = 0.35, P< 0.001) Boys: Increased intake of small fish was associated with bone status. Pearson's correlations coefficient = 0.10, P = 0.045.	B	The study in Japanese adolescent girls and boys found that increased intake of fish could improve bone status.

TABLE 3.5 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "BONE HEALTH" (cont.)**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY TYPE YEAR OF SAMPLING, STUDY DURATION AND FOLLOW-UP TIME	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	MEASUREMENT AND INTAKE OF FISH AND SEAFOOD CONSUMPTION	MEASUREMENT OF OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Tong *et al.*, 2020 EPIC-Oxford study the United Kingdom of Great Britain and Northern Ireland	Prospective cohort study Recruitment 1993–2001 Follow-up in 2010 Follow-up with record linkage in 2016 Average of 17.6 years of follow-up	n = study population included a minimum of 54 898 participants (in analyses for total fractures), of whom 30 391 had repeated measures of diet 14 years later	Questionnaires asking if participants included fish in the diet. The dietary questions were used to classify participants into four groups at baseline and follow-up: meat eaters, fish eaters, vegetarians and vegans.	Outcomes were identified through linkage to hospital records or death certificates until mid-2016. The outcomes were total fracture and site-specific fractures identified by the relevant 9th or 10th revisions of the World Health Organization's International Classification of Diseases (ICD-9/ICD-10) codes.	Fish eaters had increased risk of hip fracture compared with meat eaters, even after adjusting year of recruitment, ethnicity, Townsend deprivation index, physical activity, smoking, alcohol consumption, dietary supplement use, in women menopausal status, hormone replacement therapy, BMI, dietary calcium intake and protein intake, showing an adjusted hazard ratio (HR) (95 % CI) of 1.25 (1.01, 1.55).	B	Fish eaters had higher risk of hip fractures compared with meat eaters. These risk differences were likely partly due to their lower BMI, and possibly to lower intakes of calcium and protein.

Note: SD: standard deviation, EPIC: European Prospective Investigation into Cancer and Nutrition, BMI: body mass index.

3.2.3.3 Final weight of evidence for "Bone health"

A final weight of evidence for the theme "Bone health" was based on the 2022 VKM report and the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

The weight of evidence is only considered for the outcome of hip fracture, since that is the only outcome evaluated by VKM, and the other outcomes included only involved one study, which was considered too little to grade the weight of evidence. Using estimates from four studies, VKM graded the evidence that high fish consumption may lower the risk of hip fractures "limited, suggestive". No significant heterogeneity was found between the studies, where the estimates were on the protective side. In the one primary study on hip fracture in the current review by Tong *et al.* (2020), a higher risk of hip fracture was seen in fish eaters compared with meat eaters; however, these risk differences may be due to lower BMI in the fish-eater group. Therefore, the evidence of a "limited, suggestive" protective effect of fish intake on hip fracture remains.

3.2.4 CANCER

The literature included in the theme "Cancer" includes results from the report of World Cancer Research Fund on Diet, Nutrition, Physical Activity and Cancer, published in 2018 (WCRF, 2018b), and three systematic reviews and ten original primary studies originating from the literature search.

3.2.4.1 Summary of the findings on "Cancer" in the World Cancer Research Fund report

The information referenced is derived from the third expert report from the World Cancer Research Fund and the American Institute for Cancer Research, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective.

The 2018 WCRF report defines fish as any of various cold-blooded, aquatic vertebrates, having gills, commonly fins, and typically an elongated body covered with scales, as well as shellfish. Cantonese-style salted fish is part of the traditional diet consumed by people living in the Pearl River Delta region in Southern China. It is prepared with less salt than is used in Northern China, allowed to ferment, and eaten in a decomposed state.

The 2018 WCRF report concludes that there was "strong evidence" for a probable increased risk of nasopharyngeal cancer from increased intake of Cantonese-style salted fish, and "limited, suggestive" evidence for a decreased risk of liver and colorectal cancer from increased total fish intake. For other cancer outcomes, no conclusion could be made.

3.2.4.2 Summary on the findings on "Cancer" in the systematic reviews included from the literature search

A comprehensive literature search was conducted to identify systematic reviews examining the relationship between fish intake and the risk of cancer. Three systematic reviews that met our inclusion criteria and that were published from 2018, after the WCRF report was published, were identified in the search: Jayedi *et al.*, 2020; Kazemi *et al.*, 2021 and Gao *et al.*, 2022. All three studies included a meta-analysis. **Table 3.6** provides a comprehensive overview of these studies, presenting details including outcomes investigated, population and participant information, study design and included studies, time period, study population characteristics, fish consumption intake, as well as the overall results and conclusions derived from these systematic reviews.

One of the systematic reviews identified covered site-specific cancer risk (Jayedi *et al.*, 2020), while the other two covered the risk of pancreatic cancer (Gao *et al.*, 2022) and breast cancer (Kazemi *et al.*, 2021). All systematic reviews included participants from the general population, encompassing both males and females, except for Kazemi *et al.*, which only included women. According to Gao *et al.*, no substantial relationship was found between fish intake and the increase of pancreatic cancer risk. Their analysis encompassed 22 studies (11 case-control studies and 11 cohort studies), which investigated the association between fish intake and pancreatic cancer risk. The findings from these studies collectively suggested no significant association between fish consumption and the risk of developing pancreatic cancer. When comparing the highest and lowest levels of fish intake, the pooled RR was 1.00 (95% CI: 0.93, 1.07), indicating no substantial difference in risk. Kazemi *et al.* investigated the association between fish intake and breast cancer. Their analysis incorporated 17 studies, including case-cohort studies, nested case-control studies, cohort studies and randomized control trials. The main findings from these studies revealed no significant association between each additional 100 g/day increase in fish intake and breast cancer risk (RR = 1.0, 95 % CI: 0.93, 1.08). Furthermore, there was no evidence of a nonlinear dose–response relationship (P-nonlinearity, 0.39). The study findings suggest that fish intake does not have a substantial impact on the risk of developing breast cancer.

Jayedi *et al.* analysed 120 prospective cohort studies and found moderate-quality evidence suggesting an inverse association between fish consumption and the risk of liver cancer (summary RR = 0.65, 95% CI: 0.48, 0.87). They also found low-quality evidence for a positive association between fish consumption and the risk of myeloid leukaemia and gastric cancer. However, no significant associations were observed for cancers at other sites.

TABLE 3.6 SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "CANCER"

AUTHOR, YEAR TITLE	OUTCOME (MAIN OUTCOME AND SPECIFIC OUTCOME GROUPS)	POPULATION AND NUMBER OF PARTICIPANTS INCLUDED	NUMBER OF INCLUDED STUDIES AND TYPE OF STUDY DESIGNS INCLUDED	INFORMATION REGARDING FISH AND SEAFOOD INTAKE	OVERALL RESULTS (INCLUDE META-ANALYSIS IF APPLICABLE)	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Gao *et al.*, 2022 Poultry and Fish Intake and Pancreatic Cancer Risk: A Systematic Review and Meta-Analysis	Investigated associations between poultry and fish consumption and pancreatic cancer (PC) risk	General population. Two studies only with females, one only with males, and the rest of the studies included both males and females n = 1 367 330	n = 25 for all n = 22 including fish 11 case-control studies and 11 cohort studies	FFQ	Meta-analysis: When the highest and lowest fish intake were compared, the pooled RR was 1.00 (95% CI: 0.93–1.07), with no apparent heterogeneity (P = 0.27, I2 = 14 percent). Subanalysis: In studies without adjusted energy intake, fish intake negatively correlated with PC risk (RR = 0.84, 95% CI: 0.72, 0.99), while studies adjusted for energy intake showed no correlation.	Overall, the results achieved in this study further clarify that fish intake has no substantial relationship with the incidence of pancreatic cancer.	Moderate
Jayedi et al., 2020 Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies	Meta-analyses of observational studies evaluating the association of fish consumption with the risk of chronic disease. Fish consumption and site-specific cancer risk	General population aged 18 years or older n = 135 971	n = 120 primary studies Prospective cohort studies Meta-analyses of observational studies that combined prospective, retrospective, and cross-sectional studies in their analyses were also eligible.	FFQs, diet history, 24-hour dietary recalls, and dietary records.	Moderate quality of evidence for the relation between fish consumption and the risk of liver cancer (summary RR for each 100-g/day increment: 0.65; 95% CI: 0.48, 0.87). There was also low-quality evidence for the inverse association of fish consumption and the risk of prostate cancer mortality, as well as for the positive association of fish consumption and the risk of myeloid leukaemia and gastric cancer. Fish consumption was not associated with the risk of cancers at other sites.	For site-specific cancers, moderate-quality evidence was found that higher fish consumption was associated with a lower risk of liver cancer. There was also an inverse association for prostate cancer mortality, but the quality of the evidence was rated low. For cancers at other sites, no significant inverse associations were found and the quality of the evidence was rated low or very low.	High

TABLE 3.6 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)**

AUTHOR, YEAR TITLE	OUTCOME (MAIN OUTCOME AND SPECIFIC OUTCOME GROUPS)	POPULATION AND NUMBER OF PARTICIPANTS INCLUDED	NUMBER OF INCLUDED STUDIES AND TYPE OF STUDY DESIGNS INCLUDED	INFORMATION REGARDING FISH AND SEAFOOD INTAKE	OVERALL RESULTS (INCLUDE META-ANALYSIS IF APPLICABLE)	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Kazemi et al., 2021 Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies	Summarize the associations between food groups and risks of breast cancer Investigated the association of fish with breast cancer	Females over 18 years of age. n = N/A					
n = 17 studies Includes cohort, case-cohort, nested case-control studies, and follow-up studies of randomized controlled trials	Validated FFQ	No association was observed for each additional 100-g/day increase of fish (RR = 1.0, 95% CI: 0.93, 1.08; P-heterogeneity = 0.19. There was no evidence of a nonlinear dose-response association (P-nonlinearity = 0.39; n = 11 studies). The risk of breast cancer increased by approximately 10 percent with increasing intake of fish, up to 110 g/day.	To ameliorate the cancer risk, fish and poultry represent good substitutes for red meat in the dietary composition. As in the present meta-analysis, fish had no significant association with the risk of breast cancer.	High			

Note: N/A: not applicable, FFQ: food frequency questionnaire, RR: risk ratio, CI: confidence interval

3.2.4.3 Summary of the findings on "Cancer" in primary studies included from the literature search

3.2.4.3.1 Description of the primary studies

Ten primary studies were included with cancer as an outcome and fish intake as the exposure. **Table 3.7** describes the studies, including study name, study type, number of participants, measurements of seafood consumption and outcome, overall results, risk of bias and overall conclusion.

All ten studies were prospective cohort studies with geographic distribution, including the EPIC cohort with ten countries around Europe, in addition to other cohorts from Denmark, Japan, the Kingdom of the Netherlands, the United Kingdom of Great Britain and Northern Ireland, and the United States.

3.2.4.3.2 Description of study population

The number of study participants varied between the included studies, ranging from 26 749 to 521 324 participants. Median follow-up time, the mean age of the participants, and the number of events varied between the studies.

3.2.4.3.3 Description of fish consumption

Fish consumption was assessed by questionnaires or 24-hour dietary assessment. Fish intake was reported either as frequency or amount.

3.2.4.3.4 Results from the primary studies

3.2.4.3.4.1 Colorectal cancer

Three of the primary studies examined the association between fish intake and colorectal cancer. Aglago *et al.* (2020) used data from the EPIC cohort (521 324 participants, follow-up time – 14.9 years) and found that regular consumption of fish at the recommended levels was associated with a lower risk of colorectal cancer. Etemadi *et al.* (2018) also found an association between fish intake and a decreased risk of colorectal cancer. This study consisted of three US-based cohorts (407 270 participants in all) and had a follow-up time of 13.8 years. The UK study by Bradbury *et al.* (2020) found no association between colorectal cancer and total fish intake. This study had less than half the follow-up time (5.7 years) in comparison to the two other studies, and included 475 581 participants.

3.2.4.3.4.2 Other types of cancer

Three of the studies included, covering different types of cancer, reported an association between fish intake and a lower risk for cancer, including hepatocellular carcinoma, upper gastrointestinal cancer and bladder cancer. One study from two US prospective cohorts (Ma *et al.*, 2019) on hepatocellular carcinoma in 142 857 participants with 32 years of follow-up, suggested an inverse association of fish intake with hepatocellular carcinoma. One study on upper gastrointestinal cancer

risk (Zamani *et al.*, 2020), involving a US-based cohort from six states, with 468 952 participants and with 15.5 years of follow-up, reported an association between non-fried fish intake and a lower risk for head and neck cancer and oesophageal adenocarcinoma. One study (Dianatinasab *et al.*, 2021), including 11 cohorts from different European countries with 518 545 participants and 11.3 years of follow-up, found an inverse association between total fish intake and bladder cancer risk in men, but not in women.

Four studies were included on different types of cancer. All reported no association between fish intake and site-specific cancer, including lung cancer, cancer of unknown primary, biliary tract cancer and prostate cancer. One study from Japan (Cai *et al.*, 2020) investigated the association between fish intake and lung cancer risk in 73 187 participants with 16 years of follow-up time and reported no association between fish intake and lung cancer. Another study, from the Kingdom of the Netherlands, (Hermans *et al.*, 2021) with 120 852 participants and 20.3 years of follow-up, found no association between fish intake and the risk for cancer of unknown primary. One study from a Japan-based cohort (Makiuchi *et al.*, 2020) on biliary tract cancer, including 98 663 participants, reported no association between fish intake and biliary tract cancer risk. One study in a Danish cohort (Outzen *et al.*, 2018) involving 26 749 men with prostate cancer, with 19 years of follow-up, reported no association between any type of fish intake and the risk of prostate cancer.

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER"

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Aglago *et al.*, 2020 European Prospective Investigation into Cancer and Nutrition (EPIC) cohort 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands [Kingdom of the], Norway, Spain, Sweden, the United Kingdom of Great Britain and Northern Ireland)	1992-2014 Cohort study Median follow-up time: 14.9 years. Colorectal cancer (CRC)	n = 521 324 Cases (n = 6 291: mean age 57 years and 43 percent men Non-cases (n = 469 869): Mean age 51 years and 30% men	Fish consumption assessed by a validated centre-specific questionnaire. Total fish and shellfish intake at baseline, mean (SD): Cases: 39 (35) g/day Non-cases: 37 (36) g/day (P< 0.001).	Cases of incident cancer of unknown primary were identified through regional cancer registries or via a combination of methods, including health insurance records, pathology registries and active follow-up of participants and relatives. Cases of cancer of unknown primary were defined according to the International Classification of Diseases for Oncology (ICD-O).	Risk of CRC: Total intake of fish: Quintile 5 vs. 1: HR = 0.88, 95% CI: 0.80, 0.96; P_{trend} = .005 Fatty fish: Quintile 5 vs. 1: HR = 0.90, 95% CI: 0.82, 0.98; P_{trend} = .009 Lean fish: Quintile 5 vs. 1: HR = 0.91, 95% CI: 0.83, 1.00; P_{trend} = .016	B	Regular consumption of fish (total fish, fatty fish, lean fish and shellfish), at recommended levels, was associated with a lower risk of cancer of unknown primary. Overall, weekly intake of 100–200 g of fatty or lean fish was associated with a 7 percent lower risk of cancer of unknown primary.
Bradbury *et al.*, 2020 Diet and colorectal cancer in UK Biobank: a prospective study the United Kingdom of Great Britain and Northern Ireland	2006–2010 Cohort study Average of 5.7 years follow-up Colorectal cancer	n = 475 581 (219 329 men and 256 252 women) 40–69 years at recruitment ercent men = 46.12 percent	Touchscreen questionnaire Subsample of participants (n = 175 402) completed at least one online 24-hour dietary assessment Total fish intake: < once/week; 1.0–1.9 times/week; 2.0–2.9 times/week; ≥3 times/week	Prevalent and incident cancer cases were identified through linkage to cancer and death registries.	Total fish intake and risk of cancer (HR, 95% CI) Reference: < once/week (n = 165) vs. 1.0–1.9 times/week (n = 1 007): 0.98 (0.83,1.16) 2.0–2.9 times/week (n = 643): 0.98 (0.82,1.16) ≥3 times/week (n = 761 cases): 0.95 (0.80,1.13) The HR (95% CI) for each 25-g/day increment in fish was 0.96 (0.86, 1.07). P_{trend} = 0.470	B	No association was found between colorectal cancer and total fish intake.

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Cai *et al.*, 2019 Association between meat and saturated fatty acid intake and lung cancer risk: The Japan Public Health Center-based prospective study Japan	1995–2013 Cohort I, 1998–2013 Cohort II, median 16.0-year follow-up Lung cancer	73 187 participants (32 934 men and 40 253 women) 45 percent men 45–74 years 1 315 (901 men and 414 women) cases of lung cancer	Dietary assessment was performed using the Food Frequency Questionnaire (FFQ)	Cases were identified from major local hospitals in the study area and by data linkage with population-based cancer registries. Death certificate information was used as a supplementary source of data.	Fish intake and risk of lung cancer: Men: Q1 (reference) vs. Q4 intake: HR = 1.09, 95% CI: 0.90, 1.33. Women: Q1 (reference) vs. Q4 intake: HR = 1.01, 95% CI: 0.76, 1.34. Women, Q4, model 3, HR: 1.01 (0.76–1.34).	B	Fish intake was not associated with lung cancer risk in either women or men.
Dianatinasab et al., 2021 The association between meat and fish consumption and bladder cancer risk: a pooled analysis of 11 cohort studies Bladder cancer Epidemiology and Nutritional Determinants consortium (BLEND) These studies originated from 11 countries, Europe: European Prospective Investigation into Cancer and Nutrition cohort studies (EPIC), Denmark, France, Germany, Italy, Netherlands (Kingdom of the), Norway, Spain, Sweden, the United Kingdom of Great Britain and Northern Ireland; Netherlands cohort study (NLCS); North America: VITamins and Lifestyle cohort study (VITAL)	Cohort studies Median follow-up: 11.3 years Bladder cancer	518 545 participants 167 095 (32 percent) men and 351 444 (68 percent) women 2 848 bladder cancer cases and 515 697 non-cases Mean age: 60.6 (± 7.3) for cases and 52.5 (± 10.1) for non-cases	Dietary data were obtained using a self-administered or trained-interviewer-administered food frequency questionnaire (FFQ) that was validated on either food groups and/or energy intake.	Each study ascertained incident bladder cancer cases, defined to include all subjects with urinary bladder neoplasms according to the International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records	Marginally non-significant association between total fish and fish products with risk of bladder cancer comparing highest with lowest tertile (HR = 0.89, 95% CI 0.63, 1.25, P-trend = 0.369). Inverse association between total fish and fish products consumption and bladder cancer risk in men comparing highest with lowest tertile (HR = 0.79, 95% CI: 0.65, 0.97, P-trend = 0.04) was observed, but no association was found in women comparing highest with lowest tertile (HR = 1.07, 95% CI 0.76, 1.51, P-trend = 0.658).	B	Inverse association between total fish and fish products consumption and bladder cancer risk in men, but no association was found in women.

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Etemadi *et al.*, 2018 Anatomical subsite can modify the association between meat and meat compounds and risk of colorectal adenocarcinoma: Findings from three large US cohorts Three US-based studies; NIH-AARP Diet and Health Study (AARP), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), Agricultural Health Study (AHS)	Three cohorts AARP 1995–2011 PLCO 1993–2001–2009 AHS 1993–1997–2013 Overall median follow-up of 13.8 years Colorectal cancer subsites	407 270 participants Age (years) AARP 50–71 years PLCO 55–74 years AHS mean age from baseline in relation to quintiles of red meat intake was 56.9 (Q1), 53.5 (Q2), 52.2 (Q3), 51.6 (Q4), 50.7 (Q5) Sex (percent men) AARP 327 183 participants (191 925 men and 135 258 women) PLCO 49 850 participants (23 761 men and 26 089 women) AHS - Licensed pesticide applicators (farmer and commercial applicators) and spouses of farmer and commercial applicators – 30 237 individuals (16 295 men and 13 942 women)	NCI-Diet History Questionnaire (DHQ)	State cancer registries, medical record abstraction, Linkage to the cancer registries. The cancer endpoints were defined, based on first primary diagnosis, by anatomic site and histologic codes of the International Classification of Diseases for Oncology, third edition	Fish intake was associated with decreased risk of total colorectal cancer (HR = 0.79, 95% CI 0.68, 0.89) (P< 0.001). HR (95% CI) given for each 50 g/1 000 kcal per day increased intake in adjusted models	B	Fish intake was associated with a decreased risk of total colorectal cancer

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Hermans *et al.*, 2021 Meat consumption and cancer of unknown primary (CUP) risk: results from The Netherlands cohort study on diet and cancer The Netherlands cohort study on diet and cancer (NLCS)	Case–cohort design Cases were derived from the full cohort, while the number of person years at risk for the full cohort was estimated from a subcohort of 5 000 participants who were randomly sampled from the full cohort at baseline in 1986 1986–2006 20.3 years of follow-up Cancer of unknown primary (CUP) is a metastasised cancer for which no primary lesion could be identified during life.	120 852 participants 899 CUP cases 55–69 years Total of 92 389 women and 50 468 men (55 percent)	Self-administered questionnaire on diet Based on the distribution of the sub-cohort, participants were compared using quartiles (Q), increments of 25 g/day for fish consumption Fish intake: CUP cases vs subcohort members; 14.1 g/day vs. 12.9 g/day	Record linkage to the Netherlands Cancer Registry and the Dutch Pathology Registry	No associations were observed between fish consumption and CUP risk Increased CUP risk, but it was not statistically significant (Q4 vs. Q1: HR = 1.25, 95% CI 0.99,1.57, Ptrend = 0.29)	B	No associations were observed between fish consumption and CUP risk.
Ma *et al.*, 2019 Meat intake and risk of hepatocellular carcinoma in two large US prospective cohorts of women and men The Nurses" Health Study (NHS) and the of women and men The Nurses" Health Study (NHS) and the Health Professionals Follow-up Study (HPS) US cohorts	Two prospective cohorts 1980–2012 Up to 32 years of follow-up Hepatocellular carcinoma (HCC)	n = 142 857 Total of 92 389 women and 50 468 men (55 percent) NHS: 1976, women, 30–55 years HPFS: 1986, men, 40–75 years 163 incident HCC cases (87 women and 76 men)	Validated semiquantitative food-frequency questionnaire (FFQ) 1980, 1984, 1986 and every 4 years thereafter in the NHS In the HPFS, dietary information collected in 1986 and every 4 years thereafter using similar FFQs. Nine possible intake-frequency responses, ranging from "never" to "more than 6 times a day".	Medical records and pathological reports, the National Death Index for all deaths attributable to liver cancer.	Fish intake was inversely associated with HCC risk (HR = 0.70, 95% CI 0.47, 1.05, Ptrend = 0.10) Suggestive inverse association of fish. The substitution of poultry or fish for 1 SD of processed red meat intake was associated with a decrease in risk of HCC (HR = 0.79, 95% CI 0.61, 1.02).	B	Suggestive inverse association of fish with HCC risk

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Makiuchi *et al.*, 2019 Relationship between Meat/Fish Consumption and Biliary Tract Cancer: The Japan Public Health Center–Based Prospective Study The Japan Public Health Center-based Prospective Study (JPHC Study) Japan	Cohort study 1995 and 1999, until 2012 followed-up for 607 757.0 person-years in men and 728 820.3 person-years in women Biliary tract cancer (BTC)	98 663 participants: 43177 men (43.8 percent) and 49 323 women, 45 to 74 years 217 male and 162 female BTC cases	Food frequency questionnaire (FFQ) The validity of the FFQ for the assessment of meat consumption was evaluated using 14- or 28-day dietary records as the gold standard. Reproducibility of the FFQ was evaluated by administering two questionnaires, 1 year apart. Baseline fish intake: Men Q1; 35.7 g, Q2: 63.9 g, Q3: 92.6g, Q4: 143.8 g. Women Q1: 35.1 g, Q2: 62.7 g, Q3: 89.5 g, Q4: 135.1 g.	Active patient notification from local major hospitals in the study area and data linkage with population-based cancer registries. Death certificate information.	Fish consumption was not significantly associated with biliary tract cancer risk in either men or women. Q1 vs. Q4 fish intake: Men: HR = 1.39, 95% CI 0.92, 2.08. Women: HR = 1.04, 95% CI 0.68, 1.60.	B	Fish was not associated with biliary tract cancer risk in men and women
Outzen *et al.*, 2018 Fish consumption and prostate cancer risk and mortality in a Danish cohort study Danish "Diet, Cancer and Health" cohort Denmark	Prospective cohort study 1993–1997 until 2012–2013 19 year-follow-up period (1993–2012) Prostate cancer	26 749 men, 1 690 prostate cancer cases 50–64 years	Food-frequency questionnaire (FFQ) and a lifestyle questionnaire Both the total fish intake and the intake of subtypes of fish (lean and fatty fish) were analysed as either continuous (increment: 25 g/day) or categorical (quartiles) variables. Total fish intake baseline: Cohort: 41.9 g (12.7–99.0)	Record linkage to the Danish Cancer Registry, Danish Pathology Register, Danish Causes of Death Registry	Overall, no association was found between any type of fish intake and the risk of total or high-grade prostate cancer. Association between total fish intake and prostate cancer Q4 vs. Q1: adjusted RR = 1.12, 95% CI 0.97,1.29, P-trend 0.06 Per 25 g/day, adjusted: adjusted RR = 1.04, 95% CI 1.00,1.09.	B	No association between any type of fish intake and risk of total prostate cancer

TABLE 3.7 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "CANCER" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Zamani et al., 2020 Dietary Polyunsaturated Fat Intake in Relation to Head and Neck, Esophageal, and Gastric Cancer Incidence in the National Institutes of Health–AARP Diet and Health Study National Institutes of Health–AARP Diet and Health Study the United States	Prospective cohort study conducted in 6 states 1995–2011, study duration and 15.5 years median follow-up Upper gastrointestinal cancer risk incidence of head and neck cancer (HNC), oesophageal adenocarcinoma (EA), oesophageal squamous cell carcinoma, and gastric cancer	468 952 participants 275 948 male (58.8 percent) 193 004 females Total HNC; n = 2 453 EA; n = 855 oesophageal squamous cell carcinoma (n = 267) gastric cancer (cardia: n = 603; non-cardia: n = 631)	Dietary data was collected at baseline using a 124-item, self-administered food frequency questionnaire (FFQ) developed and validated by the National Cancer Institute to assess the frequency and portion sizes of foods The FFQ has been validated using two 24-hour recalls as criterion instruments. Total fish intake (g/day): Q1 ≤5.70, Q2 5.71–10.04, Q3 10.05–16.91, Q4 16.92–27.74, Q5 27.75–821.41	Death records, linkage with state cancer registries	Compared with the lowest quintile of total fish/shellfish intake, the highest quintile was associated with a 20 percent lower risk of HNC (HR = 0.80, 95% CI 0.69, 0.91; Ptrend = 0.0002, adjusted P-trend = 0.001), which appeared to be primarily due to consumption of fish high in n-3 PUFAs (HR = 0.76, 95% CI 0.66, 0.87; P-trend < 0.0001, adjusted P-trend = 0.0006) and nonfried fish (HR = 0.83, 95% CI 0.71, 0.96; P-trend < 0.0001, adjusted Ptrend = 0.0006).	B	Non-fried fish intake is associated with lower HNC and EA risk. Fish/shellfish intake was associated with a 20 percent to 27 percent lower risk of HNC and EA.

Note: SD: standard deviation; FFQ: food frequency questionnaire; y: years; HR: hazard ratio; CI: confidence interval; Q: quartile; PLCO: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; AHS: Agricultural health study; NIH: National Institutes of Health; CUP: cancer of unknown primary risk; HNC: head and neck cancer; EA: oesophageal adenocarcinoma; PUFA: polyunsaturated fatty acid

3.2.4.4 Final weight of evidence for "Cancer"

A final weight of evidence for the theme "Cancer" was based on the 2022 VKM report, the 2018 WCRF report and the systematic literature search. An overview of all the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

The weight of evidence for the association between dietary fish intake and cancer was based on the 2018 WCRF report, primary studies and systematic reviews included in the evaluation. The overall weight of evidence of total fish intake associated with pancreatic cancer and breast cancer was graded "limited, no conclusion." Furthermore, the weight of evidence from total fish intake associated with liver cancer and colorectal cancer was graded "limited, suggestive" for a protective effect. Lastly, the association of Cantonese-style salted fish intake with nasopharyngeal cancer was graded "strong evidence" for an increased risk, based solely on the WCRF report.

3.2.5 CARDIOVASCULAR DISEASES AND OUTCOMES

The literature included in the theme "CVD outcomes" includes results from the 2022 VKM report as well as two systematic reviews and ten primary studies originating from the literature search.

3.2.5.1 Summary of the findings on "Cardiovascular diseases and outcomes" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

VKM summarized the evidence of an association between fish consumption and the outcomes of total CVD incidence, coronary heart disease (CHD) incidence, secondary prevention, myocardial infarction (MI) incidence, stroke incidence, ischemic stroke, haemorrhagic stroke, heart failure, atrial fibrillation and venous thromboembolism.

3.2.5.1.1 Total cardiovascular disease incidence

3.2.5.1.1.1 Description of the studies included

The VKM assessment included eight primary studies for the outcome of total CVD incidence. All the primary studies were prospective cohort studies. The diet exposures included total, fatty and lean fish intakes. VKM calculated a summary RR from the primary studies.

The summary RR found a non-significant protective association between total fish intake and CVD incidence (RR = 0.94, 95% CI 0.86, 1.02) with significant heterogeneity (p = 0.01). The heterogeneity was not further explained. No clear effects were found for fatty fish intake (RR = 0.93, 95% CI 0.73, 1.19) nor for lean fish intake (RR = 1.01, 95% CI 0.90, 1.14).

3.2.5.1.1.2 Conclusion, weight of evidence

The evidence was graded "limited, suggestive" for a protective effect of total fish intake on CVD incidence, and "limited, no conclusion" for an effect of fatty or lean fish on CVD incidence.

3.2.5.1.2 Coronary heart disease

3.2.5.1.2.1 Description of the studies included

The VKM assessment included three systematic reviews, two umbrella reviews and ten primary studies for the outcome CHD. All the primary studies were prospective cohort studies. The diet exposures included total, fatty and lean fish, and shellfish intakes.

One of the systematic reviews, Zhang *et al.* (2020), also found a significant protective association between total fish intake and CHD incidence (RR = 0.91, 95% CI 0.84, 0.97), with moderate heterogeneity (I^2 = 47.4 percent). The other systematic review, Bechthold *et al.* (2019), found a non-significant protective association (RR = 0.94, 95% CI 0.88, 1.02), with moderate heterogeneity (I^2 = 52.0 percent). Both systematic reviews performed meta dose-response analyses. Zhang *et al.* found that a 20 g/day increment in fish intake was associated with a 4 percent reduction in CHD incidence and mortality. Bechthold *et al.* showed that an increment in fish intake of approximately 250 g/day was associated with a reduction of approximately 15 percent in the risk of CHD.

The summary RR of the primary studies found a significant protective association between total fish intake and CHD incidence (RR = 0.89, 95% CI 0.81, 0.98). There was significant heterogeneity among the primary studies (p = 0.002), but no report of a statistically significant adverse effect.

VKM's summary RR for fatty fish indicated a protective association between fatty fish intake and CHD incidence (RR = 0.93, 95% CI 0.83, 1.04), while there was no association for lean fish (RR = 0.99, 95% CI 0.93,1.05).

3.2.5.1.2.2 Conclusion, weight of evidence

The VKM assessment graded the evidence "probable" for a protective effect of total fish intake on CHD incidence, "limited, suggestive" for a protective effect of fatty fish, and "limited, suggestive" for no effect of lean fish on CDC incidence.

3.2.5.1.3 Myocardial infarction

3.2.5.1.3.1 Description of the studies included

The VKM assessment included one systematic review and eight primary studies for the outcome of myocardial infarction. The diet exposures included total, fatty and lean fish intakes.

The systematic review, Jayedi *et al.* (2019), showed a protective association (RR = 0.73, 95% CI 0.59, 0.87) of total fish consumption; however,

high heterogeneity was reported (I^2 = 72 percent). The systematic review also performed a meta linear dose–response analysis and found that a 15 g/day increment in fish consumption reduced by 4 percent the risk of myocardial infarction (RR = 0.96, 95% CI 0.94, 0.99).

From the primary studies, VKM calculated a summary RR. All the studies were prospective cohort studies, except for one, which was a nested case-control study. The summary RR reported by VKM suggested no association between total fish intake and incidence of myocardial infarction (RR = 0.96, 95% CI 0.82, 1.12) with borderline statistic significant heterogeneity (p = 0.051). The summary RR reported by VKM suggested a slightly non-significant protective effect of fatty fish (RR = 0.93, 95% CI 0.82, 1.05), $P_{heterogeneity}$ = 0.37), but no effect of lean fish (RR = 1.04, 95% CI 0.94, 1.14), $P_{heterogeneity}$ = 0.54).

3.2.5.1.3.2 Conclusion, weight of evidence

The evidence was graded "limited, suggestive" for a protective effect of total fish intake on incidence of myocardial infarction, "limited, suggestive" for a protective effect of fatty fish, and "limited, suggestive" for no effect of lean fish.

3.2.5.1.4 Total stroke

3.2.5.1.4.1 Description of the studies included

The VKM assessment included four systematic reviews and 19 primary studies for the outcome total stroke. The diet exposures included total, fatty and lean fish, and shellfish intakes.

Two of the systematic reviews found moderate to significant protective associations with low to moderate heterogeneity. Both Zhao *et al.* (2019) and Bechthold *et al.* (2019) found no departure from linearity and the risk of total stroke incidence decreased by 12 to 14 percent, with an increment of 100 g/day of total fish intake.

VKM calculated a summary RR from the primary studies. The summary RR suggested a significant protective association of total fish intake on total stroke incidence (RR = 0.92, 95% CI 0.89, 0.95), without significant heterogeneity (p = 0.67).

VKM also found a non-significant protective association of fatty fish intake on total stroke incidence (RR = 0.92, 95% CI 0.80, 1.05) without significant heterogeneity (p = 0.21). The same was found in one of the systematic reviews. In addition, VKM reported a non-significant protective association of lean fish intake on total stroke incidence (RR = 0.95, 95% CI 0.89, 1.01), without significant heterogeneity (p = 0.51).

In the systematic review, by Zhao *et al.* (2019), intake of shellfish was also investigated. The systematic review found no association of shellfish intake on total stroke incidence (hazard ratio (HR) = 0.96, 95% CI 0.83, 1.11).

3.2.5.1.4.2 Conclusion, weight of evidence

The evidence was graded "probable" for a protective effect of total fish intake on total stroke incidence and "limited, suggestive" for a protective effect of fatty and lean fish on total stroke incidence.

3.2.5.1.5 Ischemic stroke

3.2.5.1.5.1 Description of the studies included

The VKM assessment included three systematic reviews and eight primary studies for the outcome of ischemic stroke. The diet exposures included total fish intake.

VKM calculated a summary RR from the primary studies. The summary RR indicated a protective effect (RR = 0.93, 95% CI 0.86, 1.02), without significant heterogeneity (p = 0.27). This result was consistent with the meta-analysis by Zhao *et al.* (2019), which found: (RR = 0.96, 95% CI 0.89, 1.03).

3.2.5.1.5.2 Conclusion, weight of evidence

The evidence was graded "limited, suggestive" for a protective effect of total fish intake on ischemic stroke incidence. This was based on the calculated summary RR from the primary study and the similar results from the meta-analysis.

3.2.5.1.6 Haemorrhagic stroke

3.2.5.1.6.1 Description of the studies included

The VKM assessment included three systematic reviews and eight primary studies for the outcome haemorrhagic stroke. The diet exposures included total fish intake.

VKM calculated a summary RR from the primary studies. The summary RR indicated a non-significant protective effect (RR = 0.88, 95% CI 0.71, 1.09), without significant heterogeneity (p = 0.29). The systematic review by Zhao *et al.* (2019) found a significant protective association of total fish intake on haemorrhagic stroke (RR = 0.88, 95% CI 0.80, 0.96), with low heterogeneity (I^2 = 0 percent). In addition, Zhao *et al.* identified a linear dose–response relation between total fish intake and haemorrhagic stroke incidence.

3.2.5.1.6.2 Conclusion, weight of evidence

The evidence was graded "limited, suggestive" for a protective effect of total fish intake on haemorrhagic stroke incidence.

3.2.5.1.7 Atrial fibrillation

3.2.5.1.7.1 Description of the studies included

For the outcome of atrial fibrillation, the VKM assessment included one systematic review and five primary studies on total fish intake, four primary studies on fatty fish intake, and three primary studies on lean fish intake.

For total fish consumption, VKM calculated a summary RR from the five studies for the highest versus lowest intake of total fish in relation to atrial fibrillation. The summary RR for total fish suggested an adverse association (RR = 1.06, 95% CI 1.00, 1.13), without significant heterogeneity ($P_{heterogeneity}$ = 0.66). The systematic review, Li *et al.* (2017), based on six prospective cohort studies, indicated no association for the outcome atrial fibrillation, high versus low total fish consumption; (RR = 1.01, 95% CI 0.94, 1.09).

For fatty fish consumption, VKM calculated a summary RR from the four studies for the highest versus lowest intake of fatty fish in relation to atrial fibrillation. The summary RR for fatty fish was not statistically significant (RR = 1.26, 95% CI 0.80, 1.97), with significant heterogeneity ($P_{heterogeneity}$ < 0.001).

For lean fish consumption, VKM calculated a summary RR from the three studies for the highest versus lowest intake of total fish in relation to atrial fibrillation. The summary RR for lean fish suggested a protective association (RR = 0.85, 95% CI 0.73, 0.99), without significant heterogeneity ($P_{heterogeneity}$ = 0.39).

3.2.5.1.7.2 Conclusion, weight of evidence

In conclusion, the evidence by VKM was graded "limited, suggestive" for a potential adverse effect of total fish intake on the risk of atrial fibrillation. For fatty fish consumption, the evidence was graded "limited, no conclusion", while for lean fish consumption, the evidence was graded "limited, suggestive" for a protective effect.

3.2.5.1.8 Heart failure

3.2.5.1.8.1 Description of the studies included

The VKM assessment included one systematic review and eight primary studies for the outcome heart failure. The diet exposures included total, fatty and fried fish intake. Overall, fish intake was associated with a significantly lower risk of heart failure in one of the four studies. In the two studies on fried and non-fried fish, findings were consistent: intake of non-fried (including baked/boiled) fish was associated with lower risk and fried fish with a higher risk of heart failure. In the two studies from Sweden, fatty fish was associated with a statistically significant lower risk (except for the highest intake category) in women, but not in men.

3.2.5.1.8.2 Conclusion, weight of evidence

In conclusion, the evidence by VKM that consumption of fish reduces the risk of heart failure was graded "limited, suggestive".

3.2.5.1.9 Venous thromboembolism

3.2.5.1.9.1 Description of the studies included

The VKM assessment included three primary studies for the outcome of venous thromboembolism. The diet exposures included total fish intake. The study from Norway, Hansen-Krone *et al.* (2014), found no significant association between fish

intake for dinner (fatty or lean) and risk of venous thromboembolism in participants who did not take fish oil supplements (stratified analysis). The US study, Lutsey *et al.* (2009), reported a statistically significant adverse association for the highest versus lowest intake level, and the UK study, Zhang *et al.* (2021b), reported a statistically significant protective association.

3.2.5.1.9.2 Conclusion, weight of evidence

In conclusion, the evidence by VKM that consumption of fish reduces the risk of venous thromboembolism was graded "limited, no conclusion".

3.2.5.2 Summary of findings on "Cardiovascular diseases and outcomes" from the systematic reviews included from the literature search

Two systematic reviews were included from the literature search for "CVD outcomes". The two systematic reviews, Mente *et al.* (2009) and Chowdhury *et al.* (2012), are summarized in further detail in **Table 3.8**. These systematic reviews included the outcomes of total CHD, and total stroke.

3.2.5.2.1 Coronary heart disease

The systematic review, Mente *et al.*, included 29 prospective cohort studies and three RCTs. Because the information on the studies was not available, it was assumed that their exposure was on total fish intake. Mente *et al.* found a protective association of total fish intake on CHD incidence, based on the prospective cohort studies (RR = 0.81, 95% CI 0.70, 0.92), but found no effect, based on the RCTs. They also performed a dose–response analysis using the p values for trend of their studies, but found no linear relation.

3.2.5.2.2 Total stroke

In the systematic review, Chowdhury *et al.*(2012), the authors included 21 prospective cohort studies with total fish intake as the exposure. They found moderate to significant protective association with total stroke incidence (2–4 servings/week versus ≤ 1 serving/week: RR = 0.94, 95% CI 0.90, 0.98); ≥ 5 versus ≤ 1 serving/week: RR = 0.88, 95% CI 0.81, 0.96), with no evidence of heterogeneity (I^2 = 20–22 percent, p > 0.05). They also conducted a meta linear dose–response analysis and found that an increment of two servings/week of total fish (serving size not specified) could reduce the risk of total stroke by 4 percent (95% CI 1–7).

TABLE 3.8 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "CVD OUTCOMES"**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Chowdhury *et al.*, 2012 Association between fish consumption, long chain omega 3 fatty acid, and risk of cerebrovascular disease: systematic review and meta-analysis	Total and cause-specific cerebrovascular disease	General populations, n = 67 5048	n = 29 prospective cohort studies	Standardized categories of fish consumption (2–4 times/week and ≥5 times/week), compared with a reference category (≤1/week).	RR (95% CI): 2–4 servings/week vs ≤1: 0.94 (0.90–0.98) (18 studies); RR (95% CI): ≥5 servings/week vs ≤1 0.88 [0.81–0.96] (8 studies) Dose–response meta-analysis (18 studies) shows an increment of 2 servings/week of any fish was associated with a 4 percent reduced risk of cerebrovascular disease (95% CI 1–7%). All 21 studies showed the RR (95% CI) when comparing participants in the highest with the lowest category of fish intake was 0.88 (0.84–0.93). In a subset of studies, the RR for white fish types was 1.03 (0.90–1.19) and for fatty fish types was 0.84 (0.72–0.98).	Fish consumption is moderately but significantly associated with a reduced risk of incident cerebrovascular disease.	Moderate

Notes: CHD: congenital heart disease, RR: risk ratio, RCT: randomized controlled trial, FFQ: food frequency questionnaire.

TABLE 3.8 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "CVD OUTCOMES" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Mente *et al.*, 2009 A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease	All CHD	All populations, n = 363 228	n = 29 prospective cohort studies	Total fish	Intake of fish was significantly associated with lower risk of CHD RR (95% CI) = (0.81 (0.7–0.92)). Stratification: FFQ (0.78 [0.66–0.90) vs Food Record (1.21 [0.18–2.24)], Men (0.85 [0.70–1.01]) vs Women (0.77 [0.51–1.02]) vs Both (0.78 [0.63–0.94]); the United States (0.80 [0.70–0.95]) vs Europe (0.87 [0.66–1.07]) vs Asia (0.74 [0.47–1.01]); Primary prevention (0.83 [0.73–0.93]) vs secondary prevention (0.45 [0.12–0.79]).	Higher intake of fish was associated lower incidence of total CHD.	Moderate
			n = 3 RCTs	Total fish	Association not significant: RR (95% CI): 1.12 (0.66–1.59)	No evidence of an effect in RCTsxxyyzz	

Notes: CHD: congenital heart disease, RR: risk ratio, RCT: randomized controlled trial, FFQ: food frequency questionnaire.

3.2.5.3 Summary of findings on "Cardiovascular diseases and outcomes" from the primary studies included from the literature search

Ten primary studies were included from the literature search for "CVD outcomes". Detailed information regarding the studies, including study design, participants, fish intake, outcome, and overall results are given in **Table 3.9**. Further, each of specific outcomes according to the outcomes in the 2022 VKM assessment are summarized individually in the following sections.

3.2.5.3.1 Total cardiovascular disease incidence

3.2.5.3.1.1 Description of the primary studies included

Two primary studies were included from the literature search for the outcome "total CVD incidence". Petermann-Rocha *et al.* (2021) conducted a prospective cohort study on 422 791 participants from the United Kingdom of Great Britain and Northern Ireland, including males and females. The participants were categorized as meat-eaters, fish-eaters, fish- and poultry-eaters and vegetarians. "Fish" referred to total fish, and the meat-eaters had fish in the diet. The outcome, total CVD incidence, was defined to include CHD, myocardial infarction, total stroke and heart failure.

Zhong *et al.* (2021) conducted a substitution analysis on six prospective cohort datasets. The cohorts had 29 682 participants from the United States, including males and females. Five dietary exposures (whole eggs, processed meat, unprocessed red meat, poultry and fish) were categorized. The analysis substituted one serving per week (1 serving = 85 g) of one dietary exposure for another. The outcome, CVD incidence, was defined to include CHD, total stroke, heart failure and CVD death.

3.2.5.3.1.2 Results from the primary studies included

Petermann-Rocha *et al.* (2021) found a significant protective association between total fish intake and CVD incidence (HR = 0.93, 95% CI 0.88, 0.97).

Zhong *et al.* (2021) found that substituting one serving per week of fish for eggs and processed meat significantly reduced risks of CVD incidence (HR (95% CI) = 0.98 (0.96, 0.99) and 0.96 (0.94, 0.99), respectively), and the reduced risks further increased if the substitution was one serving per day.

3.2.5.3.2 Coronary heart disease

3.2.5.3.2.1 Description of primary studies included

Five primary studies were included from the literature search for the outcome "CHD" (**Table 3.9**): Matheson *et al.*, 2009; Lajous *et al.*, 2013; Tong *et al.*, 2019; Acosta *et al.*, 2021 and Petermann-Rocha *et al.*, 2021.

Acosta *et al.* conducted a prospective cohort study on 26 900 participants from Sweden, including males and females. "Fish" included both fish and shellfish. The outcome was total atherosclerotic cardiovascular disease, which was defined as a diagnosis of CHD, ischemic stroke, coronary artery disease and peripheral artery

disease (that is, as incidence in the original study).

Lajous *et al.* conducted a prospective cohort study on 79 569 participants from the United States, including males and females. "Fish" was defined as the sum of canned tuna, dark fish, white fish and others (such as breaded fish). Thus, the exposure was treated as total fish intake.

Matheson *et al.* conducted a prospective cohort on 13 355 participants from the United States, including males and females. Shellfish consumption was the dietary exposure (Table 3).

Tong *et al.* conducted a prospective cohort study on 48 188 participants from the United Kingdom of Great Britain and Northern Ireland, including males and females. The participants were categorized as meat-eaters, fish-eaters and vegetarians (combined with vegans).

The study by Petermann-Rocha *et al.* is described in Section 3.2.5, Cardiovascular diseases and outcomes.

3.2.5.3.2.2 Results from the primary studies included

Acosta *et al.* (2021) found total fish and shellfish intake had a significant protective effect against ACVD incidence (HR = 0.95, 95% CI 0.93, 0.98).

Lajous *et al.* found no association between total fish intake and CHD incidence for males (RR = 1.03, 95% CI 0.90, 1.15), but significant protective association for females (RR (95% CI) = 0.87 (0.76-0.98), ≥ 2 servings/week versus 0 times/week). Further, they found that the reduced risk increases with higher intake for females (RR = 0.73, 95% CI 0.57, 0.94, ≥ 3 servings/week versus 0 times/week).

Matheson *et al.* found no association between shellfish intake and CHD incidence (HR = 0.96, 95% CI 0.80, 1.16).

Petermann-Rocha *et al.* found a significant protective association of total fish intake and CHD incidence (HR = 0.79, 95% CI 0.70, 0.88). A similar association was found in Tong *et al.* (HR = 0.87, 95% CI 0.77, 0.99).

Tong *et al.* found a significant protective effect on ischemic heart disease, and that fish-eaters has lower rates of ischemic heart disease than meat-eaters (HR = 0.87, 95% CI 0.77, 0.99).

3.2.5.3.3 Myocardial infarction

3.2.5.3.3.1 Description of the primary studies included

Three primary studies were included from the literature search for the outcome "Myocardial infarction": Gammelmark *et al.*, 2016; Tong *et al.*, 2019 and Petermann-Rocha *et al.*, 2021. (**Table 3.9**).

Gammelmark *et al.* conducted a prospective cohort study on 55 547 participants from Denmark, including males and females. "Fish" included fatty and lean fish, based on the content of ω-3 fatty acids (threshold = 1 g/100 g). Tong *et al.* conducted a prospective cohort study on 48 188 participants from the United Kingdom of Great Britain and Northern Ireland, including males and females. The Petermann-Rocha *et al.* study was described in the section of CVD. The participants were categorized as meat-eaters, fish-eaters and vegetarians (combined with vegans).

3.2.5.3.3.2 Results from the primary studies included

Gammelmark *et al.* found a non-significant protective association of fatty fish intake on myocardial infarction incidence for both genders (HR_{Males} = 0.88, 95% CI 0.77, 1.00), and $HR_{Females}$ = 0.78, 95% CI 0.63, 0.96), but no association for lean fish intake (HR_{Males} = 1.05, 95% CI 0.91, 1.20), and $HR_{Females}$ = 0.93, 95% CI 0.75, 1.14). They found no dose–response relation between fatty fish intake and myocardial infarction incidence. Petermann-Rocha *et al.* found a significant protective association of total fish intake on myocardial infarction incidence (HR = 0.70, 95% CI 0.56, 0.88), while Tong *et al.* found no association (HR = 1.00, 95% CI (0.78, 1.26).

3.2.5.3.4 Total stroke

3.2.5.3.4.1 Description of the primary studies included

Two primary studies were included from the literature search for the outcome "total stroke" (**Table 3.9**): Tong *et al.*, 2019 and Petermann-Rocha *et al.*, 2021. The study by Petermann-Rocha *et al.* was described in the section of CVD, and the study by Tong *et al.* is described in Section 3.2.5, Cardiovascular diseases and outcomes. However, both primary studies used FFQ with dichotomized terms (such as yes/no). While Petermann-Rocha *et al.* conducted the FFQ at the baseline and specified the period (for instance, "Have you consumed fish over the previous year?"), Tong *et al.* used a more general question, without specifying the period (such as "Do you eat fish?") and sent out a follow-up FFQ in 2010 including identical questions.

3.2.5.3.4.2 Results from the primary studies

(Petermann-Rocha *et al.*, 2021) found a significant protective association on total stroke incidence (HR = 0.79, 95% CI (0.63, 0.98), while (Tong *et al.*, 2019) found no association (HR = 1.14, 95% CI 0.94, 1.38). However, in both included studies, no frequency of consumption was given, and the meat-eater group in both primary studies had fish in their diet. This might have caused heterogeneity.

3.2.5.3.5 Ischemic stroke

3.2.5.3.5.1 Description of the primary studies included

Two primary studies were included from the literature search for the outcome "ischemic stroke" (Table 3.9). Venø *et al.* (2018) conducted a prospective cohort study on 55 338 participants from Denmark, including both males and females. A substitution analysis was conducted by substituting fish for red meat or poultry at 150 g/week. The exposure included total, fatty and lean fish (threshold between fatty and lean fish = 1 g/100 g of ω-3 polyunsaturated fatty acid [PUFA]). The study by Tong *et al.* (2019) was described in the section on CHD.

3.2.5.3.5.2 Results from the primary studies

Venø *et al.* found no association between total fish intake and total ischemic stroke incidence, but lower risk of subtypes of ischemic stroke. Tong *et al.* also found no association (HR = 1.05, 95% CI 0.80, 1.39).

3.2.5.3.6 Haemorrhagic stroke

3.2.5.3.6.1 Description of the primary study included

One primary study, Tong *et al.*, 2019, was included from the literature search for the outcome "haemorrhagic stroke" (**Table 3.9**). This study was described in Section 3.2.5, Cardiovascular diseases and outcomes.

3.2.5.3.6.2 Results from the primary study

Tong *et al.* found no association of total fish intake on haemorrhagic stroke incidence (HR = 1.12, 95% CI 0.78, 1.61).

3.2.5.3.7 Atrial fibrillation

3.2.5.3.7.1 Description of the primary study included

One primary study was included from the literature search for the outcome "atrial fibrillation" (**Table 3.9**). The study, Frost *et al.* (2005), was a prospective cohort study from the Danish Diet, Cancer and Health Study, including 47 949 participants. The participants included in the study were both men and women from the general adult population. The study used FFQ to estimate food and fish consumption, relying on the Danish food composition tables. The intake of n-3 from fatty fish was categorized based on the frequency of consumption of herring, mackerel, sardine, trout and salmon, which are readily available and commonly consumed in Denmark.

3.2.5.3.7.2 Results from the primary study included

Frost *et al.* found no significant association between n-3 consumption from fatty fish and the risk of atrial fibrillation or flutter in their study. However, when comparing the highest quantile of intake with the reference category (quantile 1), an increased risk (HR = 1.34, 95% CI (1.02, 1.76) of atrial fibrillation was found.

3.2.5.3.8 Heart failure

3.2.5.3.8.1 Description of the primary study included

One primary study was included from the literature search for the outcome "heart failure" (**Table 3.9**). Petermann-Rocha *et al.* (2021) has already been described in the section on total CVD (3.2.5.3.1.1 Description of the primary studies included).

3.2.5.3.8.2 Results from the primary study included

Petermann-Rocha *et al.* found that after a median follow-up period of 8.5 years, individuals who consumed fish had a lower risk of heart failure compared to meat-eaters, with a HR of 0.78 (95% CI 0.63-0.97) after adjusting for confounding factors. In contrast, there was no significant difference in the risk of heart failure between individuals who consumed fish or poultry compared to meat-eaters, with a HR of 0.94 (95% CI 0.74, 1.20).

3.2.5.3.9 Peripheral arterial disease

3.2.5.3.9.1 Description of the primary study included

One primary study (Lasota *et al.*, 2019) was included from the literature search for the outcome "Peripheral arterial disease" (**Table 3.9**). This was a prospective cohort study from the Danish Diet, Cancer and Health Study, including 54 597 participants, consisting of both men and women from the general adult population. The study used FFQ for estimating food and fish consumption, relying on the Danish food composition tables.

3.2.5.3.9.2 Results from the primary study included

Lasota *et al.* (2019) suggest that substituting poultry and red meat with fish, whether lean or fatty, is associated with a reduced risk of peripheral arterial disease. Specifically, the study found that replacing red meat with total fish, particularly fatty fish, was linked to a lower risk of peripheral arterial disease. Lower risk of peripheral arterial disease was observed when fatty fish replaced unprocessed red meat (RR = 0.89, 95% CI 0.79, 1.00), processed red meat (RR = 0.88, 95% CI 0.78, 1.01), or lean fish (RR = 0.90, 95% CI 0.76, 1.07).

TABLE 3.9 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES"**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Acosta *et al.*, 2021 Malmö Diet and Cancer Study (MDCS) Sweden	Prospective cohort study 1991-1996, median follow-up time: 21.1 years	26 990 participants were included in the final analysis. Incident of atherosclerotic cardiovascular disease (n = 5 858; mean 61.8 years, males: 51.1 percent) No incident (21 132; mean 56.1 years, males: 34.5 percent)	The measurement and intake of fish and seafood were assessed using a 7-day food diary and a 168-item food frequency questionnaire that included foods regularly consumed in the past year. Complementary information was gathered through 1-hour interviews. The intake of fish and shellfish was reported in grams per week.	Risk of incident atherosclerotic cardiovascular disease (ACVD), which was defined as the composite endpoint of coronary artery disease, all-cause ischemic stroke, carotid artery disease, and peripheral arterial disease.	The study found that higher intake of fish and shellfish was associated with a reduced risk of atherosclerotic cardiovascular disease (ACVD) (HR 0.95 per SD increment, 95% CI 0.93–0.98; p = 0.001).	B	The study found that higher intake of fish and shellfish was associated with a reduced risk of atherosclerotic cardiovascular disease (ACVD)
Frost *et al.*, 2005 The Danish Diet, Cancer, and Health Study Denmark	Prospective cohort study 1993–1997 follow-up time: The follow-up time for the study mentioned in the text is not explicitly stated. Mean follow-up: 5.7 years	n = 47 949 Median age: 55.6 years n = 22 528 men (47 percent) n = 25 421 women (53 percent)	The measurement of fish intake in this study was based on a detailed semi-quantitative food frequency questionnaire (FFQ). The study participants were asked to fill in a questionnaire about the type and frequency of fish consumption, and the daily intake of specific foods and nutrients was computed from the FFQ for each participant with the use of the software program FOODCALC.	Incidence of atrial fibrillation or flutter.	Adjusted hazard ratio (HR) (95% CI) of atrial fibrillation or flutter in quantiles of n-3 PUFAs from fish consumption: Quantile 1 (reference): 0 Quantile 2: 0.86 (0.65, 1.15) Quantile 3: 1.08 (0.82, 1.42) Quantile 4: 1.01 (0.77, 1.34) Quantile 5: 1.34 (1.02, 1.76) P for trend = 0.006	B	The overall conclusion of the study was that the intake of n-3 polyunsaturated fatty acids from fish was not associated with a reduced risk of atrial fibrillation or flutter in this cohort of Danish men and women. However, the highest quantile of intake had an increased risk compared to the reference category.

TABLE 3.9 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Gammelmark *et al.*, 2016 The Danish Diet, Cancer and health study Denmark	Prospective cohort study 1993–1997 Median follow-up time: 17 years	n = 55 547 Cases: 3 028 Cases, men: 2 136 (70.5 percent) Median age: 57.7 years Cases women: 892 (29.9 percent) Median age: 59.3 years	Fish and seafood consumption was quantified using a detailed and validated food frequency questionnaire (FFQ). Different species of fish were categorized as either lean or fatty depending on their content of n-3 PUFA, below or above 1 g/100 g, respectively. Fatty fish mainly comprised herring, salmon, trout and mackerel, whereas lean fish comprised mainly plaice, flounder and cod. Intake was measured in grams per day.	The outcome of interest in this study was incident myocardial infarction (MI).	The paper reports that there was a consistent inverse association between high fish intake and incident myocardial infarction (MI). When comparing the highest and the lowest quintile of fatty fish intake, there was a 12 percent lower RR of MI in men (hazard ratio (HR) 0·88; 95% CI 0·77, 1·00) and a 22 percent lower HR in women (HR 0–78; 95% CI 0·63, 0·96), after adjustments.	B	The study found that high intake of fatty fish was inversely related to incident myocardial infarction (MI) in both men and women when comparing the highest and lowest quintiles. However, a clear dose-response relationship could not be established, and the test for trends across quintiles was not statistically significant in the adjusted analyses. Lean fish was not associated with MI. The study supports the current view that consumption of fatty fish may protect against MI.

TABLE 3.9 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Lajous *et al.*, 2013 The Health Professionals Follow-Up Study and the Nurses' Health Study the United States	2 prospective cohort studies: n = 25 979 men: 1990–2008 and n = 53 772 women: 1986–2008	n = 79 569 32.4 percent men 67.6 percent women Two prospective US cohorts: 25 797 men in the Health Professionals Follow-Up Study and 53 772 women in the Nurses' Health Study. At baseline, the average age of male participants was 56.5 years (standard deviation, 9.3). The average age of female participants at baseline was 52.1 years (standard deviation, 7.1). The study collected data on risk factors and disease every 2 years and on diet every 4 years from both cohorts.	The measurement of fish and seafood consumption in the study was conducted using a 127-food item semiquantitative food frequency questionnaire. This questionnaire was first sent to participants in the Health Professionals Follow-Up Study in 1986, to participants in the Nurses' Health Study in 1984 and 1986, and to all participants every 4 years afterward.	The outcome of the study was the risk of coronary heart disease (CHD). The researchers estimated CHD risk under different hypothetical interventions on fish consumption during mid- and later life in two prospective US cohorts of 25 797 men in the Health Professionals Follow-Up Study and 53 772 women in the Nurses' Health Study.	The risk ratios for CHD when comparing the risk if everyone had consumed at least 2 servings of fish per week with the risk if no one consumed fish during the follow-up periods were 1.03 (95% CI 0.90, 1.15) for men and 0.87 (95% CI 0.76, 0.98) for women. The results suggest that increasing fish consumption to at least 2 servings per week in mid- or later life may lower CHD risk in women but not in men.	B	Increasing fish consumption during midlife may lower the risk of coronary heart disease (CHD) in women but not men. The researchers estimated CHD risk under different hypothetical interventions on fish consumption during mid- and later life in two prospective US cohorts, and they observed 1 865 incident CHD cases among men (in 1990–2008) and 1 891 CHD cases among women (in 1986–2008).

TABLE 3.9 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Lasota *et al.*, 2019 Diet, Cancer and Health Study Denmark	Prospective cohort study Established between 1993 and 1997 Median of 13.6 years of follow up	n = 54 597 Median of 13.6 years of follow up 47 percent males: 25 725 53 percent females: 28 872	The measurement of fish and seafood consumption was conducted using a software program based on Danish food composition tables. The participants completed questionnaires about their dietary intake. Substitution of meat or poultry with fish	The measurement of outcome in this study was the incidence of peripheral arterial disease (PAD).	The overall results of this study suggest that substituting poultry and red meat with fish, whether total, lean or fatty, is associated with a lower risk of peripheral arterial disease. Specifically, the study found that replacing red meat with total fish and especially fatty fish was associated with a lower risk of PAD. The replacement of lean fish with fatty fish showed a similar association. No associations with incident PAD could be demonstrated when lean fish replaced poultry, unprocessed red meat or processed red meat. In addition, no association was observed when fatty fish replaced poultry. However, when fatty fish replaced unprocessed red meat (0.89; 95% CI 0.79–1.00), processed red meat (0.88; 95% CI 0.78–1.01), or lean fish (0.90; 95% CI 0.76–1.07), lower risks of PAD were found, although these were not statistically significant.	B	The conclusion of the study was that a higher intake of fish and a lower intake of poultry or red meat were associated with a lower risk of incident peripheral arterial disease. Specifically, replacing red meat with total fish and especially fatty fish was found to be associated with a lower risk of PAD, although the results were only borderline statistically significant. The replacement of lean fish with fatty fish showed a similar association. No associations with the risk of PAD were found in models.

TABLE 3.9 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Matheson *et al.*, 2009 Atherosclerosis Risk in Communities study, a cohort of middle-aged and elderly adults the United States	Prospective cohort study 1987–1989 (baseline) through December 31, 2001. Median follow up not given	n = 13 355 45–64 years 41.8 percent men	Shellfish consumption assessed with a modified version of a previously validated FFQ and participants were departed into three categories: Low: almost never ate shellfish Medium: ate shellfish one to three times per month High: ate shellfish once a week or more Baseline intake: Low: 62 percent Medium: 28 percent High: 9 percent	Incidence of CHD	In total, 1 382 suffered CHD events; 41.8 percent male, 58.2 percent female. Reference group: Low intake vs.: Medium intake: hazard ratio (HR) [95% CI] 0.89 [0.79-1.00] (unadjusted) and 0.96 [0.8-1.16] (adjusted); High intake: HR [95% CI] 0.91 [0.80-1.03] (unadjusted) and 0.98 [0.82-1.18] (adjusted)	B	No association was found between shellfish consumption and the risk of adverse coronary heart disease events. Possibly due to generally low consumption in the cohort, and potentially less healthy way of preparing shellfish among the cohort population compared with that from another existing study.
Petermann-Rocha *et al.*, 2021 General population recruited by UK Biobank the United Kingdom of Great Britain and Northern Ireland	Prospective cohort study 2006–2010 (baseline) up to June 2020 in England and March 2017 in Wales and Scotland. Median follow-up: 8.5 years (CVD incidence) and 9.3 years (CVD mortality).	n = 422 791 37–73 years 55.4 percent women	Diet type assessed with a touch-screen FFQ. Baseline: 94.7 percent meat-eater; fish-eater; vegetarian.	Incident and fatal event due to CVD, IHD, MI, stroke and HF (International Classification of Disease [ICD]s Tenth revision).	106 690 (24 percent) developed CVD and 6 580 died from CVD. Fish eaters had lower risks (in HR) of CVD 0.93, IHD 0.79, MI 0.70, stroke 0.79 and HF 0.78 (adjusted); no association between diets and CVD mortality.	B	Compared with meat-eaters, fish eaters had a lower risk of several cardiovascular outcomes–incident CVD, IHD, MI, stroke, and HF–independent of confounders. People who ate poultry and fish, did not have a lower risk.

TABLE 3.9 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Veno *et al.*, 2018 The Diet, Cancer and Health Cohort Study Denmark	Prospective cohort study 1993–1997 Median follow-up: 13.5 years.	n = 55 338 50–64 years old 47.6 percent men	Diet was assessed using a validated 192-item FFQ, together with a lifestyle questionnaire, and a physical examination. Substitutions of 150 g/week fish for 150 g/week of red meat or poultry	Incident IS and subtypes of IS: an acute disturbance of focal or global cerebral function with symptoms lasting more than 24 hours. Cases identified according to ICD-8 or ICD-10	1 879 IS occurred, with subtypes large artery atherosclerosis (319), cardioembolism (102), small-vessel occlusion (844), other ethology (98) and undetermined ethology (516). No association between total IS incidence and fish replacement. Lower rate of large artery atherosclerosis: HR 0.78 [0.67–0.90] (processed) and 0.87 [0.75–0.99] (unprocessed red meat). Higher rate of cardioembolism when poultry replaced total fish (1.42 [1.04–1.93]). Lower rate of small-vessel occlusion when unprocessed red meat was replaced by fatty fish (0.88 [0.77–0.99]).	B	Fish intake was not associated with risk of total IS but is associated with a lower risk of subtypes.
Tong *et al.*, 2019 EPIC-Oxford cohort the United Kingdom of Great Britain and Northern Ireland	Prospective cohort study 1993–2001. Median follow-up: 18.1 years (follow-up questionnaire sent in 2010, returned between 2010-2013)	n = 48188 Recruitment at 35–59 (general practice) years old and 20+ years old (postal recruitment) 76.6 percent women	Diet groups determined by FFQ: meat eaters (M, include fish), fish eaters (F, no meat at all), vegetarian (V, including vegan). Also, a validated semiquantitative FFQ on dietary intake over the past year.	Outcomes include ischaemic heart disease, including acute myocardial infarction, total stroke including ischaemic stroke and haemorrhagic stroke.	2 820 cases of IHD and 1 072 cases of total stroke recorded. After adjustment, fish eaters had lower rates of ischaemic heart disease than meat eaters (0.87 [0.770.99]). No significant differences between diet groups for the risk of myocardial infarction or ischemic stroke	B	Fish eaters had lower risks of ischaemic heart disease than meat eaters.

TABLE 3.9 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH IN THE THEME "CVD OUTCOMES" (cont.)**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT, MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Zhong *et al.*, 2021 Six prospective cohort studies the United States	Prospective cohort study 1985–2016. Median follow-up: 19.0 (14.1-23.7) years	n = 29682 53.7±15.7 years old 55.6 percent women	Dietary intake determined by a validated diet history or FFQ.	Incident CVD (including CHD, stroke, heart failure and CVD death); all events adjusted by each original cohort.	6 963 incident CVD cases and 8 875 deaths recorded. Substituting (1 serving per week) eggs with fish (+nuts, legumes or whole grains) was associated with 2–3 percent lower risks and 0.4–0.7 percent lower absolute risks for incident CVD; (substitution =1 serving per day) 15–21 percent lower RR and 3.4–4.8 percent lower absolute risks. Substituting processed meat with fish (+nuts, legumes or whole grains) was associated with 4–5 percent lower RR and 0.9–1.2 percent lower absolute risks for incident CVD (1/week); 28–34 percent lower RR and 7.5–9.0 percent lower absolute risks (1/day). Other substitutions with fish are not significant.	B	Substituting fish for eggs and processed meat was associated with lower risks of incident CVD. The reduced risks increase from 1 serving/week to 1 serving/day.

Notes: SD: standard deviation, CI: confidence interval, HR: hazard ratio, PUFA: polyunsaturated fatty acid, IS: ischemic stroke, IHD: ischemic heart disease, CVD: cardiovascular disease, HF: heart failure, RR: risk ratio.

3.2.5.4 Final weight of evidence for "Cardiovascular diseases and outcomes"

A final weight of evidence for the theme "CVD outcomes" was based on the 2022 VKM report and on the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

3.2.5.4.1 Total cardiovascular disease incidence

There is evidence from more than two independent, high-quality cohort studies of the association between total fish intake and reduced risk of total CVD. Among the primary studies and the 2022 VKM report, the direction of association is generally consistent on the protective side, with high heterogeneity. The biological plausibility is evident with a dose-response relation. However, dose-response analysis alone does not contribute to an upgrading factor.

In conclusion, the evidence was graded "limited, suggestive" for a protective effect of total fish intake on total CVD incidence. Due to fewer studies of the incidence of fatty and lean fish on total CVD incidence than studies on the incidence of total fish intake, and as the evidence was not significant, the evidence was graded "limited, no conclusion" for an effect of fatty and lean fish intakes on total CVD incidence.

3.2.5.4.2 Coronary heart disease

Among the literature from the 2022 VKM report and the systematic reviews and primary studies from the literature search, the direction of association is generally consistent on the protective side, but with high heterogeneity. There is evidence of this from more than two independent and high-quality cohort studies. The biological plausibility is evident with a dose–response relation.

In conclusion, the evidence is graded "probable" for a protective effect of total fish intake on CHD incidence. Due to fewer studies of fatty and lean fish, as well as shellfish, the evidence was graded "limited, suggestive" for a protective effect of fatty fish intake on CHD incidence; and the evidence was graded "limited, suggestive" for no effect of lean fish intake, and "limited, no effect" for any effect of shellfish intake on CHD incidence.

3.2.5.4.3 Myocardial infarction

In the 2022 VKM report and the primary studies included from the literature search, the direction of association is generally consistent on the protective side, with some exceptions. In conclusion, the evidence is graded "limited, suggestive" for a protective effect of total fish intake on myocardial infarction incidence. There were a few studies on the effect of fatty and lean fish on myocardial infarction incidence, and the evidence was graded "limited, suggestive" for a protective effect of fatty fish on myocardial infarction incidence and "limited, suggestive" for no effect of lean fish on myocardial infarction incidence.

3.2.5.4.4 Total stroke

Among the included literature from the 2022 VKM report, and the systematic reviews and primary studies from the literature search, the direction of association is generally consistent on the protective side and moderate heterogeneity was reported. There is evidence from more than two independent and good-quality cohort studies on total fish intake. The biological plausibility is evident with a dose–response relation. In conclusion, the evidence is graded "probable" for a protective association for total fish consumption on total stroke incidence. The evidence is graded "limited, suggestive" for a protective effect of fatty and lean fish intake, and "limited, no conclusion" for any effect of shellfish intake on total stroke incidence, due to fewer studies.

3.2.5.4.5 Ischemic stroke

There is evidence from more than two independent and good-quality cohort studies on the effect of total fish intake on ischemic stroke. Among the studies, the direction of association is generally consistent on the protective side with moderate heterogeneity, which was explained. No dose–response analysis was performed.

In conclusion, the evidence is graded "limited, suggestive" for a protective effect of total fish intake on ischemic stroke incidence.

3.2.5.4.6 Haemorrhagic stroke

There is evidence from more than two independent and good quality cohort studies on the effect of total fish intake on haemorrhagic stroke. Among the studies, the direction of association is generally consistent on the protective side with low to moderate heterogeneity. There is biological plausibility with a possible linear dose–response relation.

In conclusion, the evidence is graded "limited, suggestive" for a protective effect of total fish intake on haemorrhagic stroke incidence.

3.2.5.4.7 Atrial fibrillation

In conclusion, the evidence by VKM was graded "limited, suggestive" for a potential adverse effect of total fish intake on the risk of atrial fibrillation. For fatty fish consumption, the evidence was graded "limited, no conclusion"; while for lean fish consumption, the evidence was graded "limited, suggestive" for a protective effect. The literature search included one additional study, which did not change the weight of evidence conclusions from VKM. Thus, the final weight of evidence for the outcome atrial fibrillation are graded "limited, suggestive" for a potential adverse effect of total fish intake, "limited, no conclusion" for fatty fish intake, and "limited, suggestive" for a protective effect of lean fish intake.

3.2.5.4.8 Heart failure

VKM based its conclusion on eight studies that examined heart failure as an outcome. These studies were distinct and did not overlap. The overall trend of the findings consistently leaned towards a protective effect, with low heterogeneity observed. Furthermore, there is supporting evidence for the biological plausibility of these effects.

The summary RR conducted by VKM suggested that there is evidence indicating a protective effect of fish intake on heart failure, except when the fish is fried. In summary, the available evidence suggested that consuming fish may reduce the risk of heart failure, although this conclusion is graded "limited, suggestive". In our search, we found one additional study by Petermann-Rocha *et al.*, (2021), however this study does not alter VKM's conclusion. The overall evidence supporting the notion that fish consumption reduces the risk of heart failure remains graded "limited, suggestive".

3.2.5.4.9 Venous thromboembolism

No additional studies were found in the search, and the evidence regarding fish consumption and reduced risk of venous thromboembolism remains graded "limited, no conclusion."

3.2.5.4.10 Peripheral arterial disease

The search resulted in one study evaluating the risk of peripheral arterial disease and fish intake. A lower risk of peripheral arterial disease was observed when fatty fish replaced unprocessed meat, processed meat and fish. Due to the small number of studies available and potential methodological modifications, the evidence is graded "limited - no conclusion" for the protective effect of fish and fatty fish on the risk of PAD.

3.2.6 TYPE 2 DIABETES

The literature included for the health outcome "Type 2 diabetes" includes results from the 2022 VKM report and seven systematic reviews and one original primary study originating from the literature search.

3.2.6.1 Summary of the findings on "Type 2 diabetes" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

The report included 1 umbrella review, 3 systematic reviews and 16 primary studies for the health outcome T2D.

In the two systematic reviews, which included a meta-analysis (Schwingshackl *et al.*, 2017 and Namazi *et al.*, 2019), no strong evidence for protective or adverse associations between total fish intake and T2D were observed. In the third systematic review, which included a federated meta-analysis, an adverse modest association was

found between total fish, fatty fish and lean fish intake and T2D incidence in women, but not in men (Pastorino *et al.*, 2021).

The summary RR of the primary studies on total fish intake and T2D showed no significant association (RR =1.04, 95% CI 0.96, 1.14) and heterogeneity was high. The summary RR of the primary studies (n =7) on fatty fish intake and T2D proved a protective association (RR = 0.88, 95% CI 0.78, 0.99), and the heterogeneity was borderline significant. For lean fish intake, no significant association was observed, but significant heterogeneity was found.

In conclusion, the evidence of the association between total fish or fatty fish consumption and the risk of T2D was graded "limited, no conclusion", and the association between lean fish intake and T2D was graded "limited, suggestive" (no association).

3.2.6.2 Summary of the findings on "Type 2 diabetes" from systematic reviews included from the literature search

Seven systematic reviews and meta-analyses were included (**Table 3.10**) (Wallin *et al.*, 2012; Wu *et al.*, 2012; Xun *et al.*, 2012; Zheng *et al.*, 2012; Zhou *et al.*, 2012; Zhang *et al.*, 2013 and Muley *et al.*, 2014). All seven included prospective cohort studies with T2D as an outcome. The participants were men and women from the general population. Total fish intake was included in six of the studies, whereas fatty fish, lean fish and shellfish was included in two studies. In addition to overall risk estimates, analyses stratified by geographic region were performed in five of the studies.

The results from all meta-analyses that included total fish intake showed that there were no associations between total fish intake and risk of T2D. However, in all stratified analyses, a higher total fish intake was associated with a higher risk of T2D for Western populations, whereas the opposite was observed for the Asian population.

In one meta-analysis, fatty fish intake was associated with lower risk of T2D. However, no significant association was observed in the other meta-analysis investigating fatty fish intake separately. No significant associations were found between the intake of lean fish or shellfish and T2D.

TABLE 3.10 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "TYPE 2 DIABETES"**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Muley *et al.*, 2014 ALA, Fatty Fish or Marine n-3 Fatty Acids for Preventing DM?: A Systematic Review and Meta-Analysis	Type 2 diabetes	General adult population > 18 years old. Total n = 679 763	n =10 for fish intake n = 7 for total fish n = 2 for fish + shellfish n = 4 for fatty fish n = 3 for lean fish Prospective cohort studies	Information on fish intake was obtained by FFQ and given in mg/day or portions/week	Results from meta-analyses showed that the pooled estimate for fatty fish intake was associated with a reduced risk of T2D (RR = 0.89, 95% CI 0.80, 0.98) with a heterogeneity of I^2 = 0, p = 0.028. No significant association was found between the risk of T2D and lean fish (RR = 1.02, 95% CI 1.03, 1.12) or shellfish (RR = 0.89, 95% CI 0.70, 1.13)	Fatty fish intake, but not lean fish or shellfish, was related to decreased risk of T2D.	Moderate
Wallin *et al.*, 2012 Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective cohort studies	Type 2 diabetes	General adult population Total n = 527 441 T2D cases = 24 082	n = 10 for total fish intake based on 13 cohort studies Prospective cohort studies	11 studies used self-administered FFQ, 5 studies used interview-administered FFQ. Intakes were given as servings/week.	High degree of heterogeneity between the 13 studies included (I^2 = 81.3 percent, p < 0.001) and results across studies were not combined in one overall risk estimate but divided into geographic regions. In the United States, an increased risk of T2D was observed for an increment with one serving of total fish per week (RR = 1.05, 95% CI 1.02, 1.09). In Europe, no significant associations were observed (RR = 1.03, 95% CI 0.96, 1.11). In Asia a decreased risk was observed (RR = 0.98, 95% CI 0.97, 1.00)	Total fish intake was associated with an increased risk of T2D in the United States and with a decreased risk in Asia, and no association was observed for Europe.	Moderate

TABLE 3.10 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "TYPE 2 DIABETES" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Wu *et al.*, 2012 Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis	Type 2 diabetes	General adult population n for fish intake = 481 489 T2D cases: 20 830	For total fish intake, 13 studies included. Prospective cohort studies	Intake based on FFQ. Intakes were given as g/day.	RR for 100g/day. For total fish/seafood intake, no significant association was observed (RR = 1.12, 95% CI 0.94, 1.34). In stratified analyses, a decreased risk of T2D was observed in Asia (RR = 0.89, 95% CI 0.81, 0.98) and an increased risk was observed in the United States/Europe (RR = 1.38, 95% CI 1.13, 1.70). Substantial heterogeneity (I^2 around 80%) was observed among the studies included.	Total fish intake was not associated with increased or decreased risk of T2D in total. However, when geographic regions were investigated, total fish intake was related to lower risk of T2D in Asia and higher risk in the United States / Europe.	Moderate
Xun *et al.*, 2012 Fish consumption and incident diabetes. Meta-analysis	Type 2 diabetes	General adult population n = 438 214	9 studies included (12 independent cohorts) Prospective cohort studies	Fish intake based on FFQ. Intakes were given as servings/week.	Total fish consumption (never or less than once/month vs 2–4 times/week) was not associated with incident diabetes (RR = 1.00, 95% CI 0.85, 1.18). In stratified analyses, lower risk of T2D was observed in Eastern countries (Asia) but not in Western countries. The heterogeneity was good (I^2 = 83.7%, p=0.000).	Overall, no significant association between total fish intake and T2D was observed. However, when geographic regions were investigated, total fish intake was related to lower risk of T2D in Eastern countries but not in Western countries.	Moderate
Zhang *et al.*, 2013. Fish and marine omega-3 polyunsaturated fatty acid consumption and incidence of type 2 diabetes: a systematic review and meta-analysis	Type 2 diabetes	General adult population n = 549 955	10 studies included Prospective cohort studies	Fish intake obtained by FFQ. Reported as g/day.	No significant association between total fish intake and T2D was observed (RR = 1.04, 95% CI 0.89, 1.20). There was significant study heterogeneity (I^2 83%, P < 0.00001). Stratified analyses showed a beneficial effect of fish consumption on T2D risk in the Asian population, but not in the Western population.	Overall, no significant association between total fish intake and T2D was observed. However, when geographic regions were investigated, total fish intake was related to lower risk of T2D in the Asian population.	Moderate

TABLE 3.10 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS INCLUDED FROM THE LITERATURE SEARCH ON "TYPE 2 DIABETES" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Zheng *et al.*, 2012. Marine N-3 polyunsaturated fatty acids are inversely associated with risk of type 2 diabetes in Asians: a systematic review and meta-analysis.							
Zhou *et al.*, 2012. Association of fish and n-3 fatty acid intake with the risk of type 2 diabetes: a meta-analysis of prospective studies.	Type 2 diabetes	General adult population n = 367 757	6 publications included (9 cohort studies). Prospective cohort studies	Fish intake obtained by FFQ. Reported as g/day or categories.	Lowest vs highest category of total fish intake showed no significant association for the risk of T2D (RR = 1.14, 95% CI 0.97, 1.34) with substantial heterogeneity between the studies (I^2 = 79%, p< 0.001). The dose-response relation was also tested in linear analysis. For total fish intake, a significantly higher risk of T2D was observed (RR = 1.04, 95% CI 1.02, 1.05). No between-study heterogeneity was observed (I^2 = 0.00%, p = 0.421).	Higher total fish intake was associated with a modest higher risk of T2D in linear analysis but not in the categorical analysis.	Moderate

Notes: FFQ: food frequency questionnaire, T2D: type 2 diabetes, RR: risk ratio, CI: confidence interval, P: P-value

3.2.6.3 Summary of the findings on "Type 2 diabetes" from primary studies included from the literature search

3.2.6.3.1 Description of the primary study

One primary study by Chen *et al.* (2020) was included (**Table 3.11**). The study is a prospective cohort study, including three subcohorts with participants living in the Ommoord District of Rotterdam, the Kingdom of the Netherlands.

3.2.6.3.2 Description of study population

A total of 6 813 participants ≥ 45 years of age, without diabetes at baseline, were included. The cohort comprised both men and women, with 41.4 percent men. The mean (standard deviation) age at baseline was 65.4 (11.3) years. During a median follow-up time of 7.2 years, 643 T2D cases were documented.

3.2.6.3.3 Description of fish consumption

At baseline, dietary intake was obtained by a validated semi-quantitative 170-item FFQ. For follow-up, a validated semiquantitative 289-item FFQ was used. The participants had a median (25-75th percentile) daily intake of proteins from fish of 2.9 (0.6-5.7) g/day.

3.2.6.3.4 Results from the primary studies included

In multivariable models, intake of protein from fish was associated with an increased risk of T2D (HR = 1.65, 95% CI 1.30,2.10). In sensitivity analyses by age, sex or waist circumferences, the results were similar to those of the main analysis.

TABLE 3.11 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDY (COHORT STUDY) INCLUDED FROM THE LITERATURE SEARCH ON "TYPE 2 DIABETES"**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Chen *et al.*, 2020 The Rotterdam Study Rotterdam, the Kingdom of the Netherlands	Prospective cohort study 1993–2014	m = 6 813 Type 2 diabetes cases = 643 Follow-up time: Median 7.2 years. Mean (SD) 65.4 (11.3) years. 41.4 percent men.	Dietary intake obtained using a validated semiquantitative 170-item FFQ. Protein from fish: median (25th–75th percentile) – 2.9 (0.6–5.7) g/day.	At baseline and follow-up, type 2 diabetes was identified from general practitioners, structured home interviews, pharmacy dispensing records and follow-up examination at the research centre. Type 2 diabetes was defined according to World Health Organization guidelines.	Protein from fish intake was associated with increased risk of type 2 diabetes (HR = 1.65, 95% CI 1.30,2.10).	B	An increased risk of type 2 diabetes was observed with intake of protein from fish.

Notes: SD: standard deviation, FFQ: food frequency questionnaire, HR: hazard ratio, CI: confidence interval

3.2.6.4 Final weight of evidence for "Type 2 diabetes"

A final weight of evidence for the theme "Type 2 diabetes" (T2D) was based on the 2022 VKM report, the 2018 WCRF report and the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

In conclusion, the overall evidence of total fish and fatty fish intake associated with T2D was graded "limited, no conclusion". In addition, the evidence of lean fish intake associated with T2D was graded "limited, suggestive (no association)".

3.2.7 NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS

The literature included in the theme "Neurodevelopment and neurological disorders" includes results from the 2022 VKM report and two original primary studies originating from the literature search. No systematic reviews were included.

3.2.7.1 Summary of the findings on "Neurodevelopment and neurological disorders" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

The VKM report summarizes the evidence of an association between fish consumption and the outcomes of "maternal fish intake and neurodevelopmental outcomes in children", "child fish intake and neurodevelopment in children", "fish intake and neurocognitive and psychiatric endpoints in adults", and "fish intake and depression and other psychiatric symptoms in adults".

3.2.7.1.1 Maternal fish intake and neurodevelopmental outcomes in children

3.2.7.1.1.1 Description of the studies included

The VKM assessment included one systematic review (Hibbeln *et al.*, 2019) and 22 original primary studies investigating the association between maternal fish intake and neurodevelopmental outcomes in children.

The systematic review from Hibbeln *et al.* (2019) included 29 prospective cohort studies (106 237 mother–child pairs), which evaluated the relationship between maternal seafood consumption in pregnancy or during lactation and neurodevelopmental outcomes in the infant. The systematic review concluded that there was moderate and consistent evidence that maternal seafood consumption in pregnancy is associated with improved neurocognitive development of offspring as compared to eating no seafood. However, the evidence does not meet the criteria for "strong evidence", as there is a lack of RCTs.

Of the 22 primary studies, two were RCTs involving lean fish consumption and the rest were prospective birth cohort studies. The majority of the studies incorporated in the analysis originated from European countries, including Denmark, Italy, Norway, the Kingdom of the Netherlands, Spain, Sweden and the United Kingdom of Great Britain and Northern Ireland. Five studies were conducted in the United States, while one study focused on findings from Japan. These studies encompass

a range of large-scale cohorts, such as the Avon Longitudinal Study of Parents and Children; the Spanish Childhood and Environment project; Project Viva; Generation R; the Norwegian Mother, Father and Child Cohort Study and the Danish National Birth Cohort. Additionally, smaller studies with more limited sample sizes were also included. Most of the studies reported total fish intake, which included a summarization of all fish. Some studies also had subanalyses including lean and fatty fish.

3.2.7.1.1.2 Conclusion, weight of evidence

In summary, the direction of associations was generally consistent towards a protective effect of maternal fish consumption. In addition, there was limited, unexplained heterogeneity and evidence for biological mechanisms. However, the neurodevelopmental domains, age at assessment and assessment tools for neurodevelopment varied substantially from study to study.

In conclusion, the evidence for a protective association between maternal total fish consumption and child neurodevelopment was graded "limited, suggestive". There were fewer studies of fatty fish and lean fish than of total fish. As such, the evidence for the effects of fatty fish and lean fish on child neurodevelopment was graded "limited, no conclusion".

3.2.7.1.2 Child fish intake and neurodevelopmental outcomes in children

3.2.7.1.2.1 Description of the studies included

The VKM assessment included one systematic review (Hibbeln *et al.*, 2019) and ten primary studies investigating child fish intake and child neurodevelopment outcomes.

The systematic review by Hibbeln *et al.* included six RCTs, four prospective cohort studies and nine case-control studies, including 25 960 children altogether. The authors concluded that there was moderate and consistent evidence indicating that seafood consumption during childhood has beneficial associations with neurocognitive outcomes.

Of the primary studies, four RCTs and two prospective cohort studies studied fatty fish intake and cognition in children aged 4–18 years. Two RCTs and one prospective cohort reported findings on child fish intake and mental health from birth until 18 years of age. One prospective study reported findings on child fish intake and early child development (≤3 years). Two RCTs were from Norway, one was from Denmark and one was from Germany. The prospective studies were from Sweden and the United Kingdom of Great Britain and Northern Ireland. All studies included both girls and boys and two studies stratified the analyses by sex.

Two publications involving child cognition reported associations between total fish intake in adolescents at 15 years of age and school grades at 16 years and cognitive abilities at 18 years. Both studies reported significantly better scores with higher fish intake for all outcomes. One of the RCTs in preschool children significantly reported larger improvements in the fish-intervention group compared to the control

group in two subtests for the cognitive outcomes, but not for the 15 remaining comparisons. The other RCT study in preschool children reported no significant effects of the fish intervention compared to meat on any outcome. In four of the studies reporting findings from RCTs, estimates were presented unadjusted and adjusted for dietary compliance.

For the mental health outcomes, one RCT in preschool children reported no significant effect on scores of the Strengths and Difficulties Questionnaire. The RCT in school-aged children reported significant difference between groups in 2 out of 17 included subtests; while the RCT in adolescents reported a protective effect of fish on emotional problems and total problems in the dichotomized scores, but no such effects for the four remaining outcomes and no protective effect when scores were used on a continuous scale. The one prospective study reported no significant associations between child total fish intake at three years and mental health problems.

3.2.7.1.2.2 Conclusion, weight of evidence

In the four prospective cohort studies on the association between total child fish intake and neurodevelopment, two suggested a beneficial association in all included comparisons and one in parts of the comparisons, while two reported no significant associations. In these prospective studies, the age at outcome assessment ranged substantially (from 15 months to 18 years) and, although the two studies in adolescents reported protective associations, overall conclusions were limited by the difference in outcome measures. The direction of the effects and associations are generally consistent towards protection from fish intake with little unexplained heterogeneity and there was evidence for biological mechanisms between child fish intake and neurodevelopment (biological plausibility).

There was evidence from four independent RCTs involving fatty fish interventions and four independent prospective cohort studies on total fish intake. Findings were limited by multiple included outcome measures, multiple methods of outcome measurement, multiple comparisons, and substantial age differences at outcome assessment. In conclusion, the evidence was graded "limited, suggestive" for child fish consumption (total and fatty fish) benefitting neurodevelopment. There were few studies focusing on lean fish and, as such, this was graded "limited, no conclusion".

3.2.7.1.3 Fish intake and neurocognitive and psychiatric endpoints in adults

3.2.7.1.3.1 Description of the studies included

To investigate the association between fish intake and neurocognitive and psychiatric endpoints in adults, the outcomes included were incidence of dementia and Alzheimer's disease, risks or symptoms of cognitive decline, and general cognition.

The VKM assessment included four systematic reviews investigating the association between fish intake and cognitive decline in adults. These included the outcomes of risk of dementia and Alzheimer's disease. All four systematic reviews showed that a higher consumption of fish was associated with a lower risk of dementia and

Alzheimer's disease:

- Kosti *et al.*, 2022: Highest versus lowest intake of fish:
  - Risk of dementia: n = 9 prospective cohort studies. Summary RR = 0.80, 95% CI: 0.69, 0.93.
  - Risk of Alzheimer's disease: n = 7 prospective cohort studies. Summary RR = 0.74, 95% CI: 0.63, 0.87.
- Bakre *et al.*, 2018: Consumed fish (or consumed fish at a higher level) compared with those who did not eat fish (or consumed fish at a lower level):
  - Risk of dementia: n = 15 prospective cohort studies and cross-sectional studies. Summary RR = 0.80, 95% CI: 0.74, 0.87.
  - Risk of Alzheimer's disease: n = 7 prospective cohort studies and cross-sectional studies. Summary RR = 0.73, 95% CI: 0.65, 0.82.
- Zeng *et al.*, 2017: Highest versus lowest intake of fish:
  - Risk of dementia: n = 6 prospective cohort studies. Summary RR = 0.86, 95% CI: 0.73, 1.02
  - Risk of Alzheimer's disease: n = 7 prospective cohort studies. Summary RR = 0.80, 95% CI: 0.65, 0.97.
- Zhang *et al.*, 2015: Increment of 1 serving/week of fish:
  - Risk of dementia: n = 4 prospective cohort studies. Summary RR = 0.95, 95% CI: 0.90, 0.99
  - Risk of Alzheimer's disease: n = 5 prospective cohort studies. Summary RR = 0.93, 95% CI: 0.90, 0.95.

The VKM assessment included 24 primary studies in the evaluation of fish intake and risk of neurocognitive and psychiatric endpoints in adults. All the studies were prospective cohort studies, most originating from European countries, but some also from the United States and from Asian countries. All studies included total fish as the exposure, while one study also separated into fatty fish. VKM calculated a summary RR of the three outcomes: risk of dementia, risk of Alzheimer's disease and risk of cognitive decline:

- Risk of developing dementia: n = 5 prospective cohort studies, highest versus lowest intake of total fish. Summary RR = 0.85 (95% CI: 0.75, 0.96) without significant heterogeneity (Pheterogeneity = 0.37).
- Risk of developing Alzheimer's disease: n = 4 prospective cohort studies, highest versus lowest intake of total fish. Summary RR = 0.95 (95% CI: 0.84, 1.08) without significant heterogeneity (Pheterogeneity = 0.34).
- Risk of cognitive decline: n = 8 prospective cohort studies, highest versus lowest intake of total fish. Summary RR = 0.81 (95% CI: 0.73, 0.89) with significant heterogeneity (Pheterogeneity = 0.004).

3.2.7.1.4 Conclusion, weight of evidence

Based on the systematic reviews and primary studies, VKM concluded that there is evidence that total fish intake reduces the risk of dementia, Alzheimer's disease and cognitive decline. This was determined as there was no substantial heterogeneity between the studies and there was evidence for several plausible mechanisms, and in view of reported dose–response relationships from one meta-analysis.

In conclusion, the evidence that consumption of total fish reduces the risk of dementia, Alzheimer's disease and cognitive decline was graded "probable".

The number of studies conducted on fatty fish and lean fish was lower than those considering total fish. Thus, the available evidence on the impact of fatty fish and lean fish on the risk of dementia, Alzheimer's disease and cognitive decline was graded "limited, no conclusion."

3.2.7.1.5 Fish intake and depression in adults

3.2.7.1.5.1 Description of the studies included

The VKM assessment included four systematic reviews with meta-analyses investigating the association between fish intake and depression and other psychiatric symptoms in adults. The results of the four systematic reviews varied, though most of them pointed to a protective effect of higher fish consumption being associated with lower risk of developing depression:

> Matison *et al.* 2021: Fish intake. n = 3 prospective cohort studies and risk of depression in adults >45 years. Summary RR = 1.00, 95% CI: 0.80, 1.26.

> Yang *et al.*, 2018: Highest versus lowest intake of fish. n = 10 prospective cohort studies in adults. Summary RR = 0.89, 95% CI: 0.80, 0.99.

> Grosso *et al.*, 2016: Highest versus lowest intake of fish. n = 10 prospective cohort studies in adults. Summary RR = 0.83, 95% CI: 0.70, 0.97.

> Li *et al.*, 2016: Highest versus lowest intake of fish. n = 10 prospective cohort studies in adults. Summary RR = 0.84, 95% CI: 0.75, 0.94.

The VKM assessment included 13 primary studies in the evaluation of the association between fish consumption and the risk of depression and other psychiatric symptoms in adults. Of these, 10 studies assessed the risk of depression, and three assessed postpartum depression. All 13 primary studies were prospective cohort studies. Four were conducted in Europe, four in the United States, one in Australia, and four in Asian countries. All the studies included the association of total fish consumption with the outcomes, while one study also included fatty fish consumption. Based on the primary studies, VKM calculated summary RRs for the outcomes of depression and postpartum depression:

> Risk of developing depression: n = 8 prospective cohort studies. Summary RR = 0.88 (95% CI: 0.79, 0.98) without significant heterogeneity (Pheterogeneity = 0.64).

> Risk of developing postpartum depression: n = 2 prospective cohort studies, highest versus lowest intake of fish in pregnancy. Summary RR = 0.79 (95% CI: 0.66, 0.95) without significant heterogeneity (Pheterogeneity=0.14).

3.2.7.1.6 Conclusion, weight of evidence

Based on the systematic reviews and primary studies, VKM concluded that there was some evidence that fish intake can have a protective effect on developing depression in adults. The direction of the associations was generally consistent towards a protective effect and the heterogeneity was low. However, the plausible mechanisms were not fully explained, and the dose–response relationship was not given.

In conclusion, the evidence that consumption of total fish reduces the risk of depression in adults and post-partum depression in adults was graded "limited, suggestive". There were fewer studies of fatty fish and lean fish than studies of total fish and, as such, the evidence was graded "limited, no conclusion" for the effects of fatty and lean fish on adult depression and postpartum depression.

3.2.7.2 Summary of the findings on "Neurodevelopment and neurological disorders" from the primary studies included from the literature search

3.2.7.2.1 Description of the primary studies

Two primary studies, one RCT study by Al-Ghannami *et al.* (2019) and one birth cohort study by Mesirow *et al.* (2017), were included under the category "Neurodevelopment and neurological disorders". A description of the studies, including study name, design, time period, study population, intake of fish consumption and overall results, can be found in **Table 3.12** and in **Table 3.13**.

3.2.7.2.2 Description of study population

The Al-Ghannami *et al.* RCT study included n =132 children (mean age, 9.5 years) in Oman. The Mesirow *et al.* birth cohort study included 5 727 mother–child pairs from the Avon Longitudinal Study of Parents and Children study in the United Kingdom of Great Britain and Northern Ireland, where fish consumption was investigated at 32 weeks gestation and children were followed up between 3 and 13 years.

3.2.7.2.3 Description of fish consumption

In the RCT study, the children were randomized to receive either daily supplements with omega-3 (DHA) or a daily lunch comprising 100 g of lightly grilled fish sandwich for 12 weeks. In the birth cohort, fish consumption was measured from a validated FFQ at gestational week 32.

3.2.7.2.4 Results from the primary studies

The RCT study with fish or omega-3 supplements in children investigated the effects on several behavioural and cognitive functions using standardized tests. The 12 weeks of intervention with fish oil versus fish meals demonstrated a better effect of fish oil supplementation than fish meals on cognitive and behavioural functioning in children.

The birth cohort study showed that a diet low in fish in pregnancy was associated with early-onset persistent conduct problems, co-occurring difficulties in early adolescence (parent-reported) and increased emotional difficulties.

TABLE 3.12 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDY (INTERVENTION STUDY) INCLUDED FROM THE LITERATURE SEARCH ON "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS"

AUTHOR, YEAR REGION, COUNTRY	STUDY TYPE STUDY DURATION AND FOLLOW-UP TIME	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) AT EXPOSURE ASSESSMENT SEX (PERCENT, MEN)	MEASUREMENT AND INTAKE OF FISH AND SEAFOOD CONSUMPTION AT BASELINE	INTERVENTION AND CONTROL GROUP INFORMATION REGARDING INTERVENTION, DURATION, DOSE	MEASUREMENT OF OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Al-Ghannami *et al.*, 2019 Muscat, Oman	Randomized open-label trial 12 weeks of intervention with fish oil versus fish meals	n = 132 (66 in each intervention group) Mean (SD) age: 9.5 (0.5) years 40.9% boys in the fish oil group, 45.5% boys in the fish meal group	No information on diet at baseline, but groups had similar levels of PUFAs (EPA, DHA, DPA) at baseline. Fish oil group: Sum PUFAs mean (SD) 4.8 (1.7) Fish meal group: 4.7 (1.8)	12-week intervention period during weekdays when school was in session. Fish meal group: Daily lunch comprising 100 g of lightly grilled fish sandwich (grouper, sea beam, king fish, emperor or snapper). 100 g grilled fish was estimated to provide 150–200 mg DHA. Fish oil group: capsules containing 403 mg DHA daily during lunch break.	Main outcomes were behavioural (ADHD symptoms) and cognitive function. Three tests were used to assess various domains of cognitive function: verbal ability, learning and remembering, and executive functioning: the verbal fluency test to examine lexical ability and initiation speed of verbal responses; the Buschke Selective Reminding Test to tap into immediate recall (working memory and attentional capacity) and a trail-making test was used as part B. A standardized Arabic version of the Vanderbilt Assessment Scales-Teacher Assessment Scale was used to examine behavioural and emotional functioning.	The mean (SE) score for the Vanderbilt Assessment Scales measuring symptoms of ADHD for the fish-oil group was 22.1 (2) for the pretest and 23 (2.4) at post-test. For the fish-meal group the score was 25.7 (2.2) at pretest and 18 (2.1) at post-test. The mean difference of change between the groups was significant ($P < 0.001$). Cognitive function: Only the trail-making test for executive functioning showed a difference between the groups. Median (IQR) difference between pre- and post-intervention was 61.5 (19.3, 103.2) in the fish-oil group and 24.5 (-15.2, 74.7) in the fish-meal group ($P = 0.005$).	B	12 weeks of intervention with fish oil versus fish meals demonstrated a better effect of fish oil supplementation than fish meals on cognitive and behavioural functioning in children in Oman.

Notes: SD: standard deviation, PUFA: polyunsaturated fatty acid, EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, DPA: docosapentaenoic acid, ADHD: attention deficit hyperactivity disorder, SE: standard error, IQR: interquartile range

TABLE 3.13 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDY (COHORT STUDY) INCLUDED FROM THE LITERATURE SEARCH ON "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS"

REFERENCE AUTHOR, YEAR TRIAL OR STUDY NAME REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Mesirow *et al.*, 2017. ALSPAC study the United Kingdom of Great Britain and Northern Ireland	Birth cohort study	n = 5 727 mother–child pairs. Children 3 years old at baseline. Follow up 4–13 years	Dietary data were collected from a validated FFQ. Mothers' intake at 32 weeks gestation and report of what the mother fed her child at 38 months of age (3 years).	Early-onset persistent conduct problems (EOP CP) were created using parent-reported SDQ conduct problem scale.	Compared to low CP, mothers of EOP children consumed less fish ($P < 0.01$). For EOP, less than two servings of fish/week was associated with increased emotional difficulties.	B	Prenatal and postnatal diets low in fish were associated with an EOP CP trajectory and co-occurring difficulties in early adolescence.

Notes: ALSPAC: Avon Longitudinal Study of Parents and Children, SDQ: Strengths and Difficulties Questionnaire, FFQ: food frequency questionnaire

3.2.7.3 Final weight of evidence for "Neurodevelopment and neurological disorders"

A final weight of evidence for the theme "Neurodevelopment and neurological disorders" was based on the 2022 VKM report and the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

In the VKM report, the outcomes "maternal fish intake and neurodevelopment in children", "child fish intake and neurodevelopment in children", "neurocognitive and psychiatric endpoints in adults" and "depression in adults" were evaluated and the evidence was graded. No additional systematic reviews were identified and only two primary studies were identified in addition to the VKM report. The two primary studies included the outcomes of child mental health (parent-reported persistent problems) and behavioural and cognitive function in children. When comparing the evaluation of the weight of evidence in the primary studies with that of the VKM report, the primary studies did not change this conclusion.

Therefore, in conclusion, the final weight of evidence for the association between "maternal total fish intake and neurodevelopment in children" and "child total and fatty fish intake and neurodevelopment in children" is graded "limited, suggestive". The evidence for the association between "total fish consumption and neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease and cognitive decline) is graded "probable, suggestive". The evidence of the association between "total fish consumption and depression and post-partum depression in adults" is graded "limited, suggestive".

3.2.8 MORTALITY

3.2.8.1 Summary of the findings on "Mortality" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

3.2.8.1.1 Description of the literature included

The VKM assessment included nine systematic reviews and meta-analyses (three umbrella reviews and six meta-analyses) on the association between fish intake and mortality. A significant inverse association between fish intake and all-cause mortality was concluded from four meta-analyses and one meta-analysis among T2D patients. An inverse association was also found between fish intake and mortality from cardiovascular disease (CVD) and coronary heart disease (CHD).

The VKM assessment included 25 primary studies of fish intake and all-cause mortality, as well as cause-specific mortality, in addition to five primary studies, including patient-based populations with CVD/CHD/MI, and three primary studies with diabetes populations.

The primary studies included in the VKM report were from several different countries, including Australia; China; China, Hong Kong SAR; Denmark; Finland; the Islamic Republic of Iran; Italy; Japan; the Kingdom of the Netherlands; Norway; Spain; Sweden; the United Kingdom of Great Britain and Northern Ireland and the United States.

3.2.8.1.2 Weight of evidence

3.2.8.1.2.1 Mortality from Alzheimer's disease

The VKM assessment included two primary studies on fish intake and mortality from Alzheimer's disease. The summary RR (RR = 0.76, 95% CI 0.53, 1.09) was not statistically significant and the evidence for an association between fish intake and mortality from Alzheimer's was graded "limited, no conclusion".

3.2.8.1.2.2 Mortality from cardiovascular disease

The VKM assessment included 20 primary studies on fish intake and mortality from CVD. Eighteen studies included participants from the general population while two were on patients with prior CVD or high risk of CVD from vascular disease, or having T2D.

The summary RR for total fish and CVD mortality indicated a protective association for the highest versus lowest intake (RR = 0.92, 95% CI: 0.86, 0.98). For intake of fried fish (two studies), VKM's summary RR suggested a small, increased risk of CVD mortality (RR = 1.03, 95% CI: 0.99, 1.07). For non-fried fish (three studies), VKM's summary RR suggested no association with CVD mortality (RR = 0.89, 95% CI: 0.67, 1.19). For total fish intake in the patient-based populations, VKM's high–low summary RR for CVD mortality in patients with a CVD history or at high risk of CVD (one publication, three studies) suggested a statistically significant, lower risk (RR = 0.84, 95% CI: 0.77, 0.92) without significant heterogeneity ($P_{heterogeneity}$ = 0.66).

Lower CVD mortality for the highest intakes of total fish (18 studies) was indicated by VKM according to the summary RR for primary studies. In one primary study with patients with T2D, a statistically significant protective association was observed. VKM reported evidence for an inverse dose–response relation from two independent meta-analyses as an upgrading factor.

VKM concluded that the published evidence suggested a protective association between fish intake and CVD mortality that was statistically significant. The evidence was graded "probable" for a protective effect of fish consumption on CVD mortality in the general population.

3.2.8.1.2.3 Mortality from total heart disease

The VKM assessment included two primary studies on mortality from all heart conditions as the outcome, both from the United States. One study demonstrated a protective association, while the other study demonstrated no significant association. VKM concluded that the evidence that fish intake was associated with mortality from all heart diseases was graded "limited, no conclusion".

3.2.8.1.2.4 Mortality from coronary heart disease

The VKM assessment included 22 primary studies on mortality from CHD as the outcome, three studies included CHD mortality in patient-based populations

– survivors of CHD or MI or populations with T2D. VKM's high–low summary RR, based on 18 studies, indicated lower CHD mortality for high overall fish intakes (RR = 0.91, 95% CI: 0.82, 1.01). The estimate was borderline statistically significant without significant heterogeneity ($P_{heterogeneity}$ = 0.16). VKM's high–low summary RR for CHD mortality in patients with coronary artery disease was based on two studies of secondary prevention with few cases and did not suggest an association with total fish intake (RR = 1.03, 95% CI: 0.58, 1.84), $P_{heterogeneity}$ = 0.99). A dose–response meta-analysis was also included where an increase in fish intake by 20 g/day was associated with a 4 percent reduction in CHD mortality and a suggested threshold with no further risk reduction above 60 g/day fish intake. The evidence was graded "probable" for a protective effect of fish intake on CHD mortality. Two pooled studies with results on fatty and lean fish were included, where the high–low summary RR (95% CI) for fatty fish was 0.94 (0.81–1.10) without significant heterogeneity, and 0.95 (0.75–1.21) for lean fish, also without significant heterogeneity. The evidence was graded "limited, no conclusion" for the effects of fatty and lean fish on CHD mortality.

3.2.8.1.2.5 Mortality from myocardial infarction

The VKM assessment included five primary studies on mortality from MI. The summary RR indicated significantly lower MI mortality for the highest versus lowest intakes (RR = 0.63, 95% CI: 0.46, 0.85). Heterogeneity was significant ($P_{heterogeneity}$ = 0.01), but all estimates were consistent in the direction of the association. The evidence that consumption of total fish reduces MI mortality was graded "probable".

3.2.8.1.2.6 Mortality from stroke and stroke sub-types

The VKM assessment included 12 studies (prospective, observational in the general population on the mortality from total stroke/CVD). Among the studies, eight were based on study populations in Asia and five on populations in the United States, most included both men and women. The summary RR reported from VKM for fish overall intake indicates lower mortality of total stroke (RR = 0.86, 95% CI: 0.81, 0.90), without significant heterogeneity ($P_{heterogeneity}$ = 0.64).

For subtypes of stroke, the haemorrhagic stroke mortality RR, based on six studies, was statistically significant (RR = 0.86, 95% CI: 0.78, 0.96, $P_{heterogeneity}$ = 0.64), indicating lower mortality for the highest overall fish intake. The summary RR for ischemic stroke was not statistically significant (RR = 0.92, 95% CI: 0.82,1.03, $P_{heterogeneity}$ = 0.36).

The evidence that consumption of fish reduces stroke mortality was graded "probable". For subtypes of stroke, the evidence was graded "limited, suggestive" for a protective effect of total fish intake on both ischemic stroke and haemorrhagic stroke mortality.

3.2.8.1.2.7 Mortality from type 2 diabetes

The VKM assessment included four publications on cause-specific mortality from T2D (prospective, observational design), all from China or the United States and including both men and women. Three of the studies were from general population groups, while one study was in a population with T2D.

The summary estimates from the three studies from the general population were not statistically significant (summary RR = 0.92, 95% CI: (0.59, 1.43) with borderline significant heterogeneity ($P_{heterogeneity}$ = 0.048). The evidence was graded "limited, no conclusion" for an effect of total fish intake on T2D mortality.

3.2.8.1.2.8 All-cause mortality

The VKM assessment included 23 primary studies (prospective, observational design) on the association between fish intake and all-cause mortality. A statistically significant protective association (RR = 0.93, 95% CI: 0.90, 0.97), and significant heterogeneity ($P_{heterogeneity}$ < 0.001) was found for overall fish consumption based on these publications.

Regarding overall fish intake in patients with previous CVD or at high risk of CVD, the RR suggested a statically significant protective association based on four prospective studies (RR = 0.83, 95% CI: 0.76, 0.90) without significant heterogeneity ($P_{heterogeneity}$ = 0.50). For overall fish intake in subpopulations with T2D, the RR for all-cause mortality (RR = 0.95, 95% CI: 0.90, 1.01), based on five studies, suggested a protective association as well.

For intake of fried fish (high–low intake) in relation to all-cause mortality (three studies), VKM suggested a potentially small increased risk based on the summary RR (RR = 1.02, 95% CI: 1.00, 1.03, $P_{heterogeneity}$ = 0.74). For non-fried fish (four studies), the summary RR by VKM suggested a protective association that was borderline statistically significant (RR = 0.93, 95% CI: 0.86, 1.00, $P_{heterogeneity}$ = 0.16).

In conclusion, the evidence was graded "probable" for a protective effect of fish consumption on all-cause mortality in the general population. The evidence for an effect of fatty and lean fish on all-cause mortality was graded "limited, no conclusion", based on one study.

3.2.8.2 Summary of the findings on "Mortality" from the systematic reviews included from the literature search

Three systematic reviews (He *et al.*, 2004; Geelen *et al.*, 2007 and Szymanski *et al.*, 2010) were included under the category "mortality". A summary of the main outcome, population, studies included, seafood intake, overall results and conclusion is provided in **Table 3.14**.

The systematic review by Szymanski *et al.* (2010) included a meta-analysis of fish intake and prostate cancer-specific mortality, including four cohort studies with 49 661 men and 740 fatal prostate cancers. The overall results demonstrated that high consumption of fish was associated with a significant reduction in prostate cancer-specific mortality.

The meta-analyses by Geelen *et al.* (2007) investigated the association between fish consumption and colorectal cancer mortality, including four cohort studies ranging from 3 158 to 265 118 persons (both men and women) in the different cohorts. This meta-analysis demonstrated no evidence of an association between fish consumption and colorectal cancer mortality.

He *et al.* (2004) performed a meta-analysis of 14 cohorts with 222 354 persons (men and women), investigating the association between fish intake and CHD mortality. This meta-analysis demonstrated that each 20 g increase in fish intake per day was associated with a lower risk for CHD mortality, concluding an inverse association between fish intake and fatal CHD.

TABLE 3.14 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH ON "MORTALITY"**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Szymanski *et al.*, 2010 Fish consumption and prostate cancer risk: a review and meta-analysis	Prostate cancer and prostate cancer-specific mortality	Adult men 4 cohort studies (n = 49 661) on cancer-specific mortality 740 fatal prostate cancers	n = 4 Cohort studies (n = 4)	Median fish intake from the four studies: - 1.3 times/month - Moderate part - 0.5 servings/week - 3.25 times/week	High consumption of fish was associated with a significant 63% reduction in fatal disease (prostate cancer-specific mortality) (RR = 0.37, 95% CI: 0.18, 0.74; P = 0.005) In univariate meta-regression analysis, larger studies reported a weaker inverse association with prostate-cancer mortality (P = 0.15). With stratification on the number of study participants, studies (15, 37) with > 17 000 participants showed fish consumption to have a 34% protective association (RR = 0.66, 95% CI: 0.43, 1.01), although the results were not significant at the 0.05 level. Studies (23, 28) with < 7 000 participants showed a significant pooled risk reduction of 80% (RR = 0.20, 95% CI: 0.09, 0.43).	Total fish intake was associated with 63% reduction in prostate cancer–specific mortality	Moderate

TABLE 3.14 **SUMMARY OF RESULTS FROM SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH ON "MORTALITY" (cont.)**

AUTHOR, YEAR STUDY TITLE	OUTCOME	POPULATION	STUDY INFORMATION	FISH AND SEAFOOD INTAKE	OVERALL RESULTS	OVERALL CONCLUSION	RISK OF BIAS (AMSTAR 2)
Geelen *et al.*, 2007 Fish Consumption, n-3 Fatty Acids, and Colorectal Cancer: A Meta-Analysis of Prospective Cohort Studies	Colorectal cancer mortality	Not reported in the systematic review for mortality. Findings of the four primary studies included: - n = 265 118 (male, n = 12 226; female, n = 142 857) adults aged 40 and above were followed up for 17 years (1966–1982) and age standardized mortality rates for cancer of each site - n = 17 633 white males aged 35 and older, 20 years of follow-up, 120 colon cancer and 25 rectal cancer deaths - In Hokkaido by analysing n = 1 524 men and n = 1 634 women separately, aged 40 and over - n = 45 181 men and n = 62 643 women aged 40–79 years enrolled in the Japan Collaborative Cohort Study	4 cohort studies on colorectal cancer mortality	Exposure definition in the four studies included: - Fish: daily consumption - Fish: number of times/ month - Boiled fish - Fish: number of times/ week	The pooled RR (95% CI) for the highest compared with the lowest fish consumption category was 1.02 (0.90–1.16).	No evidence of an association between fish consumption and colorectal cancer mortality was found.	Moderate
He *et al.*, 2004 Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies	Coronary heart disease (CHD) mortality	Women and men (>16) 222 364 individuals with an average 11.8 years of follow-up (3 032 CHD deaths)	13 cohorts (from 11 studies)	Fish consumption was standardized and categorized into 5 intervals: "never or 1/ month", "1 to 3/month", "1/week", "2 to 4/week", and "≥5/week."	RRs (95% CI) for CHD mortality were 0.89 (0.79, 1.01) for fish intake 1 to 3 times per month, 0.85 (0.76, 0.96) for once per week, 0.77 (0.66, 0.89) for 2 to 4 times per week, and 0.62 (0.46, 0.82) for 5 or more times per week. Each 20-g/day increase in fish intake was related to a 7% lower risk of CHD mortality (P for trend = 0.03)	Fish consumption is inversely associated with fatal CHD.	Moderate

Notes: RR: relative risk, CHD: coronary heart disease, CI: confidence interval

3.2.8.3 Summary of the findings on "Mortality" from the primary studies included from the literature search

3.2.8.3.1 Descriptions of the primary studies

Five primary studies were included (Walda *et al.*, 2002; Iso *et al.*, 2006; Streppel *et al.*, 2008; Pertiwi *et al.*, 2021 and Sun *et al.*, 2021). **Table 3.15** describes the studies, including study name, type, number of participants, measurements of seafood consumption and outcome, overall results, risk of bias and overall conclusion. All five studies were prospective cohort studies with the geographical distribution including Finland, Italy, the Kingdom of the Netherlands and the United States.

3.2.8.3.2 Description of study population

The number of study participants varied between the studies, ranging from 1 373 to 366 048. Median follow-up time and the mean age of the participants also varied. The number of fatal events varied from a low of 62 fatal to a high of 1 877.

3.2.8.3.3 Description of fish consumption

Dietary intake was assessed by FFQs, the cross-check dietary history method or by 24-hour dietary recall. Fish intake was reported either as frequency or amount.

3.2.8.3.4 Results from the primary studies

3.2.8.3.4.1 Cardiovascular disease mortality

Four of the five primary studies included evaluated the association between seafood intake and mortality from CVD. Iso *et al.* (2006) found no association between sudden cardiac death or fatal CHD and fish intake. Similarly, Sun *et al.* (2021) found no association between seafood intake and CVD mortality. However, the study by Pertiwi *et al.* (2021), demonstrated a lower risk of CHD mortality, but not with CVD mortality. The study by Streppel *et al.* (2008) also found a lower risk for CHD death with long-term fish consumption, in addition to lower risk for sudden cardiac death with fatty fish consumption. In agreement with this, Yamagishi *et al.* (2019) reported higher mortality from total aortic disease with low/seldom fish intake.

Overall, two studies reported no association between CVD mortality and fish intake, while three studies reported a lower risk for CVD mortality with fish intake.

3.2.8.3.4.2 Chronic obstructive pulmonary disease mortality

One study (Walda *et al.*, 2002) investigated chronic obstructive pulmonary disease (COPD) death and found no association between seafood intake and COPD death.

3.2.8.3.4.3 All-cause mortality

Two studies, (Pertiwi *et al.*, 2021 and Sun *et al.*, 2021), found no association between fish intake and all-cause mortality.

TABLE 3.15 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "MORTALITY"**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Iso *et al.*, 2006 The Japan Public Health Center-Based (JPHC) study Cohort 1 Japan	Prospective cohort study 1990–1992 to 2001 Maximum 11-year follow-up time	n = 41 578 Fatal coronary events = 62 Sudden cardiac death = 37 40–59 years 27 053 men, 27 435 women	Dietary intake assessed by FFQ at two different time points (1990 + 1995) Fish intake at baseline; lowest quintile: once per week (median 23 g/day), highest quintile: 8 times per week (median 180 g/day)	Cardiovascular disease registered at main hospitals in the region by medical records reviewed by physicians. For fatal myocardial infarctions and sudden cardiac deaths: a systematic search for death certificates was performed.	Fish intake was not associated with fatal coronary heart disease or sudden cardiac death. HR (95% CI) for quintile 5 vs 1 in multivariable-adjusted models: Sudden cardiac death: 1.14 (0.36, 3.63), fatal coronary events 1.08 (0.42, 2.76).	B	Intake of fish was not associated with fatal coronary heart disease (CHD) or sudden cardiac death. The low number of cases, respectively 62 and 37, and thus low statistical power, may have influenced the results.
Pertiwi *et al.*, 2021 Alpha Omega Cohort Netherlands (Kingdom of the)	Prospective cohort study Baseline 2002–2006, follow-up to 2018 (median follow-up time of 12 years)	n = 4 067 Coronary heart disease deaths (CHD) = 515 Cardiovascular disease (CVD) deaths = 834 Mean (SD) 69.0 (5.6) years 79.2% men	Dietary intake assessed by a validated 203-item FFQ. Total fish intake: median (IQR) 14 (5 to 20 g/day. Oily fish intake: 5 (1 to 11 g/day)	Information on CVD and deaths obtained from national mortality registries and the International Classification of Diseases.	Total fish consumption inversely associated with CHD mortality (HR (95% CI) = 0.73, (0.54, 0.99) for >20–40 vs ≤5 g/day). Finding for oily fish was similar (HR (95% CI) 0.72 (0.54, 0.95) for >11 vs <1 g/day. No associations were observed for CVD or all-cause mortality.	B	Total fish and oily fish intake was associated with lower risk of CHD mortality, but not with CVD and all-cause mortality.
Streppel *et al.*, 2008. The Zutphen Study Netherlands (Kingdom of the)	Prospective cohort study. Baseline 1960 + a new cohort included in 1985. Follow-up until 2000.	n = 1 373 CHD deaths = 348 Sudden coronary deaths = 66 Mean (SD) age (1960): 49 (6), 1985: 71 (5). 100% men	Dietary intake collected by the cross-check dietary history method, conducted by dieticians (assessed every 5th year). Total fish intake: Mean range from 16 to 21 g/day. Lean and fatty fish also included.	Causes of death were ascertained by a clinical epidemiologist and coded according to the Eighth revision of the International Classification of Disease.	Long-term fish consumption (cumulative average), average 22 g/day had a 22% lower CHD death risk, recent fish consumption was not associated with CHD death. Fatty fish intake (no vs yes) was associated with decreased risk of sudden coronary death (multivariate model: HR = 0.46, 95% CI: 0.27, 0.78). Long-term fatty fish consumption, average 7 g/day, 54% lower sudden cardiac death risk.	B	Long-term fish consumption lowered the risk of CHD death. Fatty fish consumption lowered the risk of sudden cardiac death.

TABLE 3.15 SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) INCLUDED FROM THE LITERATURE SEARCH ON "MORTALITY" (cont.)

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Sun *et al.*, 2021 The National Health and Nutrition Examination Survey (NHANES) the United States	Prospective cohort study Included 2003 to 2012. Follow-up until 31 December 2015.	n = 17 295 All-cause mortality = 1 076 CVD deaths = 181 Mean (SD) age 45.9 (17.1) years. 46.7% men	Dietary intake assessed by two 24-hour dietary recall. HR for an increase in seafood consumption of 1 oz (28 g) equivalent per day increase	Death status determined using the NHANES Public Use Linked Mortality File, based on the results of a probabilistic match between NHANES and the National Death Index.	No associations between an increase in seafood consumption of 1 oz-equivalent per day and all-cause (HR = 0.84, 95% CI: 0.66, 1.07) and CVD-related mortality (HR = 0.89, 95% CI: 0.54, 1.47).	B	No associations between seafood consumption and deaths.
Walda *et al.*, 2002 A study from three European countries. Finland, Italy and Netherlands (Kingdom of the) (two Finnish, two Italian and one Netherlands cohort of the Seven Countries Study are involved)	Prospective cohort study. Baseline 1970 Follow-up 20 years (1990)	n = 2 917 Chronic obstructive pulmonary disease (COPD) death = 73 Age 50–69 years 100% men	Dietary intake assessed by cross-check dietary history method. Mean fish intake, Finland 40 (47) g/day, Italy 20 (21) g/day, Netherlands (Kingdom of the) 17 (19) g/day	Information on cause of death determined by two investigators who reviewed clinical records from family doctors, specialists and relatives. Primary mortality coded according to the International Classification of Diseases (ICD) of the WHO.	No associations between fish intake and COPD mortality (RR (95% CI) for highest vs lowest tertile 1.02 (0.59–1.78).	B	No associations between seafood consumption and COPD death.

Notes: CHD: coronary heart disease, FFQ: food frequency questionnaire, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, SD: standard deviation, NHANES: The National Health and Nutrition Examination Survey (NHANES), WHO: World Health Organization, COPD: chronic obstructive pulmonary disease

3.2.8.4 Final weight of evidence for "Mortality"

A final weight of evidence for the theme "Mortality" was based on the 2022 VKM report and the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

The weight of evidence for all-cause mortality and disease-specific mortality were based on the VKM report and on primary studies and systematic reviews included in the evaluation. In conclusion, the overall evidence of total fish intake associated with mortality from Alzheimer's disease, total heart disease, T2D, colorectal cancer and prostate cancer were all graded "limited, no conclusion". In addition, the evidence of fatty fish and lean fish intake associated with all-cause mortality and mortality from CHD was also graded "limited, no conclusion". Furthermore, the evidence from total fish intake associated with ischemic stroke and haemorrhagic stroke were graded "limited, suggestive" for a protective effect. Lastly, the association of total fish intake with all-cause mortality and mortality from CVD, CHD, MI and stroke were graded "probable" for a protective effect.

3.2.9 OVERWEIGHT AND OBESITY IN ADULTS

The literature included in the theme "Overweight and obesity" includes results from the 2022 VKM report and from three original primary studies originating from the literature search. No systematic reviews were included.

3.2.9.1 Summary of the findings on "Overweight and obesity" in the VKM report, Benefit and risk assessment of fish in the Norwegian diet

VKM conducted a comprehensive literature search and performed an analysis of a systematic review and three primary prospective cohort studies to investigate the relationship between fish intake and body weight in adults. The studies were conducted across diverse geographic regions, encompassing Asia, Europe and the United States.

The systematic review contained three studies (including two prospective studies on abdominal obesity in adults) that showed that higher total fish intake was related to reduced abdominal obesity. However, one study on the risk of developing overweight/obesity showed no association with fish intake.

As there were few studies and due to heterogenous presentation of results, no summary RR was calculated on the basis of the primary studies. One study, which included a large number of participants, reported no association between fish consumption and abdominal obesity, while another study found a protective association.

In conclusion, from the VKM report, the association between fish intake and adult body weight was graded "limited, no conclusion", considering that there were few studies, reporting different endpoints, and that the results showed weak or no associations between fish consumption and weight gain (general or abdominal obesity).

3.2.9.2 Summary of the findings on "Overweight and obesity" in primary studies included from the literature search

3.2.9.2.1 Description of the primary studies

Three primary studies on the association between fish and seafood intake and overweight and obesity (Smith *et al.*, 2015; Tørris *et al.*, 2017 and Beulen *et al.*, 2018) were identified and met the inclusion criteria. A description of the three studies, including study name, design, time period, population, intake of fish consumption and overall results, is provided in **Table 3.16**.

Two of the studies are prospective cohort studies conducted in Europe (Spain) and the United States. The third study is an epidemiological, population-based study comprising several cross-sectional surveys, primarily involving participants from Norway.

3.2.9.2.2 Description of study population

All three studies included healthy participants from the general adult population. Two studies, Beulen *et al.* (2018) and Tørris *et al.* (2017), included both men and women, while one study, Smith *et al.* (2015), had separate data sets including only women (n= 2 datasets) and men (n = 1 dataset).

3.2.9.2.3 Description of fish consumption

All three studies used validated FFQs for estimating fish and food consumption. Beulen *et al.* assessed the daily substitution of one portion of red meat with oily fish or white fish and how this affects weight gain. Smith *et al.* assessed the intake of proteins from seafood in relation to other protein foods and long-term weight changes. Tørris *et al.* assessed the intake of lean fish or fatty fish and waist circumference in both men and women.

3.2.9.2.4 Results from the primary studies

Beulen *et al.* examined the daily substitution of one portion of red meat with oily fish and white fish. The effects on body weight were estimated using generalized equations. The results showed weight changes of up to -0.75 kg (95% CI: -1.13, -0.38) and -0.87 kg (95% CI: -1.17, -0.56) for oily fish and white fish, respectively.

In Smith *et al.*, dose-response analyses were performed using generalized models. It was found that increasing seafood consumption by one serving per day was associated with a weight loss of 0.45 kg (95% CI: -0.83, -0.09 kg) when glycaemic load was simultaneously increased. However, when glycaemic load was simultaneously decreased, weight loss increased to 1 kg (95% CI: -1.24, -0.76 kg).

Tørris *et al.* investigated the association between lean and fatty fish consumption and waist circumference. The study found that consuming lean fish once a week or more was significantly associated with decreased waist circumference (-1.15, 95% CI: -1.96 to -0.35). On the other hand, consuming fatty fish was significantly associated with increased waist circumference for both genders (women: 0.97, 95% CI: 0.29 to 1.65; men: 0.6, 95% CI: 0.01 to 1.18). Lean fish consumption in particular seemed to be associated with reducing waist circumference.

TABLE 3.16 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) FROM THE LITERATURE SEARCH ON "OVERWEIGHT AND OBESITY"**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Beulen *et al.*, 2018 Prevención con Dieta Mediterránea (PREDIMED) (Prevention through the Mediterranean diet) Spain	2003–2009 Prospective cohort study Median follow-up time: 4.8 years	n = 6 942 Mean age: 67 years, 47% obesity at baseline. Control group: advice on following a low-fat diet. Non-control group: Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts.	Semiquantitative 137-item FFQ	Anthropometric measurements per year. Continuous outcome: body weight Dichotomized outcomes: cut-off of body weight (a change ≥10%), incidence (increasing to a BMI ≥30 kg/m^2) and reversion of obesity (decreasing to a BMI <30 kg/m^2).	Daily substitution of one portion of red meat with white meat, oily fish or white fish showed weight changes up to: -0.64 kg (95% CI: -0.94, -0.35), -0.75 kg (95% CI: -1.13, -0.38) and -0.87 kg (95% CI: -1.17, -0.56), respectively.	B	Reductions in red meat consumption coupled with respective increases in white meat or fish would lead to less weight gain.
Smith *et al.*, 2015 3 prospective US cohorts: Nurses' Health Study (NHS), Nurses' Health Study II (NHS II), and Health Professionals Follow-Up Study (HPFS) the United States	Prospective cohort study Follow-up: 4 years, 16 years and 24 years.	In total, n = 120 784 healthy participants, including 46 994 in the NHS, 47 928 in the NHS II, and 25 862 in the HPFS. Baseline: NHS: 1 976, female, age (mean+SD): 48.9 ±2.7 years Weight: 64.0 ±4.1 kg, BMI: 23.7 ±1.4 kg/m^2 NHS II:1 989, female, age (mean ±SD): 37.7 ±3.2 years Weight: 62.6 ±7.7 kg, BMI: 23.0 ±2.4 kg/m^2 HPFS: 1 986, male, age (mean ±SD): 47.3 ±2.7 years Weight: 79.4 ±4.5 kg, BMI: 24.8 ±1.1 kg/m^2 Weight gain during follow-up: NHS: 1.1 kg/4 years NHS II:2.1/4 years HPFS: 0.7/4 years	Validated food-frequency questionnaires. Mean (SD) seafood intake at baseline (servings/day*, See Smith et al., 2015, Supplemental Table 2): NHS: 0.34 (0.13) NHS II: 0.27 (0.2) HPFS: 0.37 (0.15) Mean 4-year change: mean (95% CI) NHS: -0.02 (-0.2, 0.14) NHS II: -0.01 (-0.11, 0.09) HPFS: -0.01 (-0.17, 0.14)	-Protein foods and glycaemic load every 4 years using food frequency questionnaires. -Weight change every 4 years	Negative association between changes in protein seafood and long-term weight change: Mean (95% CI) (kg) NHS: -0.77(-0.88, -0.66) (p<0.0001) NHS II: -0.78(-0.93, -0.64) (p<0.0001) HPFS: -0.54(-0.67, -0.41) (p<0.0001) Pooled: -0.70(-0.85, -0.54) (p<0.0001) (Smith *et al.*, 2015, Supplemental Table 4). - A 1-serving/day increase in seafood was associated with 0.45 kg (CI: -0.83, -0.09 kg) weight loss when glycaemic load was simultaneously increased, yet 1kg (CI: -1.24, -0.76 kg) weight loss when glycaemic load was simultaneously decreased.	B	Seafood intake was negatively associated with long-term weight gain.

TABLE 3.16 **SUMMARY OF RESULTS FROM ORIGINAL PRIMARY STUDIES (COHORT STUDIES) FROM THE LITERATURE SEARCH ON "OVERWEIGHT AND OBESITY" (cont.)**

AUTHOR, YEAR STUDY TITLE REGION, COUNTRY	STUDY INFORMATION	NUMBER OF PARTICIPANTS IN THE STUDY (N) AGE (YEARS) SEX (PERCENT MEN)	FISH AND SEAFOOD INTAKE	OUTCOME	OVERALL RESULTS	RISK OF BIAS	OVERALL CONCLUSION
Tørris *et al.*, 2017 Data from the Norwegian Tromsø Study Tromsø, Norway	Prospective cohort study 13-year follow-up period. Tromsø Study 4: 1994–1995 Tromsø Study 6: 2007–2008	Tromsø Study 4 (1994–1995): n = 23 907, 26–69 years. Tromsø Study 6 (2007–2008): n = 12 981, 30–87 years. Baseline characteristics of the participants (1994–1995): n = 23 907 Age (mean ±SD): 44.1 ±11.5 years, 48% men BMI:25.1 ±3.8 kg/m^2 38% reported as daily smokers.	Fish consumption assessed by a validated centre-specific questionnaire. The nutrients were computed based on the food frequency questionnaire (FFQ). Almost 80% of the participants reported lean fish consumption at dinner once or more per week, while 64% reported consuming processed fish and 37% reported consuming fatty fish.	-Physical variables: waist circumference (WC) and blood pressure (BP). -Non-fasting blood samples: triglycerides (TG), HDL-cholesterol (HDL-C), and blood glucose (BG). Metabolic score (MetS) ranging from 0 to 5 (abdominal obesity, increased TG, decreased HDL-C, hypertension and hyperglycaemia) was performed.	Lean fish consumption once a week or more was significantly associated with decreased future MetS (women: -0.05, 95% CI: -0.09 to -0.01, men: -0.1, 95% CI: -0.15 to -0.05), decreased TG (women: -0.04, 95% CI: -0.08 to -0.00, men: -0.11, 95% CI: -0.17 to -0.06), and increased HDL-cholesterol (women: 0.03, 95% CI: 0.01 to 0.05, men: 0.04, 95% CI: 0.02 to 0.05), whereas decreased WC (-1.15, 95% CI: -1.96 to -0.35) and BP (SBP: -0.86, 95% CI: -1.66 to -0.06; DBP: -0.63, 95% CI: -1.18 to -0.07) was identified only for men (age-adjusted models). Fatty fish consumption was significantly associated with increased WC for both genders (women: 0.97, 95% CI: 0.29 to 1.65, men: 0.6, 95% CI: 0.01 to 1.18) and increased HDL-C levels in men (0.02, 95% CI: 0.00 to 0.03).	B	Fatty and lean fish consumption likely influence MetS differently. Lean fish consumption seems to be associated with beneficial changes in the MetS components.

Notes: BMI: body mass index, CI: confidence interval, SD: standard deviation

3.2.9.3 Final weight of evidence for "Overweight and obesity"

A final weight of evidence for the theme "Overweight and obesity" was based on the 2022 VKM report and the systematic literature search. An overview of the literature included in the final weight of evidence is given in Appendix 3, **Table A3.35**.

Three more primary studies that complemented the VKM 2022 assessment were discovered through the literature search; however, each study reported a different outcome, such as substitution, long-term weight gain and waist circumference. The present body of evidence regarding a link between fish consumption and adult body weight was rated "limited, no conclusion" by VKM due to a limited number of papers and inconsistent methods of measuring the outcome. The three additional studies were not sufficient to change VKM's conclusion, and, as such, the association between fish intake and obesity is rated "limited, no conclusion".

3.3 FINAL WEIGHT OF EVIDENCE FOR "HEALTH BENEFITS OF FISH CONSUMPTION"

A summary of the final weight of evidence for the different outcomes included in the chapter "Evidence of health benefits of fish consumption" is given in **Table 3.17**. More information of the data for the weight of evidence can be found in each specific outcome section in **Section 3.2.** The weight of evidence was based on a summarization of the available evidence from previously published risk-benefit assessment reports (WCRF, 2018b and VKM, 2022) and the systematic literature search, including systematic reviews and original primary studies. An overview of the literature included in the final weight of evidence for each health outcome is given in Appendix 3, **Table A3.35**.

TABLE 3.17 SUMMARY OF FINAL WEIGHT OF EVIDENCE FOR "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION"

HEALTH OUTCOME	FISH INTAKE	CONCLUSION "WEIGHT OF EVIDENCE"[1]
ALLERGY AND IMMUNOLOGY		
Allergic rhinitis in children	Maternal total fish intake in pregnancy	Limited, no conclusion
	Early fish introduction	Limited, no conclusion
Allergic sensitization in children	Maternal total fish intake in pregnancy	Limited, no conclusion
	Child total fish intake	Limited, no conclusion
Asthma in children	Maternal total fish intake in pregnancy	Limited, no conclusion
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
Eczema in children	Maternal total fish intake in pregnancy	Limited, no conclusion
	Child total fish intake	Limited, suggestive (protective for intake in the first year of life, but not later)
Multiple sclerosis	Total fish intake	Limited, suggestive (protective)
Rheumatoid arthritis	Total fish intake	Limited, no conclusion

TABLE 3.17 **SUMMARY OF FINAL WEIGHT OF EVIDENCE FOR "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION" (cont.)**

HEALTH OUTCOME	FISH INTAKE	CONCLUSION "WEIGHT OF EVIDENCE"[1]
BIRTH AND GROWTH OUTCOMES		
Preterm birth	Maternal total fish intake in pregnancy	Probable (protective effect)
	Maternal fatty and lean fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
Small for gestational age	Maternal total fish intake in pregnancy	Limited, suggestive (protective)
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
Birth weight	Maternal total fish intake in pregnancy	Limited, suggestive (protective)
	Maternal fatty fish intake in pregnancy	Limited, suggestive (protective)
	Maternal lean fish intake in pregnancy	Limited, suggestive (protective)
Low birth weight	Maternal total fish intake in pregnancy	Probable (protective effect)
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
High birth weight	Maternal total fish intake in pregnancy	Limited, suggestive (increased risk)
	Maternal fatty fish intake in pregnancy	Limited, suggestive (increased risk)
	Maternal lean fish intake in pregnancy	Limited, suggestive (increased risk)
Birth length	Maternal total fish intake in pregnancy	Limited, no conclusion
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
Head circumference	Maternal total fish intake in pregnancy	Limited, no conclusion
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
BONE HEALTH		
Hip fracture	Total fish intake	Limited, suggestive (protective)
CANCER		
Liver cancer	Total fish intake	Limited, suggestive (protective)
Liver cancer	Total fish intake	Limited, suggestive (protective)
Colorectal cancer	Total fish intake	Limited, suggestive (protective)
Nasopharyngeal cancer	Cantonese-style salted fish[2]	Strong evidence (increased risk)
Pancreatic cancer	Total fish intake	Limited, no conclusion
Breast cancer	Total fish intake	Limited, no conclusion
CARDIOVASCULAR DISEASES		
Total cardiovascular disease	Total fish intake	Limited, suggestive (protective effect)
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
Coronary heart disease	Total fish intake	Probable (protective effect)
	Fatty fish intake	Limited, suggestive (protective effect)
	Lean fish intake	Limited, suggestive (no effect)
Myocardial infarction	Total fish intake	Limited, suggestive (protective effect)
	Fatty fish intake	Limited, suggestive (protective effect)
	Lean fish intake	Limited, suggestive (no effect)

TABLE 3.17 **SUMMARY OF FINAL WEIGHT OF EVIDENCE FOR "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION" (cont.)**

HEALTH OUTCOME	FISH INTAKE	CONCLUSION "WEIGHT OF EVIDENCE"[1]
CARDIOVASCULAR DISEASES		
Total stroke	Total fish intake	Probably (protective effect)
	Fatty fish intake	Limited, suggestive (protective effect)
	Lean fish intake	Limited, suggestive (protective effect)
Ischemic stroke	Total fish intake	Limited, suggestive (protective effect)
Haemorrhagic stroke	Total fish intake	Limited, suggestive (protective effect)
Atrial fibrillation	Total fish intake	Limited, suggestive (adverse effect)
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, suggestive (protective effect)
Heart failure	Total fish intake	Limited, suggestive (protective effect)
Venous thromboembolism	Total fish intake	Limited, no conclusion (protective effect)
Peripheral arterial disease	Total fish intake	Limited, no conclusion
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
TYPE 2 DIABETES		
Type 2 diabetes	Total fish intake	Limited, no conclusion
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, suggestive (no association)
NEURODEVELOPMENT AND NEUROLOGICAL DISEASES		
Neurodevelopment in children	Maternal total fish intake in pregnancy	Limited, suggestive (protective)
	Maternal fatty fish intake in pregnancy	Limited, no conclusion
	Maternal lean fish intake in pregnancy	Limited, no conclusion
	Child total fish intake	Limited, suggestive (protective)
	Child fatty fish intake	Limited, suggestive (protective)
	Child lean fish intake	Limited, no conclusion
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease and cognitive decline)	Total fish intake	Probable (protective effect)
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
Depression and post-partum depression	Total fish intake	Limited, suggestive
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
MORTALITY		
Alzheimer's disease mortality	Total fish intake	Limited, no conclusion
Cardiovascular disease (CVD) mortality	Total fish intake	Probable (protective)
Total heart disease mortality	Total fish intake	Limited, no conclusion
Coronary heart disease (CHD) mortality	Total fish intake	Probable (protective)
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
Myocardial infarction (MI) mortality	Total fish intake	Probable (protective)
Stroke mortality	Total fish intake	Probable (protective)
Stroke subtypes: ischemic stroke- and haemorrhagic stroke mortality	Total fish intake	Limited, suggestive (protective)
Type 2 diabetes mortality	Total fish intake	Limited, no conclusion

TABLE 3.17 **SUMMARY OF FINAL WEIGHT OF EVIDENCE FOR "EVIDENCE OF HEALTH BENEFITS OF FISH CONSUMPTION" (cont.)**

HEALTH OUTCOME	FISH INTAKE	CONCLUSION "WEIGHT OF EVIDENCE"[1]
MORTALITY		
Colorectal cancer mortality	Total fish intake	Limited, no conclusion
Prostate cancer-specific mortality	Total fish intake	Limited, no conclusion
All-cause mortality	Total fish intake	Probable (protective)
	Fatty fish intake	Limited, no conclusion
	Lean fish intake	Limited, no conclusion
OBESITY		
Obesity in adults	Total fish intake	Limited, no conclusion

Notes: [1]Final weight of evidence is based on the World Cancer Research Fund grading system (WCRF, 2018 and WCRF, 2018a). [2]Cantonese-style salted fish is part of the traditional diet of people living in the Pearl River Delta region in southern China. It is prepared with less salt than is used in northern China and allowed to ferment.

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CHAPTER 4

RESULTS AND SUMMARIZATION OF THE LITERATURE REVIEW "TOXIC EFFECTS OF DIOXINS AND dl-PCBs"

4.1 LITERATURE SEARCH AND QUALITY ASSESSMENT

Literature searches for the systematic review on the "Toxic effects of dioxins and dl-PCBs" were performed in the databases PubMed and Web of Science. A flow diagram of the results from the literature searches is given in **Figure 4.1**. The literature searches in Web of Science and PubMed resulted in 2 770 records. Of these, 372 duplicate records were identified and removed, leaving 2 398 records, which were screened by title and abstract using the online screening tool, Rayyan. As a result of the screening, 264 duplicates were removed, and 1 736 records were excluded based on inclusion and exclusion criteria. Thus, 396 records (33 systematic reviews and 363 primary articles) were assessed in full text.

4.1.1 SYSTEMATIC REVIEWS

In the current literature search, the EFSA Dioxin Report from 2018 was included, as it was considered sufficiently comprehensive for the evaluation of the toxic effects of dioxins. To avoid reporting duplicate publications, only studies published from 5 July 2016 onwards were included further. (All the remaining systematic reviews identified in literature search were excluded for further assessment, either because they were not relevant according to the criteria or they consisted of studies published before 2016 [see Appendix 4, **Table A4.3**]). The EFSA report was quality assessed with the risk-of-bias tool AMSTAR 2 (Appendix 4, **Table A4.6**) and graded "high" according to the overall confidence in the results.

4.1.2 PRIMARY STUDIES

A total of 363 primary studies were assessed in full text after title and abstract screening. Of these, 271 studies were excluded based on inclusion and exclusion criteria during the full-text assessment (Appendix 4, **Table A4.4**) and 12 were excluded as they were already assessed in the EFSA 2018 systematic review (Appendix 4, **Table A4.5**). Thus, 80 primary studies were quality assessed with the OHAT risk-of-bias tool (Appendix 4 **Table A4.7**). Based on the risk of bias assessment, 20 primary studies were graded Tier 1, 51 primary studies were graded Tier 2, and 9 studies were graded Tier 3. Only studies graded Tier 1 were included for further assessment in the final review.

4.2 RESULTS AND SUMMARIZATION OF THE LITERATURE INCLUDED

The 2018 EFSA report and the primary studies included from the literature search (rated Tier 1) are summarized in the following sections with regard to the relevant health outcomes.

4.2.1 CHLORACNE AND OTHER DERMAL EFFECTS

The most unequivocal effect of dioxins is chloracne. Chloracne is a cystic and hyperkeratotic skin disorder caused by high exposure to TCDD. EFSA considers chloracne the most reliable and specific indicator of acute TCDD toxicity; however, its occurrence has only been shown following accidental, deliberate or occupational high-dose exposure. EFSA therefore deemed it of little pertinence for risk assessment of background exposure. No further studies were found reporting on chloracne in the literature search.

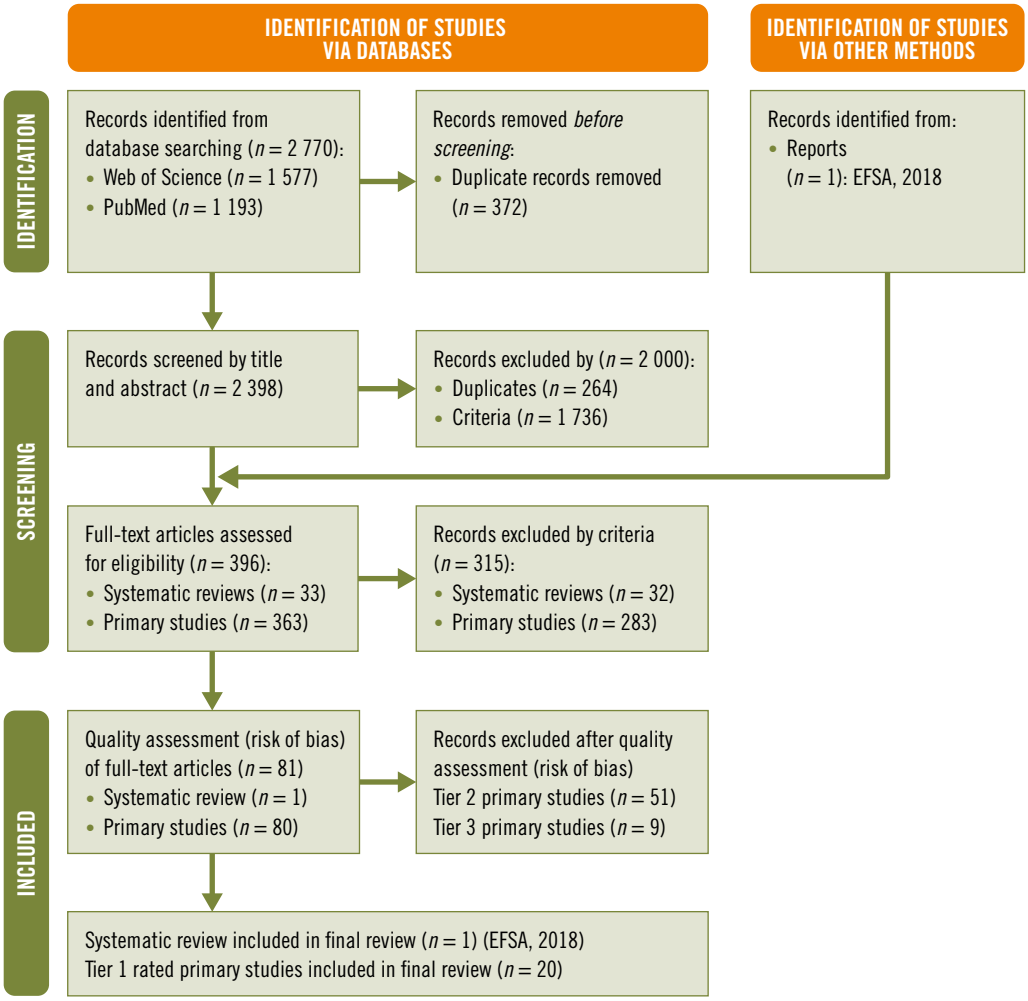
4.2.2 REPRODUCTIVE EFFECTS (INCLUDING ORGANS)

In addition to the EFSA report, nine primary studies were found in the literature search investigating the outcome of reproductive effects. A summarization of these studies is given in **Table 4.1**.

As mentioned in the EFSA report, changes in sex hormones were not considered to be an adverse health effect. However, as they can contribute to a mechanistic explanation for the effect on reproduction, they were still reported. We found

eight additional studies in our literature search investigating changes in different sex hormones following dioxin and dl-PCB exposure. These outcomes were not considered adverse health effects, but the studies are summarized in **Table 4.1**. In short, the studies showed conflicting results, and no conclusion can be made on the effect on sex hormone regulation following dioxin and dl-PCB exposure.

FIGURE 4.1. **FLOW DIAGRAM FOR THE LITERATURE REVIEW "TOXIC EFFECTS OF DIOXINS AND dl-PCBs"**



Source: Prepared by the authors based on: Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L. *et al.* 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71.

4.2.2.1 Effects on semen quality

The most sensitive dioxin-induced health endpoint concerning semen quality was reduced sperm concentration, although total count, motility, morphology, volume and viability have also been assessed. In their evaluation of epidemiological studies, EFSA found seven studies on male reproduction as an outcome. Three of these were rated Tier 1, while four were rated Tier 2. One additional study was found in the literature search, which was rated Tier 1. The EFSA considered associations between exposure to TCDD during infancy/prepuberty and impaired semen quality to be causal. This was based on the weight of evidence from epidemiological observational studies and from corroborating experimental animal studies. The EFSA report

weighted particularly two studies from the Seveso cohort (Mocarelli *et al.*, 2008 and Mocarelli *et al.*, 2011), and one from the Russian children's study (Mínguez-Alarcón *et al.*, 2017). These studies showed a particularly sensitive period of effect from infancy to prepuberty, and the most pronounced effect was reduced sperm concentration after exposure to dioxins.

The EFSA based the TWI for dioxin and dl-PCB on the no-observed-adverse-effect serum level for PCDD/F (measured in WHO toxic equivalent quotients, or WHO-TEQ) of 7.0 pg WHO-TEQ/g fat from the Russian children's study, in which reduced semen concentration was the main health outcome (Mínguez-Alarcón *et al.*, 2017). It should be noted that the Russian children's study did not show any association between sperm concentration and total TEQ of dioxins and dl-PCBs up to a quartile level of 47.8 pg WHO-TEQ/g fat, nor any associations of dl-PCB with decreased sperm concentration.

Complementing the search from EFSA, one more study was found in the literature search on the relationship between dl-PCB and semen quality (Paul *et al.*, 2017). This was a case-control study, where a group of men with low sperm quality (cases; $n = 24$) was compared to a group of men with normal sperm quality (controls; $n = 26$). In this study, individuals with low sperm quality exhibited significantly higher levels of non-ortho PCBs (949.49 ± 624.97 pg/g lipid; $p = 0.020$) and total dl-PCBs (7029.96 ± 3023.97 pg/g lipid; $p = 0.028$; 22.52 ± 21.2 pg WHO-TEQ/g lipid) than the control group (508.40 ± 324.44 pg/g lipid and 4805.92 ± 2205.02 pg/g lipid 14.00 ± 10.82 pg WHO-TEQ/g lipid, respectively). However, following a multivariate regression, only semen volume was found to be significantly affected by sum dl-PCB.

In conclusion, the additional study does not conflict with the EFSA conclusion on causality between PCDD/Fs and reduced sperm quality since only dl-PCBs were measured in the additional study. No clear association between total dl-PCBs and sperm quantity was found, which is in accordance with the observational studies presented by EFSA.

4.2.2.2 Cryptorchidism

Cryptorchidism is the failure of the testicles to descend to the bottom of the scrotum during development. EFSA found two nested case-control studies dealing with this endpoint, in which one of these found no association between placenta levels of dioxins and dl-PCBs and cryptorchidism, and the other study did find associations to sum PCDD/F levels in subcutaneous adipose tissue biopsies, but only in the adjusted analysis. However, due to weight of evidence, EFSA concluded that these two studies did not provide sufficient evidence for an effect of dioxins and dl-PCBs on cryptorchidism. No additional studies were found in the literature search to further assess this health outcome.

4.2.2.3 Pubertal development

EFSA found seven studies on pubertal development, three rated Tier 1 and four rated Tier 2. Pubertal development was defined using the Tanner staging system (Marshall *et al.*, 1970), which includes: genital development, pubic hair growth, auxiliary hair growth, testicular volume, and age at first ejaculation. EFSA determined that the three Tier 2-rated studies contained too low sample size for certain conclusions. The three Tier 1-rated studies were all from one cohort (the Russian children's study), and these reported a dose-related association between serum TCDD and delayed puberty onset. However, these studies also showed high correlation between total TEQ and organochlorine pesticides, which also can impact the timing of puberty onset. Taken together, EFSA deemed the interpretation of a causal relationship between pubertal development and total TEQ difficult, and therefore concluded that there was insufficient information to conclude on the effects of dioxins and dl-PCBs on pubertal development. No further studies on pubertal development were found in the literature search.

TABLE 4.1 **OVERVIEW OF PRIMARY STUDIES WITH REPRODUCTIVE OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Boda *et al.*, 2017 Viet Nam	Cross-sectional study	Reproduction: Oestradiol and testosterone	Pregnant women (n = 210) enrolled and followed-up with their newborns (n = 162)	17 OCDD and PCDF measured in breast milk (lipid adjusted). Mean (SD) TCDD: 2.2 (2.1) pg/g TEQ Mean (SD) PCDD/F: 8.8 (1.6) pg/g TEQ	In generalized linear models (β (95% CI): Reduction in testosterone levels of girls and boys: > Negative association between 1,2,3,6,7,8-HxCDD and testosterone concentrations in girls (β= -0.320 (-0.538, -0.101). > Reduction in testosterone levels in umbilical cord blood for boys with 2,3,7,8-TCDD ≥ 5.5 pg/g lipid compared to levels <1 pg/g > Reduction in testosterone levels in umbilical cord blood for girls with 2,3,7,8-TCDD 1-3 pg/g lipid compared to levels <1 pg/g > Reduction in testosterone levels in umbilical cord blood for girls with TEQ-PCDD/Fs between 9 and 12 pg/g lipid compared to levels < 1 pg/g lipid. In conclusion, increased exposure of dioxins in breast milk was associated with decreased concentrations of testosterone in cord blood of newborns.
Lambertino *et al.*, 2020 the United States	Cross-sectional study (NHANES)	Reproduction: LH and FSH hormones	n = 87 post-menopausal women	All 29 congeners measured in blood (lipid adjusted). Mean (95% CI) Ln sum TEQ 0.11 (0.09, 0.13) pg/g	In Pearson's correlation coefficients: > Sum TEQs negatively associated with LH concentrations: r = -0.26 > Mono-ortho PCBs negatively associated with LH concentrations: r = -0.22 > A doubling of sum TEQ was associated with a decrease in LH of 11.9% (CI: -21.3, -21.4%) (P = 0.03).
Luong *et al.*, 2018 Viet Nam	Cross-sectional study	Reproduction: Reproductive hormones; FSH, LH, progesterone, prolactin, oestradiol, testosterone	n = 42 men (mean (SD) age: 41 (10) years)	17 PCDD/Fs and 4 non-ortho PCBs, measured in blood (lipid adjusted). Mean (SD) sum PCDD/F and non-ortho PCB TEQ: 37.8 (2.1) pg/g lipid	Significant findings in the study: > Negative correlation between PCDF and testosterone: r = -0.376, *P* = 0.022 > Negatic correlation between PCBs and testosterone: r = -0.339, *P* = 0.04 > Strong positive correlation between PCDD/Fs and prolactin: r = 0.458, *P* = 0.004. > Strong correlation between sum PCDD/F and PCBs: r = 0.445, *P* = 0.006 In conclusion, higher dioxin levels were associated with lower testosterone and higher prolactin levels in men.
Miyashita *et al.*, 2018 Japan	Prospective birth cohort	Reproduction: Progesterone, oestradiol, testosterone, androstenedione, DHAEA, cortisol, cortisone, SHBG, prolactin, LH, FSH, Inhibin B, insulin-like factor 3.	n = 183 mother–child pair	All 29 congeners measured in blood (lipid adjusted) in pregnancy (2nd or 3rd trimester). Total TEQ median (IQR): 14.5 (10.4–18.6) pg/g lipids	In multivariate linear regression: No associations for PCDD/F, sex-dependent association between non-ortho PCB and ratio testosterone/oestradiol β (95% CI) = -0.18 (-0.39, 0.03) interaction (P = 0.018), sex-dependent association between total DLC and ratio testosterone/oestradiol β (95% CI) = -0.22 (-0.54, 0.10) (P = 0.049), association between non-ortho PCB and DHEA beta 0.27 (CI 0.01-0.54) (P < 0.05).

TABLE 4.1 **OVERVIEW OF PRIMARY STUDIES WITH REPRODUCTIVE OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Oanh *et al.*, 2018 Viet Nam	Case-control study	Reproduction: Cortisol, cortisone, 17-OH-P4, progesterone, DHEA, androstenedione, testosterone, 3β-HSD, 17βHSD, CYP17 lyase in children.	Cases: n = 35 mother-child pairs in hotspot area Controls: n = 50 mother–child pairs in non-sprayed area Children followed up at age 5 years	17 PCDD/Fs in breast milk (lipid adjusted) Mean (SD) TEQ total PCDDs/Fs: > Cases (hotspot): 10.6 (1.4) pg/g > Controls (non-sprayed): 3.4 (1.5) pg/g	Many single congeners were correlated to changes in hormones and enzymes measured in children. But for Total TEQ PCDD/Fs the following correlation coefficients were found for each hormone/enzyme: DHEA r -0.41 p value < 0.001, Androstenedione r 0.35 p value < 0.001, testosterone r -0.45 p value < 0.001, CYP lyase r 0.36 p value 0.004, 17β-HSD r -0.52 p value < 0.001, 3β-HSD r -0.31 p value < 0.001. Further, a multiple regression showed for sum TEQ for DHEA β of -0.41 p value < 0.001, for Androstenedione β 0.28 p value 0.005, testosterone β -0.46 p value < 0.001.
Oyama *et al.*, 2021 Viet Nam	Prospective case-control study	Reproduction: Cortisol, Cortisone, 17-hydroxyprogesterone, progesterone, testosterone, DHEA, estrone, oestradiol. enzyme activity of 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD), and cytochrome P450 17,20-lyase (CYP17 lyase) in children.	Cases: n = 45 mother–child pairs in hotspot area Controls: n = 51 mother–child pairs in non-sprayed area Followed-up 4 to 16 weeks after birth, and at 1, 3, 5 and 7 years old	17 PCDD/Fs in breast milk (lipid adjusted) Mean (SD) TEQ total PCDDs/Fs: > Cases (hotspot): 10.8 (1.4) pg/g > Controls (non-sprayed): 3.2 (1.5) pg/g	Same as at age 5, lower testosterone levels in hotspot children (both boys, -66.7%; and girls, -45.7%), more significant in boys. Calculated 17β-HSD activity lower in only boys. DHEA higher in hotspot area, but only in boys. DHEA level decreases at ages 3 and 5 in girls, but recovered to normal range by age of 7 (DHEA levels significantly increased in boys at age 7). A-dione levels increased in boys at age 5 in hotspot. At age 7, no differences for boys compared to control. For girls, at age 5, A-dione levels now decreased and no differences between hotspot and control. In boys, the serum testosterone level and 17β-HSD activity had a strong inverse correlation with the TEQ total PCDD/Fs level in the breast milk ($r = -0.47$, $p = 0.001$, and $r = -0.62$, $p < 0.001$, respectively). However, this was not seen in the girls ($r = -0.21$, $p = 0.139$, and $r = -0.18$, $p = 0.22$, respectively). On the other hand, a positive correlation ($r = 0.49$, $p < 0.001$, and $r = 0.56$, $p < 0.001$) was observed between the progesterone and TEQ total PCDD/Fs in boys and girls. In boys, DHEA and CYP17 lyase were specifically observed to have positive correlations ($r = 0.5$, $p < 0.001$, and $r = 0.4$, $p < 0.01$) with the TEQ total PCDD/Fs in breast milk. However, this was not observed in girls ($r = 0.12$, $p = 0.39$, and $r = -0.01$, $p = 0.972$). The cortisol, cortisone and 17-OH progesterone concentrations were not significantly correlated with the dioxin congeners in either the boys or girls (data not shown).
Paul *et al.*, 2017 Spain	Case-control study	Reproduction: Sperm concentration, volume, percent motile sperm, and percent morphologically normal sperm	Cases: n = 24 men with low semen quality Controls: n = 26 men with normal semen quality	12 dl-PCB measured in serum (lipid adjusted). Cases (low-semen-quality group): Mean (SD) total TEQ 22.52 (21.2) pg/g. Controls (normal-semen-quality group): Mean (SD) total TEQ 14.00 (10.82) pg/g.	Individuals with altered semen parameters exhibited significantly higher levels of non-ortho PCBs (949.49 ± 624.97 pg/g lipid; $p = 0.020$) and total DI-PCBs (7029.96 ± 3023.97 pg/g lipid; $p = 0.028$) than in the control group (508.40 ± 324.44 pg/g lipid and 4805.92 ± 2205.02 pg/g lipid, respectively). But this was only significant for the individual congener PCB 105 ($p = 0.031$). For the low-semen-quality group, negative significant correlation between PCB 126 in serum, the most toxic dioxin-like PCB, and viability ($r = -0.645$; $p = 0.013$). Moreover, sperm morphology was positively correlated with two non-ortho PCBs, PCB 77 ($r = 0.671$; $p = 0.009$) and PCB 81 ($r = 0.552$; $p = 0.041$). Finally, positive correlations between sperm volume and PCB 118 ($r = 0.556$; $p = 0.039$), total mono ortho PCBs ($r = 0.583$; $p = 0.029$) and total DI-PCBs ($r = 0.593$; $p = 0.025$) were found.

TABLE 4.1 **OVERVIEW OF PRIMARY STUDIES WITH REPRODUCTIVE OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Shi *et al.*, 2020 China	Cross-sectional study	Reproduction: Testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), androstenedione (A-dione), 3β-hydroxysteroid dehydrogenase 3β-HSD	n = 78 men (mean [SD] age: 66 [5] years) living in an e-waste region in China	17 PCDD/Fs measured in serum (lipid adjusted). Mean (SD) TEQ PCDD/Fs: 19.8 (13.8) pg/g	In general, linear models the significant findings were: Adjusted means (95% CI) by quartiles of dioxins and dl-PCBs: DHEA: PCDFs TEQ: Quartile 1 (reference: <3.80 pg/g): 1 447 (1 114, 1 780) vs. quartile 2 (3.80 – 6.31 pg/g): 1 933 (1 568, 2 298) ($P < 0.05$). No difference with Q3 or Q4. DHEA: PCDD/Fs TEQ: Quartile 1 (reference: < 8.57 pg/g): 1 360 (1 043, 1 678) vs. quartile 2 (8.57 –15.11 pg/g): 1 966 (1 666, 2 326) ($P < 0.01$). No difference with Q3 or Q4. 3β-HSD: TCDD: Quartile 1 (reference: < 1.30 pg-TEQ/g): 496 (326, 665) vs. quartile 2 (1.30 – 1.67 pg-TEQ/g): 719 (545, 893) ($P < 0.05$), and vs. quartile 4 (≥ 2.64 pg-TEQ/g): 807 (618, 996) ($P < 0.01$).
Sun *et al.*, 2017 Viet Nam	Case-control study	Reproduction: Testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), oestradiol, 3β-hydroxysteroid dehydrogenase 3β-HSD	Cases: n = 50 from dioxin hotspot Controls: n = 48 from non-sprayed regions	17 PCDD/Fs and 4 non-ortho PCB, measured in serum (lipid adjusted) Sums and TEQ not given but calculated in ng TEQ/g lipid. Cases mean: 34.0 ng TEQ/g Controls mean: 10.6 ng TEQ/g	No significant association between serum hormones and any congener after adjustment in multiple linear regression. But unadjusted simple correlation found effect for certain congeners and certain hormones.

Notes: OCDD: octachlorodibenzodioxin, PCDF: polychlorinated dibenzofurans, SD: standard deviation, TEQ: toxic equivalent quotient, NHANES: National Health and Nutrition Examination Survey, CI: confidence interval, PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans, r: spearman correlation coefficient, LH: Luteinizing hormone, P: P-value, PCB: polychlorinated biphenyls, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, HxCDD: hexachlorodibenzo-p-dioxin, FSH: follicle-stimulating hormone, DHAEA: dehydroepiandrosterone , SHBG: sex hormone binding globulin.

4.2.3 FEMALE REPRODUCTIVE EFFECTS

The main endpoints referenced by EFSA on female reproductive effects were on endometriosis, pubertal development, and other effects on female reproduction. No further studies on female reproduction were found in the literature search.

4.2.3.1 Endometriosis

Twelve studies addressing endometriosis were assessed by EFSA, one of which was a prospective cohort study, while the rest were cross-sectional case-control studies. No dose-response was observed in the prospective cohort study, and EFSA found limitations in the cross-sectional studies. Therefore, EFSA concluded that the studies were insufficient to conclude on the association between serum levels of dioxin and dl-PCB, and endometriosis.

4.2.3.2 Pubertal development

Four studies addressing pubertal development were assessed by EFSA, and no association between dioxin and dl-PCB exposure and female pubertal development was found.

4.2.3.3 Other effects on female reproduction

EFSA reported on three studies that investigated the effect of dioxins and dl-PCBs on the menstrual cycle. EFSA reported that the results gave no consistent support for an association between exposure levels and irregular menstrual cycles. Furthermore, EFSA reported on four studies addressing the effect of dioxins and dl-PCBs on either time to pregnancy, ovarian function, leiomyomas, or age at menopause. EFSA concluded that, since there was only one study per outcome, the evidence was insufficient.

4.2.4 BIRTH OUTCOMES

For birth outcomes, EFSA divided the main effects into sex ratio, birth weight and other birth outcomes. One further study was found in the literature search addressing birth weight as an outcome (**Table 4.2**).

4.2.4.1 Sex ratio

EFSA reported on four studies investigating the difference in sex ratio of children born to parents exposed to dioxins and dl-PCBs. EFSA rated three of these as Tier 2 studies, and one as a Tier 1 study. Although there were some uncertainties in the back-calculation of the levels of dioxins in the parents, a pattern of reduced sex ratio (number of newborn males divided by total births) was observed across three different cohorts. EFSA therefore concluded that the decreased sex ratio in response to dioxin exposure likely is causal. No further studies were found in the literature search reporting on this outcome.

4.2.4.2 Birth weight and other outcomes

EFSA assessed 18 studies on birth weight and other outcomes (12 Tier 2 studies and 6 Tier 1 studies). The other outcomes assessed were: Yusho disease, gestational age, child head circumference, birth defects, parity, spontaneous abortion, preterm delivery, pregnancy loss, congenital anomalies and infant death. EFSA concluded that the studies were inconclusive and could not be used for risk assessment. One additional study (Kobayashi *et al.*, 2017) was found which investigated an association between birth weight and total dioxin exposure with regard to polymorphism in three dioxin-metabolizing enzymes as a factor. The genes assessed were AhR, CYP1A1 (Cytochrome P450 1A1) and GST (Glutathione S-Transferase). This study only found a significant correlation between birth size and dioxin exposure, when combined with the GST null genotype. However, this study, taken together with the findings from the EFSA report, still shows inconsistent data, rendering it difficult to determine a conclusion of effect.

4.2.5 THYROID DISEASE AND THYROID HORMONES

The EFSA report concluded that there was insufficient evidence for an association with thyroid function/disease in adults from studies resulting from accidental exposure or incidents (high exposure to TCDD or PCDD/F and dl-PCBs). One study from the EFSA report (Baccarelli *et al.*, 2008), provided relatively strong support for a causal association between prenatal exposure to TCDD and increased neonatal blood thyroid stimulating hormone (TSH) concentration, indicating possible subclinical hypothyroidism in highly exposed children from Seveso. Studies with background exposure in newborns or children did not suggest any adverse effects on thyroid function in children. Four further studies were found in the literature search addressing the outcome of thyroid hormone function. A summarization of these is given in Table 4.3.

4.2.5.1 Studies in adults

Two studies from the literature search assessed thyroid hormone function in adults (**Table 4.3**). One study (Li *et al.*, 2019) assessed maternal thyroid hormone associations in mothers from the LUPE cohort (n = 99 breast milk samples) by investigating the association between background exposure to seventeen PCBs and five PCDD/PCDFs and levels of total thyroxine (T4), triiodothyronine (T3), and reverse T3 (rT3). The study found that total T3 was significantly inversely associated with OCDD. The study suggested that dioxin levels in breast milk may be associated with maternal thyroid disruption, but that the study has limited power due to the small sample size. The other study included from the literature search (Li *et al.*, 2018) assessed total concentrations of T4, T3 and rT3 in placenta samples from mothers who gave birth to boys only (n = 58) and background exposure of dioxins and dl-PCBs (also measured in placenta). In that study, T4 was inversely associated with TCDD and positively associated with 1,2,3,4,6,7,8-HpCDF; T3 was positively associated with TCDF and PCDF; and rT3 was positively associated with PCB 81, PCDF and 2,3,4,6,7,8-HxCDF. The study suggested that dioxin exposure is associated with thyroid hormone levels in placenta, but that it has limited power due to the small sample size.

TABLE 4.2 **OVERVIEW OF PRIMARY STUDIES WITH BIRTH WEIGHT AND OTHER OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Kobayashi *et al.*, 2017 Japan	Prospective birth cohort study	Reproduction: birth weight, length, head circumference, polymorphism in AhR, CYP1A1 and glutathione-S-transferase	Pregnant women (n = 356) enrolled and followed up with their newborns (n = 148)	All 29 congeners measured in maternal blood (lipid adjusted). Mean TEQ level: 17.5 pg/g lipid.	In multiple linear regression: Regression coefficient divided in polymorphisms groups: Mothers carrying the GSTM1 null genotype showed a tenfold increase in TEQ, associated with a decrease in birth weight of β = -345 g (95% CI -584, -105). Mothers carrying the CYP1A TT/TC genotype showed a significant decreasing effect on birth weight β = -202 g (95% CI -387, -17)

Notes: AhR: aryl hydrocarbon receptor, TEQ: toxic equivalent quotient, CI: confidence interval.

4.2.5.2 Studies in newborns or children

Two studies from the literature search assessed thyroid hormone function in newborns or children (**Table 4.3**). One study investigated the association between low background exposure of 29 congeners of PCDD/PCDF and dl-PCBs in mothers (n = 386) at gestational week 30 and thyroid hormones (TSH and free T4[FT4]) in infants (n = 410) and mothers (Baba *et al.*, 2018). The mothers were recruited at a hospital in Hokkaido, Japan and median whole blood total TEQ was 13.8, with a range of 3.42 to 43.4 pg/g lipid. There was a positive association between mother dioxin TEQ and neonatal FT4. Total dioxin-TEQ and coplanar PCBs were positively associated with neonatal FT4, and the association was stronger in boys. Several PCDD/F and PCB isomers were also positively associated with neonatal FT4. Total PCBs or non-dioxin-like PCBs were not associated with any maternal or neonatal thyroid hormones. The results suggest that perinatal exposure to background-level of dioxin-like substances increases neonatal FT4, especially in boys. The other study included from the literature search (Warner *et al.*, 2020a), reported on the association between mothers (n = 383) in the Seveso Women's Health Study exposed to high concentrations of TCDD from the factory explosion, and thyroid hormones (TSH, FT4, free T3 [FT3] and total T4) in children (n = 288 female, n = 282 male). Maternal serum TCDD was estimated at pregnancy (14.4 [6.4-33.3 ppt]) based on an initial measurement of 60.2 (28.4 – 156 ppt). Maternal TCDD was associated with lower FT3 and FT4 in offspring.

The study by Baba *et al.* (2018) provided evidence for an association between prenatal low/moderate exposure and increased neonatal blood FT4. However, no firm conclusions could be made on the association between thyroid hormones and exposure of dioxins in children (inconsistency of direction of effect). In conclusion, the additional studies on thyroid hormones are in line with the EFSA conclusion that studies with background exposure to TCDD, other PCDDs, PCDFs or dl-PCBs do not suggest any adverse effects on the thyroid.

TABLE 4.3 **OVERVIEW OF PRIMARY STUDIES WITH BIRTH WEIGHT AND OTHER OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Baba *et al.*, 2019 Japan	Prospective birth cohort study	Thyroid hormone function: TSH and FT4	Pregnant women (n = 514) enrolled and followed up with their infants (n = 410).	All 29 congeners measured in maternal blood (lipid adjusted). Median maternal total (range) TEQ: 13.8 (3.42–43.4) pg/g lipid.	In multiple linear regression (β, 95% CI): Effect between maternal PCDD/F and neonatal FT4 (β = 0.224, 95% CI: 0.016, 0.433), and between dl-PCB and neonatal FT4 (β = 0.206 [0.034, 0.378]). This effect was higher for boys compared to girls. Maternal non-ortho PCBs were positively associated with maternal FT4 (β = 0.185, P = 0.023). In conclusion, the study suggested that perinatal exposure of dioxins and dl-PCBs increases neonatal FT4 concentrations, especially in boys.
Li *et al.*, 2018 Denmark	Nested case-control study	Thyroid disease and thyroid hormones: Total T4, T3, rT3 in placenta	n = 58 placenta samples collected from mothers of boys born with: Cases (cryptorchidism): n = 28 Controls: (cryptorchidism): n = 30	14 PCDD/Fs and 35 PCBs measured in placenta (lipid adjusted). Geometric mean: PCDD TEQ: 12.6 and PCB TEQ: 2.41	T4 was inversely associated with 2378-TeCDD, and positively associated with 1234678-HpCDF; T3 was positively associated with 2378-TeCDF and 12378-PeCDF; and rT3 was positively associated with PCB 81, 12378-PeCDF, and 234678-HxCDF (p<0.05 and p<0.01).
Li *et al.*, 2019 Germany	Cohort study	Thyroid disease and thyroid hormones: Total T4, T3, rT3 in placenta	n = 99 mothers including breast milk samples two months after birth	17 PCDD/Fs and five PCBs measured in breast milk (lipid adjusted). Sum total PCBs: Mean (range): 9 090 (2 222–20 225) pg/g Sum total PCDD/Fs: Mean (range): 35.7 (0.00–115) pg/g	Total T3 was inversely associated with OCDD (95% CI: −0.20, −0.003)
Warner, Rauch and Ames *et al.*, 2020 Italy	Prospective birth cohort (SWHS study)	Thyroid disease and thyroid hormones: TSH, FT3, FT4	Women (40 years of age) exposed during Seveso explosion in 1976. Children who were born after the explosion in 1976 of the pregnant women were included and followed from age 2–17 years (n = 570)	Median (IQR) maternal 1976 serum TCDD: 50.2 (28.4-156) ppt (lipid adjusted) Median (IQR) estimated TCDD at pregnancy (estimated from measured value in 1976): 14.1 (6.4–33.3) ppt (lipid adjusted)	Effect measured in adjusted β (95% CI). Compared to the lowest quartile (Q1), maternal TCDD was associated with lower free T3 (Q2: adj-β = −0.13; Q3: adj-β = −0.22; Q4: adj-β = −0. 14; p-trend = 0.02). In participants with high thyroid antibody status, inverse associations between maternal initial serum TCDD and free T3 were significantly stronger than in participants with normal antibody status (p-interaction = 0.02). Positive association between maternal initial serum TCDD and TSH concentrations in participants with high thyroid antibody status (Q2: adj-β = 11.4%; Q3: adj-β = 49.0%; Q4: adj-β = 105.5%; p-trend < 0.01) but not in those participants with normal antibody status. Similar results were found for TCDD estimated at pregnancy.

Notes: TEQ: toxic equivalent quotient, PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans, PCDD: polychlorinated dibenzo-p-dioxin, PCB: polychlorinated biphenyls, dl-PCB: dioxin-like polychlorinated biphenyls, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin.

4.2.6 TYPE 2 DIABETES AND OBESITY

As both T2D and obesity belong to the cluster of metabolic conditions, which are closely associated and represent risk factors for the development of CVD metabolic syndrome, the two outcomes were evaluated and presented together by EFSA in their 2018 assessment. EFSA included in their assessment 20 epidemiological studies investigating associations between exposure to PCDD/Fs and dl-PCBs and T2D and obesity. Fourteen of the studies were rated Tier 2 and six were rated Tier 1. Several methodological weaknesses were pointed out for the majority of studies included in the assessment. Uncertainties in the results were described with regards to the possibility of reverse causality in cross-sectional studies, but also flawed study design or reporting (very low number of participants or cases, undefined study populations, poor quality of outcome assessment, selection bias). Four studies, highlighted by EFSA as the most convincing evidence, showed mixed results, and EFSA concluded that the studies on T2D and obesity were inconclusive and could not be used as a basis for the risk assessment.

Three additional studies were found in the literature search investigating associations between exposure to dioxins and obesity or diabetes. The studies are described in the following sections and details are shown in **Table 4.4**. The three studies investigate different outcomes. Thus, evidence presented in these studies may not be sufficient to change the conclusion made by EFSA.

4.2.6.1 Prenatal exposure in the Seveso Second Generation Study

Two studies of the Seveso Second Generation Study were included (Warner *et al.*, 2019 and Warner *et al.*, 2020b). Warner *et al.*, 2019 reported on metabolic outcomes of 611 children (n = 314 girls, n = 297 boys) born to 402 mothers of the Seveso Women's Health Study, who had been exposed to high concentrations of TCDD during or before their childbearing years from the factory explosion in 1976. In utero TCDD exposure was estimated from the body burden measured in sera soon after the accident or during follow-ups (1996 or 2008), using a first-order kinetic model with a half-life adjusted to the initial dose, age and other co-variates. In addition, the assessed outcome parameters were tested towards maternal initial TCDD burden in sera. The outcome parameters recorded in the offspring were BMI, waist circumference, elevated triglyceride levels, total cholesterol, HDL-C, glucose in plasma from a fasting blood draw and blood pressure measurement. The outcome parameters were classified and combined to assess development or presence of metabolic syndrome. The study found sex-dependent associations between the initial maternal TCDD levels and the cardiometabolic outcomes. A tenfold increase in initial maternal TCDD concentration was inversely associated with BMI in girls, but not boys. In contrast, in boys only, initial maternal TCDD was associated with an increased risk for metabolic syndrome. Results for TCDD estimated at pregnancy were comparable.

In the second study included in the literature, Warner *et al.*, 2020b, the authors investigated associations between maternal TCDD exposure and glucose metabolism

in the same study population. However, analysis was restricted to their children of 18 years and older to exclude variation from decreased insulin sensitivity during puberty, rendering 426 adult children born to 303 mothers, who were included in the analysis. The relationship of maternal TCDD burden (estimated as explained above) and different endpoints (serum insulin and plasma glucose from a fasted blood draw and the computer-based homeostatic model assessments for insulin resistance [HOMA2-IR] and beta-cell function [HOMA2-B]) were assessed. In line with the previous study, sex-specific effects were reported. The maternal TCDD burden estimated at pregnancy was inversely associated with serum insulin and HOMA2-B among daughters, but not among sons. Similar effect modification was observed for TCDD estimated at pregnancy and HOMA2-IR. However, as reported by Warner *et al.*, 2019, the associations observed between serum insulin and HOMA2-B in female offspring suggested to be mediated by BMI.

4.2.6.2 Metabolic effects in pregnant women

One study (Liu *et al.*, 2019) investigated the association between dioxin-like compounds and the prevalence of gestational diabetes mellitus (GDM) and with a nested case-control study in a population of pregnant Chinese women. The main aim of the study was to establish human-based relative-effect potencies. As this is not relevant for the risk assessment of dioxins, the results on relative-effect potencies are not discussed. There were 439 pregnant women recruited in the study. GDM was diagnosed based on an oral glucose tolerance test and fasting and postprandial blood glucose levels. Seventy-seven diagnosed cases and 2 pair-matched controls per case (154 controls in total) were included in the study (overall study participation rate – 53 percent of initially recruited population). An association with obesity was not apparent for either exposure or GDM outcome. Seventeen PCDD/Fs and 12 dl-PCBs were measured in serum. The median (interquartile range) of total TEQ for GDM and controls were 9.9 (range: 7.3–13.2) and 6.9 (range: 5.8–9.2) pg/g lipids, respectively. The association between total TEQ exposure and GDM risk was calculated from prevalence in the interquartile ranges. Significantly increased prevalence for GDM was found in Q3 and Q4 with quartile levels of total TEQ ≥7.72 pg/g lipid. In addition, an association was found between per SD increase in total TEQ and increase risk in GDM (OR = 2.12, 95% CI: 1.57, 2.86).

TABLE 4.4 **OVERVIEW OF PRIMARY STUDIES WITH TYPE 2 DIABETES AND OBESITY OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCBs EXPOSURE	RESULTS AND CONCLUSIONS
Liu *et al.*, 2019 Viet Nam	Prospective nested case-control study	Type 2 diabetes and obesity: Gestational diabetes mellitus (GDM) and fasting blood glucose	Cases with gestational diabetes mellitus: n = 77 Controls: n = 154	All 29 congeners measured in blood (lipid adjusted). Total TEQ whole group median (IQR): 7.72 (6.14-10.36) pg/g lipids	Total TEQ cases: Median (IQR): 9.9 (7.3-13.3) g/g Total TEQ controls: Median (IQR): 6.9 (5.8-9.2) g/g In adjusted analyses (BMI and foetal sex) of risk of GDM and association with total TEQ: OR (95% CI): 2.12 (1.57, 2.86) per change in SD of total TEQ. When departed into quartile levels of total TEQ (pg/g): Q1 (<6.14 pg/g): Reference Q2 (6.14-7.72 pg/g): 2.04 (0.78, 5.35) Q3 (7.72-10.36): 4.02 (1.61, 10.06) Q4 (≥ 10.36): 7.74 (3.10, 19.29) Ptrend <0.001
Warner, Rauch and Brambilla *et al.*, 2020 Italy	Prospective birth cohort (SWHS study)	Type 2 diabetes and obesity: Glucose, insulin HOMA2-IR, HOMA2-B,	Women (40 years of age) exposed during Seveso explosion in 1976. Children who were born after the explosion in 1976 of the pregnant women were included and followed up at age 18 or older (n = 426)	Median (IQR) maternal 1976 serum TCDD: 53.1 (25.1-112) ppt (lipid adjusted) Median (IQR) estimated TCDD at pregnancy (estimated from measured value in 1976): 20.6 (9.4-47.1) ppt (lipid adjusted)	Effect measured in adjusted β (95% CI). TCDD estimated at pregnancy was inversely associated with insulin (adj β = −1.24 µIU/mL, 95% CI: −2.38, −0.09) and HOMA2-B (adj β = −10.2% decrease, 95% CI: −17.8, −1.9) among daughters, but not sons (insulin: adj β = 0.57 µIU/mL, 95% CI: −0.84, 1.98, P for interaction = 0.04; and HOMA2-B: adj-β = 0.8% increase, 95% CI: −10.7, 13.9, P for interaction = 0.11). Similar effect modification was observed for TCDD estimated at pregnancy and HOMA2-IR (P for interaction = 0.13). The observed associations in daughters showed evidence of mediation by BMI, which we have previously found to be associated with prenatal TCDD exposure in female offspring.
Warner *et al.*, 2019 Italy	Prospective birth cohort (SWHS study)	Type 2 diabetes and obesity: BMI, metabolic syndrome (MetS) based on waist circumference, fasting plasma TAG, HDL-cholesterol, total cholesterol, glucose and blood pressure.	Women (40 years of age) exposed during Seveso explosion in 1976. Children who were born after the explosion in 1976 of the pregnant women were included and followed from age 2 to 17 years (n = 611)	Median (IQR) maternal 1976 serum TCDD: 51.0 (24.4–108) ppt (lipid adjusted) Median (IQR) estimated TCDD at pregnancy (estimated from measured value in 1976): 10.6 (5.5–25.3) ppt (lipid adjusted)	A tenfold increase in initial maternal TCDD concentration was inversely associated with BMI in girls (adj-β = −0.99 kg/m2), but not boys. In contrast, in boys only, initial maternal TCDD was associated with increased risk for MetS (adj RR = 2.09, 95% CI 1.09, 4.02). Results for TCDD estimated at pregnancy were comparable.

*Notes:*TEQ: toxic equivalent quotient, PCDD: polychlorinated dibenzodioxins, PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans, PCB: polychlorinated biphenyls, dl-PCBs: dioxin-like polychlorinated biphenyls, BMI: body mass index, SWHS: Seveso Women's Health Study, IQR: interquartile range, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, CI: confidence interval, TAG: triacyl glycerides

4.2.7 CARDIOVASCULAR EFFECTS

EFSA reported on 12 epidemiological studies covering the effects of dioxins and dl-PCBs on different cardiovascular endpoints, such as: cardiovascular mortality, heart disease, ischemic heart disease and hypertension. Ten studies were rated Tier 2, while two studies were rated Tier 1. EFSA pointed to one study strongly supporting increased cardiovascular risk after exposure to TCDD (Steenland *et al.*, 1999), however, this study was conducted on workers with very high occupational exposure (serum TCDD > 1000 pg/g fat). Studies assessing lower exposures to dioxins and dl-PCBs were, according to EFSA, inconclusive in finding associations between cardiovascular risk and dioxin or dl-PCB exposure. No further studies were found in the literature search on cardiovascular risk factors after dioxin exposure.

4.2.8 HEPATIC DISORDERS AND DIGESTIVE EFFECTS

EFSA reported on five studies that compared blood PCDD/F levels of occupationally or accidentally exposed cohorts and potential non-cancer hepatic and digestive disorders or abnormal function. Three of the studies were rated Tier 1. No further studies were found in the extensive literature search. In summary, based on the few existing studies, EFSA concluded that there is no evidence for an association of hepatic or digestive diseases with prolonged accidental or occupational exposure to PCDD/Fs.

4.2.9 EFFECTS ON THE IMMUNE SYSTEM

EFSA reported on 14 studies, which did not present strong evidence for an effect of dioxin exposure on the immune system at adolescence or adulthood. Only one of these studies (Dinse *et al.*, 2016) was rated Tier 1, and this study examined an association between autoimmunity and serum concentrations of PCDD/Fs and dl-PCBs in a cross-sectional study with 4 340 participants from the National Health and Nutrition Examination Survey cohort. No associations were observed in this study. Further, the studies in adults were retrospective and had shortcomings related to exposure evaluation and confounding factors. Moreover, the studies measured different immune parameters, making it difficult to compare them. In addition to the studies in adults, EFSA reported on eight studies on exposure during development. Half of these studies were given a Tier 1 rating, and these are summarized here. Weisglas-Kuperus *et al.* (2000) investigated immunological and clinical parameters in children. After primary vaccination against mumps, measles and rubella, associations with antibody levels were observed for the non-dl-PCBs in blood. PCDD/Fs and dl-PCBs were not examined. PCDD/Fs and dl-PCBs were measured in milk but did not show a relation with the levels of antibodies or illness parameters investigated. Van Den Heuvel *et al.* (2002) performed a study on 207 adolescents and found a decreased prevalence of allergic responses with increasing exposure. (Nagayama *et al.*, 2007) assessed lymphocyte subsets in peripheral blood of 92 children and correlated this to the concentration of organochlorine compounds in their mothers'

breast milk. They found an association of exposure to PCDD/Fs and dl-PCBs and an increased ratio of CD4/CD8 cells, as well as an increased percentage of CD3 cells. However, EFSA concluded that the clinical relevance of this finding is unclear. Miyashita *et al.* (2011) correlated prenatal exposure to dioxin-like compounds with allergies and infections during infancy (birth cohort n = 514). Higher levels of exposure in males were found to be associated with increased incidence of otitis media. In addition, the authors reported a minor significant association with allergies during infanthood. Since this study measured an extended number of outcomes, the possibility for type 1 errors was considered likely.

According to EFSA, the available studies did not provide sufficient evidence for an association between PCDD/Fs or dl-PCBs and effects on the immune system. No further studies were found in the literature search on the effects on the immune system after dioxin exposure.

4.2.10 EFFECTS ON THE NERVOUS SYSTEM

EFSA reported on 15 studies in children and 7 occupational studies in adults for the outcome "effects on the nervous system". Various neurodevelopmental outcomes at different ages were investigated in children, but few outcomes were assessed consistently in more than one cohort or at similar age. No association or conflicting results were observed between dioxins and cognitive and motor development in infants and children (> 11 years old). In a Norwegian maternal-exposure cohort study, there was a small increase in OR for negative effects on grammar skills in children. Girls had increased OR for moderate to severe language delay and reduced communication skills. Results from occupational cohorts indicated a persistent association between TCDD exposure and different neurophysiological outcomes. However, back calculation to original exposures based on levels in blood sampled decades after the exposure are highly uncertain. Also, the occupational studies suffer from lack of participants. Thus, EFSA concluded that the available information was not sufficient to form a basis for the risk assessment on neurodevelopment in children. There was insufficient information to draw conclusions on effects on the nervous system after exposure in adult life. There is also no apparent mode of action.

In addition to the EFSA report, one additional study was found in the literature search on neurodevelopment in children (**Table 4.5**). In this study, neurodevelopmental outcomes were measured at 2 years of age, showing an association between neonatal electroencephalography brain signals with increased TCDD exposure (Pham *et al.*, 2021). However, a direct association between gaze behaviour and TCDD was not reported.

Due to limited novel evidence following the EFSA report, EFSA's conclusion still stands: There is not sufficient evidence to conclude on neurodevelopmental outcomes.

TABLE 4.5 **OVERVIEW OF PRIMARY STUDIES WITH NERVOUS SYSTEM OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs".**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Pham *et al.*, 2021 Viet Nam	Prospective birth cohort	Nervous system: Intra-uterine brain activity (measured by EEG 2 days after birth). 2 years after birth: gaze behaviour, cognitive, language and motor skills measured by Bayley-III	n = 51 mother–infant pairs	17 PCDD/Fs measured in breast milk sample one month after birth (lipid adjusted). Mean (SD) TEQ PCDD/Fs: 7.9 (1.6) pg/g	Perinatal dioxin exposure, particularly TCDD exposure above 2.8 pg/g, influenced relative EEG power values mainly in the intra-burst-interval part of the trace alternant pattern in the quiet sleep stage. In intra-burst-intervals, decreased frontal delta power and increased frontal and parietal alpha power values in the left hemisphere and temporal beta power values in the right hemisphere were associated with increased TCDD exposure, with significant dose–response relationships.

Notes: dl-PCB: dioxin-like polychlorinated biphenyl, EEG: electroencephalogram, PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, SD: standard deviation, TEQ: toxic equivalent quotient.

4.2.11 EFFECTS ON TEETH AND BONES

EFSA assessed three studies investigating associations between dioxins and dl-PCBs and teeth development from three different population groups. A dose–response relationship was observed for tooth enamel hypomineralization or enamel defects. The hypomineralization of permanent teeth is likely to be causally related to postnatal exposure. Increased incidents of hypodontia were also associated with exposure to TCDD serum levels. Tooth defects have also been reported to be the most sensitive response to TCDD in animal models. Unlike teeth, bone is undergoing a constant remodelling process. Limited evidence from one cohort indicates associations between PCDD/F and dl-PCB exposure and some changes in bone parameters.

Although, in the previous EFSA report, the Panel on Contaminants in the Food Chain concluded that exposure to PCDD/Fs via breast milk may lead to increased enamel defects in children, these data were deemed less suitable for dose–response assessment. No further studies on the effect of dioxins on teeth and bones were identified in the literature search.

4.2.12 CANCER

EFSA divided the studies on cancer into two categories: industrial accidents or contamination incidents and occupational exposure. For industrial accidents and contamination incidents, EFSA included five studies. Two were rated Tier 1, and three were rated Tier 2. For occupational exposure, 17 studies were included, five of which were rated Tier 1 and twelve were rated Tier 2. In their summary, EFSA reported that many studies showed a positive association between dioxin exposure and all cancers combined. However, there was no clear link to any specific site, nor did the studies show a clear dose–response relationship. Therefore, EFSA deemed these studies unsuitable for risk assessment.

Two further studies were found in the literature search on the effects of dioxins and dl-PCBs on cancers (**Table 4.6**). Koual *et al.* (2019) conducted a case-control study with 91 participants, in which 38 displayed metastatic breast cancer and 53 displayed non-metastatic breast cancer. All 29 congeners were measured in adipose tissue. The study found a positive association between TCDD concentration in adipose tissue and risk of metastasis in patients with a BMI ≥25 kg/m^2 (p-value 0.03). However, most results showed no, or weak, association between dioxins, PCBs, or groups thereof and metastasis of breast cancer. This study was conducted on all cancer patients and explored only the prevalence of metastasis and tumour size. Furthermore, the study was small (n = 91). The second study (Lim *et al.*, 2017), also a case-control study, investigated prostate cancer risk in a Korean cohort. The authors randomly selected 1 879 participants from a cohort of 159 844. Of these, 256 controls and 110 cases (diagnosed with prostate cancer) were used for the analyses. Twelve dl-PCBs were assessed, and a hazard ratio for TEQ was found at 1.40 (1.21–1.62). However, the hazard ratio for dl-PCBs did not show a positive association.

The two additional studies from the literature search showed low causality, had a low number of observations, and did not change the conclusion made by EFSA. As such, it was concluded that the studies found do not display a clear association between dioxins and dl-PCBs and cancers.

TABLE 4.6 **OVERVIEW OF PRIMARY STUDIES WITH CANCER OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF DIOXINS AND dl-PCBs"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	DIOXIN AND dl-PCB EXPOSURE	RESULTS AND CONCLUSIONS
Koual *et al.*, 2019 France	Case-control study	Cancer: Metastasis in breast cancer	Cases: n = 38 metastatic breast cancer Controls: n = 53 non-metastatic breast cancer	All 29 congeners measured in blood (lipid adjusted). Metastatic median (IQR) total TEQ: 22.5 (16.9–30.8) pg/g. Non-metastatic median (IQR) total TEQ: 24.1 (16.1–35.2) pg/g	TCDD concentration in adipose tissue was positively associated with the risk of metastasis in patients with a BMI≥ 25 kg/m2: (OR [95% CI]: 4.48 [1.32, 20.7] P = 0.03). Furthermore, the concentrations of TCDD and PCB 126, 118 and 123 in adipose tissue were positively associated with lymph node metastasis and tumour size.
Lim *et al.*, 2017 Republic of Korea	Case-control study	Cancer: Prostate cancer	Cases: n = 110 Controls: n = 256	12 dl-PCBs, measured in blood (lipid adjusted). Levels not given, only the association with health outcome.	Hazard ratio (95% CI) for TEQ: 1.40 (1.21, 1.62) (*P* = 0.073) Hazard ratio (95% CI) for dl-PCBs: 1.39 (0.89, 2.19) (*P* = 0.146) In conclusion, the findings suggested a possible role of dl-PCBs in the aetiology of prostate cancer.

Notes: IQR: interquartile range, TEQ: toxic equivalent quotient, dl-PCB: dioxin-like polychlorinated biphenyl, BMI: body mass index, OR: odds ratio, CI: confidence interval, TCDD: 2,3,7,8-tetrachlorodiobenzo-p-dioxin, PCB: polychlorinated biphenyls.

4.2.13 OTHER EFFECTS

In addition to the effects described above, EFSA found two studies (Michalek *et al.*, 2001 and Gupta *et al.*, 2006) which could not be attributed to any of the aforementioned groups. These studies were included in the EFSA report as they met the criteria. However, since risk assessment should not be based on single studies, they were not included in the assessment. Both studies were conducted on veterans from Viet Nam (Operation Ranch Hand). Michalek *et al.* (2001) reported on haematological changes in response to TCDD, and no clear effects were found. Gupta *et al.* (2006) showed that higher TCDD levels were associated with decreased risk of benign prostatic hyperplasia. No additional studies were found in the literature search.

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CHAPTER 5

RESULTS AND SUMMARIZATION OF THE LITERATURE REVIEW "TOXIC EFFECTS OF MeHg"

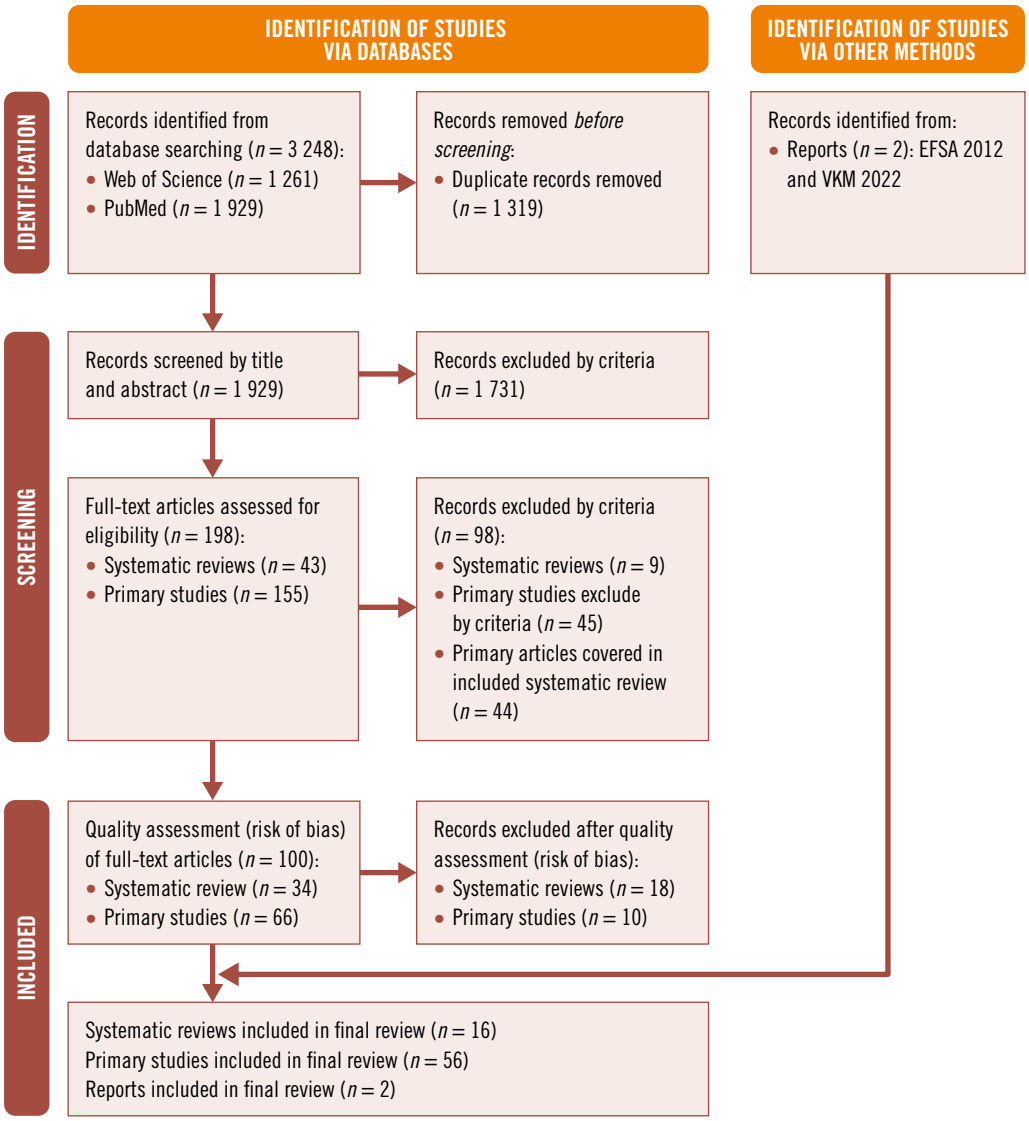
5.1 LITERATURE AND QUALITY ASSESSMENT

Literature searches for the review on the "Toxic effects of MeHg" were performed in the databases PubMed and Web of Science. A flow diagram of the results from the literature searches is given in **Figure 5.1**. The parallel literature searches performed in Web of Science and PubMed resulted in 3 248 records. Of these, 1 319 were found to be duplicate records. Following duplicate removal in Endnote, 1 929 records were subjected to title and abstract screening using Rayyan. Based on the predefined inclusion and exclusion criteria (**Table 2.10**), 1 731 records were excluded and 198 records (comprising 43 systematic reviews and 155 primary articles) were retained for full-text screening.

5.1.1 SYSTEMATIC REVIEWS

A total of 43 systematic reviews were assessed in full text after title and abstract screening. Of these, nine additional records were excluded based on the inclusion and exclusion criteria (Appendix 5, **Table A5.3**), leaving 34 systematic reviews that were assessed with the AMSTAR 2 risk-of-bias tool. Following the assessment with AMSTAR 2, the studies were graded into categories according to the overall confidence in the results from the review (Appendix 5, **Table A5.5**). Four studies were graded "high" and 12 were graded "moderate". These were included for further assessment in the report. Thirteen studies were graded "low" and five studies were graded "critically low". These were excluded for further assessment.

FIGURE 5.1. **FLOW DIAGRAM FOR THE REVIEW "TOXIC EFFECTS OF MeHg"**



Source: The figure was prepared based on Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L. *et al.* 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71

5.1.2 PRIMARY STUDIES

A total of 155 primary studies were assessed in full text after title and abstract screening. Of these, 45 primary studies were excluded based on the inclusion and exclusion criteria (Appendix 5, **Table A5.4**) and 44 primary studies were excluded for further assessment as they were already covered in one of the systematic reviews included (Appendix 5, **Table A5.6**). This left 66 primary articles, which were subjected to risk-of-bias assessment using the OHAT risk-of-bias tool (Appendix 5, **Table A5.7**).

Based on the risk-of-bias assessment, 56 primary studies were graded Tier 1, 10 were graded Tier 2, and 0 were graded Tier 3. Only the 56 studies graded Tier 1 were included in the final assessment.

5.2 RESULTS AND SUMMARIZATION OF THE LITERATURE INCLUDED

The systematic reviews and original articles included in this extensive literature review covered a diverse range of health outcomes associated with exposure to MeHg. These were grouped into four primary domains: (i) neurological outcomes, (ii) cardiovascular outcomes, (iii) growth and (iv) other outcomes. Narrative summaries of the findings from the systematic reviews and original primary studies are reported in the following sections. In addition, summaries of the reports from the 2012 EFSA and the 2022 VKM assessments are provided.

5.2.1 NEUROLOGICAL OUTCOMES

The following sections provide short narrative summaries of the neurological outcomes obtained from the systematic reviews and original articles excluded from the literature review.

5.2.1.1 Systematic reviews

Six articles were identified that reviewed the effects of Hg exposure in relation to neurological outcomes **Table 5.1**). Three of the systematic reviews (Jafari *et al.*, 2017, Saghazadeh *et al.*, 2017 and Zhang *et al.*, 2021a) considered autism spectrum disorders, and a fourth (Yoshimasu *et al.*, 2014) considered both autism and ADHD. One systematic review (Puty *et al.*, 2019) assessed neurological effects in adults and another (Hibbeln *et al.*, 2019) concerned neurodevelopment in children exposed prenatally to Hg.

The relationship between autism spectrum disorders and Hg in blood was explored in three systematic reviews. Each of these conducted a meta-analysis of case-control studies and came to similar conclusions, stating that in subjects with autism spectrum disorders, higher concentrations of Hg were detected when compared to the respective control groups. The authors note that the observed differences were small, that there was evidence of heterogeneity across the studies included in the respective meta-analysis, and that the study designs employed limited causal inference in relation to Hg exposure and autism. One of the systematic reviews (Yoshimasu *et al.*, 2014) considered both autism and ADHD. The authors reviewed four studies and obtained inconsistent results, with two of the four studies suggesting that Hg contamination in fish-consuming populations may be related to an increased risk of autism or ADHD.

One systematic review (Hibbeln *et al.*, 2019), surveyed 25 studies for the associations of prenatal Hg exposure and neurocognition. This review found six studies that reported null associations between maternal Hg levels and neurocognition, while

seven studies (45 957 mother–infant pairs) were found to report paradoxical findings indicating that higher levels of Hg seemed to have beneficial effects in relation to neurocognitive development. Overall, Hibbeln *et al.* concluded that no net adverse neurocognitive outcomes were reported among offspring at the highest ranges of seafood intakes, despite associated increases in Hg exposures.

The final review concerning neurological effects (Puty *et al.*, 2019) focused on disorders in relation to dietary Hg exposure in adults living in areas with environmental exposures. The review reached no conclusion among the six studies reviewed, citing low level of evidence and high risk of bias.

TABLE 5.1 **OVERVIEW OF SYSTEMATIC REVIEWS WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Yoshimasu *et al.*, 2014 A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/ hyperactivity disorder in childhood	Neurological; ADHD and autism spectrum disorders (ASD)	Total n = 4 studies involving MeHg exposure from fish consumption: Cohort studies (n = 2), case-control study (n = 1) and cross-sectional study (n = 1)	-	Meta-analysis: Summary OR from two of the included studies for the evaluation of a relationship between Hg exposure and ADHD (OR = 1.60, 95% CI: 1.10, 2.33). The two other studies included found no effect.	Hg exposure from fish consumption might be related to an increased risk of ADHD, but the results were not consistent. The results suggest that prenatal or early infant mercury exposures by vaccination did not have serious adverse effects on increasing risks of ASD or ADHD, while environmental mercury exposure caused by air pollution or maternal fish consumption might promote incidence of ASD and ADHD, respectively.
Jafari *et al.*, 2017 The association between mercury levels and autism spectrum disorders: A systematic review and meta-analysis	Neurological; ASD	Total n = 44: Case-control studies (n = 44)	See results from meta-analysis.	Meta-analysis: The Hg level in whole blood (n = 16 studies with 1 239 cases vs. n = 1 039 controls: Mean difference: 0.43, 95% CI: 0.12, 0.74, P = 0.007); the Hg level in red blood cells (n = 5 studies with 251 cases vs. n = 915 controls, Mean difference: 1.61, 95% CI: 0.83, 2.38, P < 0.001); and the Hg level in brain (n = 3 studies with 16 cases vs. n = 20 controls: Mean difference: 0.61 ng/g, 95 % CI, 0.02, 1.19, P = 0.043) was significantly higher in ASD patients than in healthy subjects, whereas mercury level in hair (n = 23 studies with 1 038 cases vs. n = 933 controls: Mean difference: –0.14 mg/g, 95% CI: –0.28, –0.01, P = 0.039) was significantly lower in ASD patients than in healthy subjects. The mercury level in urine was not significantly different between ASD patients and healthy subjects (n = 8 studies with 491 cases vs. n = 417 controls: Mean difference: 0.51 mg/g creatinine, 95% CI: –0.14, 1.16, P = 0.121).	Subjects with ASDs had higher Hg concentrations compared to healthy subjects. However, the study design limited any causal conclusion.
Saghazadeh *et al.*, 2017 Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: Higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury	Neurological; ASDs	Total n = 38: Case-control studies (n = 38)	See results from meta-analysis.	Meta-analysis: Autism spectrum disorders patients vs. controls: Standardized mean difference (95% CI) (P-value): Hg blood, serum, plasma (overall) (n = 629 vs. n = 476): 1.32 (0.51, 2.13) (P = 0.001) Hg blood, serum, plasma (without outlier) (n = 584 vs. n = 431): 0.43 (-0.064, 0.92) (P = 0.089) Hg blood (overall) (n = 547 vs. n = 422): 1.42 (0.47, 2.37) (P= 0.003) Hg blood (without outlier) (n = 502 vs. n = 377): 0.19 (-0.28, 0.66) (P = 0.422) Hg erythrocyte: (n = 216 vs. n = 184): 1.56 (0.42, 2.70) (P= 0.007) Hg hair (overall): (n = 1092 vs. n = 973): 0.49 (-0.056, 1.03) (P = 0.079) Hg hair (without outlier) (n = 948 vs. n = 829): 0.082 (-0.20, 0.36) (P = 0.570) Hg hair (developed and transition countries): (n = 653 vs. n = 537): -0.18 (-0.45, 0.092) (P = 0.195) Hg hair (developing countries): (n = 295 vs. n = 292): 0.77 (0.31, 1.23) (P = 0.001) Hg urine (n = 111 vs. n = 229): 0.25 (-0.11, 0.36) (P = 0.306)	ADS patients had higher Hg concentrations compared to control for some specimens; however, the differences were rather small.

TABLE 5.1 **OVERVIEW OF SYSTEMATIC REVIEWS WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Zhang *et al.*, 2021 Trace elements in children with autism spectrum disorder: A meta-analysis based on case-control studies	Neurological; ASDs	Total n = 12: Case-control studies (n = 12)	See results from meta-analysis.	Meta-analysis: Overall standardized mean difference in Hg concentrations between ASDs and healthy controls: 1.37 (95% CI: 0.46, 2.28).	Children with ASDs had some higher levels of Hg compared to healthy controls; however, there was evidence of heterogeneity.
Hibbeln *et al.*, 2019: Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews	Neurological; Neurodevelopment; Intelligence/ Cognition	Total n = 25 (but included n = 44 articles for overall seafood assessment): RCTs (n = 4), prospective cohort studies (n = 33), case-control studies (n = 5)	Pregnant women: Range mean hair Hg 0.-6.9 ppm	Prenatal exposure: Six studies reported null associations between maternal mercury levels and neurocognition, while seven studies (45 957 mother–infant pairs) reported seemingly paradoxical findings; that higher levels of mercury had beneficial relationships to neurocognitive development. Eight of the studies had mean hair Hg exposures above 1.1 ppm, and all the studies had participants with exposures that were many times higher than the reference dose. None of the studies reported any net adverse effects on neurocognitive development from seafood consumption in any amount. Childhood: Two studies reported measurements of mercury exposure in the children. Although mercury levels were not reported in the remainder of the studies, it is highly likely that greater seafood consumption in those studies resulted in higher mercury exposures. Since no study reported net adverse outcomes from seafood consumption in children, it is unlikely that mercury exposure from seafood was associated with substantive neurocognitive harms.	Consuming seafood during pregnancy and childhood was likely beneficial and clearly not adverse to neurocognition. No net adverse neurocognitive outcomes were reported among offspring at the highest ranges of seafood intakes, despite associated increases in mercury exposures.
Puty *et al.*, 2019 Association between methylmercury environmental exposure and neurological disorders: A systematic review	Neurological; neurotoxicity in adults; neurobehavioral alterations, memory, communicative and cognitive disorders, motor and visual dysfunctions.	Total n = 6: Case-control studies (n = 4) and cross-sectional studies (n = 2)	Hair Hg concentrations given in two of the studies (mean): 8.8 and 2.6 ppm.	The studies suggested alterations related to the psychosensory, motor and coordination system, as well as motor speech, hearing, visual impairment, mood alterations and loss of intelligent quotient. However, two of the six studies presented a high risk of bias, with methodological problems related to confounding factors, and all studies presented evidence levels ranging from very low to low.	The study could not demonstrate an association of MeHg and neurological alterations.

Notes: OR: odds ratio, ADHD: attention deficit hyperactivity disorder, ASD: autism spectrum disorder.

5.2.1.1.1 Primary studies

The literature search identified 31 original articles that assessed neurological effects associated with dietary Hg exposure (**Table 5.2**). Of these, nineteen reported that one or more outcomes measured were associated with Hg, whether positively or negatively. Six of the studies were cross-sectional studies, while 25 were cohort studies (of which 23 were pregnancy cohorts that specifically included at least one pre- or perinatal time point). Among the 25 cohort studies, 13 unique cohorts were identified, indicating that multiple articles were published using data from the same established cohorts. With four articles each, the "Seychelles Child Development Study" and the "Arctic Cord Blood Monitoring Program/Nunavik Environmental Contaminants" were found to be the two most called-upon cohorts in the articles assessed.

The types of neurological effects investigated were primarily neurodevelopment in children (28 articles), followed by two articles concerning depression in adults, and one article concerning neurotoxicity in adults. Under the subheading "Neurodevelopment", the outcomes assessed were sorted into ten different subcategories: behaviour, brain morphology, intelligence/cognition, memory and learning, mental and psychomotor development, motor function, nerve signalling, reactions and reflexes, speech and language, and visual-motor integration. In the following sections, the findings are described for depression and neurotoxicity and, subsequently, summaries are provided concerning the ten categories of neurodevelopment. Sixteen of the articles included in this section focused on more than one of the neurodevelopmental categories listed above. As such, the outcomes of these articles are described under multiple section headings.

5.2.1.1.2 Depression

Two cross-sectional studies, Berk *et al.*, 2014 and Rossa-Roccor *et al.*, 2021, considered associations of Hg exposure with depression in adults. Both studies used data from the National Health and Nutrition Examination Survey study, conducted in the United States. Rossa-Roccor *et al.* reported no association between MeHg and depression, and reported that all levels of MeHg in blood samples were below the US Environmental Protection Agency's reference dose of 5.8 µg/L. Berk *et al.* reported an inverse association between Hg and depression; however, the levels of Hg in blood were not provided. Thus, neither of the two studies provided evidence that Hg is associated with increased depression in adults.

5.2.1.1.3 Neurotoxicity in adults

Nakamura *et al.* (2014) performed a cross-sectional analysis of adults living in towns with traditional whaling practices. Hair MeHg levels were 8.2 times higher than the general Japanese population, at 14.9 pg/g (geometric mean), 1.1–101.9 (range), with a sample size of 194. The authors found no correlations between hair Hg levels and any of the neurological outcomes measured, including motor function, reactions and reflexes, nerve signalling, hearing loss and brain morphology.

5.2.1.1.4 Neurodevelopment

Twenty-eight articles were identified that investigated neurodevelopmental outcomes in children. Nineteen of the articles reported one or more significant associations with Hg, whether positive or negative. Brief descriptions of the articles reporting significant findings are provided in the following sections (sorted by the ten neurodevelopmental categories). The health outcomes for ASD and ADHD were topics of systematic reviews (above), but no additional original articles were found that were not included in the systematic reviews.

5.2.1.1.4.1 Behaviour

Eleven articles that included behaviour as an outcome potentially associated with exposure to Hg were identified. Of these, nine reported no associations with adverse behaviour outcomes (Cao *et al.*, 2010; Marques *et al.*, 2011; Van Wijngaarden *et al.*, 2013a; Boucher *et al.*, 2014a; Strain *et al.*, 2015; Golding *et al.*, 2016a; Golding *et al.*, 2016b; Barbone *et al.*, 2020 and Myers *et al.*, 2020). Concerning the remaining two studies, Ng *et al.* (2013) and Al-Saleh *et al.* (2016), Ng *et al.* stratified participants according to whether these were carriers of the Apolipoprotein E epsilon 4 allele, a risk factor associated with Alzheimer's disease. Among carriers of the allele, the authors reported that prenatal Hg exposure was associated with all tested aspects of development, but especially, with the social developmental quotient as a behaviour outcome. For their part, Al-Saleh *et al.* investigated developmental delays using two composite metrics that each included behaviour outcomes as one of several outcomes. Significant effects were not parsed out for the different outcome categories; therefore, an association with behaviour specifically cannot be discerned.

5.2.1.1.4.2 Brain morphology

One article was identified that assessed brain morphology in children and its association with Hg (Nišević *et al.*, 2019). This study reported two brain morphometrics (cerebellum length and superior frontal gyrus) to be different between exposed (n = 19, cord blood Hg > 5.8 µg/L) and unexposed (n = 29, cord blood Hg < 5.8 µg/L) groups. The authors did not suggest whether the measured differences were to be considered adverse outcomes or not.

5.2.1.1.4.3 Intelligence/cognition

Ten articles considered intelligence and/or cognition and associations with Hg in children: Cao *et al.*, 2010; Ng *et al.*, 2013; Van Wijngaarden *et al.*, 2013a; Boucher *et al.*, 2014a; Choi *et al.*, 2014; Wang *et al.*, 2014; Jacobson *et al.*, 2015; Debes *et al.*, 2016; Al-Saleh *et al.*, 2020 and Llop *et al.*, 2020.

Three of these articles (Jacobson *et al.*, Debes *et al.* and Al-Saleh *et al.*) reported negative associations between Hg exposure and child intelligence specifically. Jacobson *et al.* reported an association of prenatal Hg exposure with poorer performance on a school-age intelligence quotient assessment. Children with cord Hg ≥ 7.5 µg/L were four times as likely to have an intelligence quotient score < 80, the clinical cut-off for

borderline intellectual disability. Debes *et al.* reported a follow-up study on a Faroe Islands birth cohort, at age 22. Within a battery of over 30 tests, significant negative associations were primarily found in tests that assessed crystalized intelligence/ verbal comprehension. Finally, Al-Saleh *et al.* reported an association between lower intelligence scores with both higher infant urine Hg, and higher mothers' blood MeHg.

Two of the ten articles assessing intelligence and/or cognition however, Wang *et al.*, 2014 and Llop *et al.*, 2020, found positive associations with Hg levels. Llop *et al.*, 2020 reported that higher hair total mercury (THg) was associated with all scales of an assessment that considered general cognition. Wang *et al.* also reported positive associations with Hg in a suite of assessments that included intelligence/cognition. The authors of both studies suggested that the positive effects related to higher Hg levels may be caused by a higher fish or seafood intake.

5.2.1.1.4.4 Memory and learning

Six studies were identified that investigated associations between Hg exposure and memory and learning: Boucher *et al.*, 2014a; Choi *et al.*, 2014; Orenstein *et al.*, 2014; Wang *et al.*, 2014; Debes *et al.*, 2016 and Llop *et al.*, 2020. Three of these studies reported significant negative effects in memory and learning. Boucher *et al.* used several assessments and reported that higher prenatal Hg was associated with poorer performance on the A-not-B test – a test that depends on working memory and is an early measurement of executive function. Choi *et al.* reported that prenatal exposure was associated with a deficit in recall for short delay at 7 years of age, and there were marginal associations with verbal learning. In both studies, the significant associations were strengthened when adjusted for seafood consumption or n-3 fatty acids. Orenstein *et al.* reported an adverse relationship between low-level prenatal Hg and memory and learning, particularly for visual memory.

Two of the studies in this category reported positive associations with low levels of Hg: Wang *et al.*, 2014 and Llop *et al.*, 2020 (see Section 5.2.1.1.4.3 Intelligence/ cognition). In the sixth and final study addressing memory and learning, Debes *et al.* reported no effects relating to memory and learning specifically, but they reported effects in intelligence/cognition (again see Section 5.2.1.1.4.3).

5.2.1.1.4.5 Mental and psychomotor development

Nine articles measured mental and psychomotor development and the association with prenatal Hg exposure: Cao *et al.*, 2010; Boucher *et al.*, 2014a; Strain *et al.*, 2015; Rothenberg *et al.*, 2016; Kim *et al.*, 2018; Tatsuta *et al.*, 2018; Nišević *et al.*, 2019; Castriotta *et al.*, 2020 and Rothenberg *et al.*, 2021. While this outcome category is similar to intelligence/cognition (Section 5.2.1.1.4.3), in the present literature review the studies were summarized under mental and psychomotor development if the researchers used the Bayley Scales of Infant Development II. The Bayley Scales of Infant Development II contains two parts, the mental developmental index and the psychomotor developmental index. Five of the nine articles identified in this category reported no significant results.

Four studies, all of which were pregnancy cohort studies, reported significant results. Kim *et al.* (2018) found a relationship between Hg in early pregnancy and both motor and psychomotor development at 6 months of age, after adjusting for fish intake, but not at 12, 24 or 26 months. Rothenberg *et al.* (2016) and Rothenberg *et al.* (2021) published studies concerning a Chinese population whose primary MeHg intake was from rice, not fish. At both 12 months (Rothenberg *et al.*, 2016) and 35 months of age (Saghazadeh *et al.*, 2017), lower scores on the mental developmental index were associated with low levels of MeHg after adjusting for confounders. The associations the authors reported were at MeHg levels well below most prior studies among seafood consumers that also used the Bayley scales. Finally, Tatsuta *et al.* (2018) reported that cord blood Hg was not associated with mental and psychomotor development; however, when the data were stratified by child gender, in boys only, Hg exposure was found to be associated with lower psychomotor development.

5.2.1.1.4.6 Motor function

Eleven articles assessed associations of Hg exposure with motor function: Marques *et al.*, 2011; Ng *et al.*, 2013; Van Wijngaarden *et al.*, 2013a; Choi *et al.*, 2014; Wang *et al.*, 2014; Al-Saleh *et al.*, 2016; Boucher *et al.*, 2016; Debes *et al.*, 2016; Golding *et al.*, 2016; Barbone *et al.*, 2020 and Llop *et al.*, 2020. Two of these studies reported associations of impaired motor function with higher prenatal Hg exposure. Boucher *et al.* (2016) showed in a pregnancy cohort of Inuit children which were followed up at 11 years of age that Hg cord blood levels were associated with effects on fine motor function before adjusting for confounders. Total blood Hg levels at 11 years of age also were associated with effects on fine motor function, both with and without adjusting for confounders. Barbone *et al.* (2020) reported that children whose mothers' hair MeHg was greater than 1 ppm were more likely to perform as expected or poorer than expected in a fine motor-control assessment than children whose mothers' hair MeHg was below 1 ppm. Another three studies also report an association between Hg and motor function. As already observed in the studies summarized in the sections on memory and learning and intelligence/cognition, Wang *et al.* (2014) and Llop *et al.* (2020) also reported that positive associations for neurological development generally (which may include motor function) were observed with higher Hg levels due to fish consumption. Finally, Al-Saleh *et al.* (2016) reported developmental delays in a composite metric that included motor function as one of several outcomes; but significant effects were not parsed out for the different outcome categories.

5.2.1.1.4.7 Nerve signalling

Two studies were identified focusing on nerve signalling: Boucher *et al.*, 2010 and Yorifuji *et al.*, 2013. Both were pregnancy cohort studies and both reported significance with prenatal Hg exposures. Boucher *et al.* (2010) reported that prenatal Hg was associated with altered attentional mechanisms that modulated early processing of sensory information in Inuit children at 11 years of age. Yorifuji *et al.* (2013) reported in Faroese children aged 3.75 years, that higher Hg concentrations, particularly in maternal hair, were associated with prolonged latencies of visual evoked potentials, which is a measure of optical nerve signalling to the brain.

5.2.1.1.4.8 Reactions and reflexes

The one article identified that measured reactions and reflexes, Marques *et al.* (2011), reported no significant associations between Hg and these endpoints.

5.2.1.1.4.9 Speech and language

Nine studies were identified that investigated the outcome speech and language: Marques *et al.*, 2011; Ng *et al.*, 2013; Choi *et al.*, 2014; Wang *et al.*, 2014; Al-Saleh et al, 2016; Debes *et al.*, 2016; Barbone *et al.*, 2020; Llop *et al.*, 2020 and Young *et al.*, 2020. Three of these studies reported significant effects associated with Hg exposure (Choi *et al.*, Debes *et al.* and Llop *et al.*). This outcome is related to both intelligence/cognition and memory and learning. As such, overlapping results may be found among these categories. Debes *et al.* report negative associations between prenatal Hg and verbal comprehension, the Boston Naming Test, synonyms and antonyms test, and the California Verbal Learning Test. Choi *et al.* reported marginal, yet significant associations with verbal learning. In contrast, Llop *et al.* reported a positive association between Hg and the verbal portion of an abilities assessment; although the association was weaker after adjusting for fish intake. Finally, in a fourth study, Al-Saleh *et al.* reported developmental delays in a composite metric that includes speech and language as one of several outcomes. In that study, the type of neurological effects was not parsed out for the different outcome categories, as with behaviour and motor function.

5.2.1.1.4.10 Visual-motor integration

One study was identified that measured visual-motor integration: Al-Saleh *et al.*, 2020. This outcome is similar to, and may overlap with, psychomotor development, motor function, nerve signalling, and reactions AND reflexes. This outcome was reported individually because of the specificity of the metric used – the Beery Visual-Motor Integration assessment. In a cross-sectional study of children aged 5 to 8 years, Al-Saleh *et al.* reported a decrease in visual–motor integration with higher infant urine Hg levels. However, a positive association was found between visual–motor skill and MeHg in mothers' and infants' hair.

TABLE 5.2 **OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Rossa-Roccor *et al.*, 2021 the United States	Cross-sectional	Neurological, Depression: Depressive symptoms	Adults, pregnant women were excluded, age >18 years; n = 3 930 (56% female)	MeHg in blood: median 0.36 µg/L, IQR 0.14–0.99	Low-dose MeHg did not seem to be associated with depression in this study.
Berk *et al.*, 2014 the United States	Cross-sectional	Neurological, Depression: Depressive symptoms	Adults, median age 46, (IQR range 31–63); n = 15 140 (51% female)	THg in blood: levels not provided	There was an inverse association between mercury and depressive symptoms observed (contrary to other pollutants tested). May be explained by a protective role for fish consumption.
Nakamura *et al.*, 2014 Japan	Cross-sectional	Neurological, Neurotoxicity in adults: Motor function Reactions and reflexes Nerve signalling Hearing loss Brain morphology	Adults, residents of coastal town where whaling is a tradition, age 20 to 85 years; n = 194 (40% female)	THg in hair: median 17.8 pg/g, range 1.1–102	Multivariate regression analysis demonstrated no significant correlations between hair mercury levels and neurological outcomes. These findings suggested that sufficient Se intake might be one of causes of the absence of adverse effects of MeHg exposure in this study.
Myers *et al.*, 2020 Seychelles	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour	Children, born in the Seychelles, age: birth to 107 months (= 8.9 years); n = 643 (gender not provided)	Prenatal: THg in maternal hair: mean 6.8 ppm, SD 4.5 Postnatal: THg in child hair at 107 months: mean 6.1 ppm, SD 3.5	At 107 months of age in the Seychelles, no clear pattern of adverse association was found between behaviours measured by the Child Behaviour Checklist and either prenatal or postnatal MeHg exposure at the levels achieved by consuming a diet high in fish.
Castriotta *et al.*, 2020 Italy (northern Adriatic Sea)	Pregnancy cohort	Neurological, Neurodevelopment: Mental and psychomotor development	Children, age: 40 months, ranging from 38 to 42 months; n = 456 (48% female)	THg in maternal blood: mean 3.4 ng/g, SD 3.8 THg in cord blood: 5.6 ng/g, SD 4.9 THg in breast milk: 0.36 ng/g, SD 1.49	There was no clear relation between maternal Hg exposure in pregnancy and adverse effects on children's neurodevelopment at 40 months of age.

TABLE 5.2 **OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Kim *et al.*, 2018 Republic of Korea	Pregnancy cohort	Neurological, Neurodevelopment: Mental and psychomotor development	Children, of women (> 18 years) in early pregnancy (< 20th week) living in targeted locations (Seoul, Cheonan and Ulsan), age 20 weeks of gestation until 3 years; n = 1 251 (48% female)	THg in maternal blood; GM (10th percentile; 90th percentile): Early pregnancy: 3.3 µg/L (1.81; 5.91) Late pregnancy: 3.0 µg/L (1.68; 5.57) Cord blood: 5.1 µg/L (2.94; 8.93)	Prenatal Hg exposure during early pregnancy was adversely associated with early neurodevelopment at 6 months, after adjusting for fish and n-3, n-6 fatty acid intake.
Marques *et al.*, 2011 Brazil (Rio Madeira Basin, Amazon)	Cross-sectional	Neurological, Neurodevelopment: Behaviour Motor function Reactions and reflexes Speech and language	Children, transitioning from a traditional lifestyle, age 1–59 months; n = 249 (gender not provided)	THg in hair: mean 4.33 µg/g, SD 1.7	Multiple regression analysis showed that children's hair mercury had no impact on Gesell Development Scores, but some variables did interact significantly with specific domains (motor and language development).
Boucher *et al.*, 2010 Canada (Nunavik)	Pregnancy cohort	Neurological, Neurodevelopment: Nerve signalling	Children, Inuit, age at birth, 11 years, mean (range 10.2–12.9); n = 118 (65% female)	THg in cord blood: mean 21.5 µg/L, range 1.8–99.3 THg in child blood mean 4.69 µg/L, range 0.2–28.1	These data suggested that prenatal MeHg exposure alters attentional mechanisms modulating early processing of sensory information.
Boucher *et al.*, 2016 Canada (Nunavik)	Pregnancy cohort	Neurological, Neurodevelopment: Motor function	Children, Inuit, age at birth and 11 years; n = 265 (52% female)	THg in cord blood: mean 21.4 µg/L, range 1.0–99.3 THg in child blood at 11 years: mean 4.8 µg/L, range 0.1–34.1	Hg levels at school age were associated with poorer fine motor function.
Boucher *et al.*, 2014 Canada (Nunavik)	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Intelligence/ cognition Memory and learning Mental and psychomotor development	Children, Inuit, age at birth, 6.5 months, 11 months, and 11 years; n = 60–94 (36% female)	THg in cord blood: mean 22.5 µg/L, SD 16.6, range 2.4–97.3	Prenatal Hg was associated with poorer performance on A-not-B, which depends on working memory and is believed to be a precursor measurement of executive function; Hg was not associated with BSID-II assessment. Statistical control for seafood nutrients also led to the detection of stronger adverse associations between prenatal Hg exposure and cognitive function in previous studies.

TABLE 5.2 OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Jacobson *et al.*, 2015 Canada (Nunavik)	Pregnancy cohort	Neurological, Neurodevelopment: Intelligence/ Cognition	Children, Inuit, age at birth and 8.6–14.3 (mean 11.3); n = 70–282 (51% female)	THg in cord blood: mean 21.8 µg/L, SD 17.5, range 1.0–99.3 THg in maternal hair: mean 4.9 µg/g, SD 2.8, range 1.4–15.1	Data suggest an association of prenatal mercury exposure with poorer performance on a school-age assessment of IQ. The association was seen at levels in the range within which many US children of Asian-American background are exposed.
Rothenberg *et al.*, 2021 China (Daxin County)	Pregnancy cohort	Neurological, Neurodevelopment: Mental and psychomotor development	Children, rural, age: at birth, 12, and 36 months; n = 391 (49% female)	THg in maternal hair: median 0.40 µg/g, range 0.08–1.7	In conclusion, for young children living in rural China, where rice consumption is the primary source of MeHg exposure, a biomarker of prenatal MeHg exposure was associated with decrements in cognitive function assessed between 12 and 36 months of age. These associations were demonstrated at MeHg exposure levels well below most prior studies among seafood consumers, in which the Bayley scales were assessed.
Rothenberg *et al.*, 2016 China (Daxin County)	Pregnancy cohort	Neurological, Neurodevelopment: Mental and psychomotor development	Children, age: followed-up at birth and 12 months; n = 270 (53% female)	THg in maternal hair: GM 0.47 µg/g, range 0.078–1.7 MeHg in maternal hair: GM 0.26 µg/g, range 0.048–1.4	For 12-month-old offspring living in rural China, prenatal methylmercury exposure was associated with statistically significant decrements in offspring cognition, but not psychomotor development. In rural China, where 85% of mothers ingested rice daily and 41% of mothers rarely or never ingested fish, statistically significant inverse associations were observed for 12-month-old offspring between MDI scores and log10 hair THg, after adjustment for fish/shellfish ingestion, rice ingestion, maternal energy intake, and maternal/offspring characteristics.
Nisevic *et al.*, 2019 Croatia and Italy	Pregnancy cohort	Neurological, Neurodevelopment: Brain morphology Mental and psychomotor development	Children, age: followed-up at birth and at birth and 18 months old; n = 19–257 (48% female)	THg in cord blood, exposed > 5.8 µg/L THg in cord blood, unexposed < 5.8 µg/L	This analysis demonstrated the existence of morphological brain changes in newborns which were prenatally exposed at mercury concentrations above 5.8 µg/L blood. There was no demonstrated correlation of THg concentration in umbilical cord blood with the neurodevelopmental scores at the age of 18 months.

TABLE 5.2 **OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Debes *et al.*, 2016 Faroe Islands	Pregnancy cohort	Neurological, Neurodevelopment: Intelligence/ cognition Memory and learning Motor function Speech and language	Adults, age: 22 years (sampling also done at birth, 7 years and 14 years); n = 814 (51% female)	THg in cord blood: mean 22.91 µg/L THg in maternal hair: mean 4.24 µg/g THg child blood, age 22: mean 2.53 µg/L THg in child hair, age 22: mean 0.68 µg/g	The results from age 22 years suggested that cognitive deficits associated with prenatal methylmercury exposure remained through young adult age, with effect sizes somewhat lower than those observed at ages 7 and 14 years.
Choi *et al.*, 2014 Faroe Islands	Pregnancy cohort	Neurological, Neurodevelopment: Intelligence/ cognition Memory and learning Motor function Speech and language	Children, age: followed-up at birth and 7 years; n = 176 (50% female)	Hg in cord blood: geometric mean 21.4 µg/L, range 1.90–101.8 Hg in maternal hair: geometric mean 4.10 µg/g, range 0.32–16.3	Prenatal exposure to methylmercury was associated with deficits at school age in domains known to be sensitive to this neurotoxicant, with associations being strengthened after fatty acid adjustment.
Barbone *et al.*, 2020 Italy (northern Adriatic Sea)	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Motor function Speech and language	Children, of mothers residing in coastal fishing towns, age 3 months and 18–30 months; n = 53 (47% female)	THg in maternal hair; THg in child hair; MeHg in maternal hair; and MeHg in child hair: Summary data are not clearly presented	These pilot findings are suggestive of an association between children's fine motor skills and their prenatal methylmercury exposure from maternal fish consumption.
Tatsuta *et al.*, 2018 Japan (Tohoku Region)	Pregnancy cohort	Neurological, Neurodevelopment: Mental and psychomotor development	Children. One cohort from an urban area and one cohort from a coastal area, followed-up at birth and age 18 months (range, 17 to 24); n = 1016 (48% female)	Urban area: THg in cord blood: median 10.0 ng/g, 5–95 percentile range 4.2–22.4 THg in maternal hair: median 2.0 µg/g, 5–95 percentile range 0.9–4.4 Coastal area: THg in cord blood: median 16.0 ng/g, 5–95 percentile range 5.6–39.3 THg in maternal hair: median 2.6 µg/g, 5–95 percentile range 0.9–6.0 THg in breast milk: median 0.8 ng/g, 5–95 percentile 0.1–1.8	These findings suggested prenatal exposure to low levels of methylmercury may have adverse effects on child development, especially in boys.

TABLE 5.2 OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Young *et al.*, 2020 Seychelles	Pregnancy cohort	Neurological, Neurodevelopment: Speech and language	Children, born in Seychelles, age at birth and 5.5 years; n = 544 (gender not provided)	THg in maternal hair: mean 6.8 ppm, SD 4.6, range <1–26.7 THg in child hair: mean 6.5 ppm, SD 3.3, range <1–24.8	No adverse associations between articulatory and phonologic speech skills and prenatal MeHg exposure were detected. The findings of this investigation are compatible with previous developmental assessments of Seychellois children that have indicated no adverse effects of prenatal MeHg exposure from fish consumption.
van Wijngaarden *et al.*, 2013 Seychelles	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Intelligence/ cognition Motor function	Children, born in Seychelles, age prenatal until 19 years of age; n = 553 (not provided)	THg in maternal hair: mean 6.9 ppm THg in child hair: mean 10.3 ppm	There were no adverse associations between prenatal MeHg and any of the measured endpoints. The findings continue to provide no evidence for an adverse effect of prenatal MeHg exposure on development in [a Seychellois] cohort that consumes fish daily.
Strain *et al.*, 2015 Seychelles	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Mental and psychomotor development	Children, born in Seychelles, age birth and 1.66 years; n = 1 265 (gender not provided)	MeHg in maternal hair: mean 3.92 ppm, range 0–31.66	No overall adverse association between prenatal MeHg exposure and neurodevelopmental outcomes at 20 months of age.
Al-Saleh *et al.*, 2016 Saudi Arabia	Cross-sectional	Neurological, Neurodevelopment: Behaviour Motor function Speech and language	Children, age 2–12 months; n = 245–944 (48% female)	THg in maternal urine: mean 1.73 µg/L THg in maternal hair: mean 1.79 µg/g dw THg in breastmilk: mean 0.97 µg/L THg in maternal blood: mean 0.88 µg/L THg in infants' urine: mean 0.90 µg/L THg in infants' hair: mean 1.17 µg/g dw MeHg in maternal hair: mean 0.20 µg/g dw MeHg in infants' hair: mean 0.14 µg/g dw	In summary, both the DDST-II and PEDS tests showed some evidence of developmental delays in infants that were related to some measures of Hg exposure, despite the low levels of Hg and regardless of the infant's breastfeeding status.
Al-Saleh *et al.*, 2020 Saudi Arabia	Cross-sectional	Neurological, Neurodevelopment: Intelligence/ cognition Visual-motor integration	Children, who had in a previous study failed neurodevelopment screening tools and/or had elevated mercury, age 5–8 years, mean 6.81, SD 0.64; n = 82 (56% female)	THg child urine: median 0.359 µg/L, range 0.010– 5.641 MeHg child hair: median 0.182 µg/L, range 0.003– 4.470	The results showed that early exposure to mercury measured in infants' urine had an adverse association with the performance of children on a nonverbal IQ test and on the integration of their visual and motor abilities. Whereas methylmercury in mother's blood was inversely associated with children's nonverbal IQ, methylmercury in the hair of mothers and their infants was associated with enhanced visual-motor skills.

TABLE 5.2 OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Ng, *et al.*, 2013 Taiwan	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Intelligence/ cognition Motor function Speech and language	Children, age 2 years; n = 168 (44 percent female)	THg in cord blood: 80 measurements were <12 µg/L, and 88 measurements were >12 µg/L	Prenatal Hg exposure was associated with significant adverse effects on cognition, social and whole neurodevelopment development quotients among subjects who have at least one *Ap oe e*4 allele. The inter-population difference prevalence of the alleles might be one of explanations for the inconsistent findings related to prenatal Hg exposure and neurodevelopment.
Golding, *et al.*, 2016 (Prenatal mercury exposure and offspring behaviour in childhood and adolescence) the United Kingdom of Great Britain and Northern Ireland (Avon)	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour	Children, age 47 months, 81 months, 7–8 years, 10–11 years, 11–12 years, 13 years, 16–17 years; n = 1 599–2 776 (gender not provided)	THg in maternal blood: median 1.86 µg/L, range <LOD-12.8	There were no adverse effects of maternal prenatal mercury levels on the behaviour of the offspring. A similar lack of relationship was found when the analyses were confined to those offspring whose mothers had eaten fish in pregnancy, and no consistent differences were found between the fish and non-fish eaters.
Golding, *et al.*, 2016 (Associations between prenatal mercury exposure and early child development in the ALSPAC study) the United Kingdom of Great Britain and Northern Ireland (Avon)	Pregnancy cohort	Neurological, Neurodevelopment: Behaviour Motor function	Children, age 6, 18, 30, and 42 months; n = 2 394–3 264 (gender not provided)	THg in prenatal blood: range 0.17–12.76 µg/L	No evidence of adverse associations was found between maternal prenatal blood mercury and child development between 6 and 42 months of age.
Orenstein *et al.*, 2014 the United States (New Bedford, Massachusetts)	Pregnancy cohort	Neurological, Neurodevelopment: Memory and learning	Children, whose mother's residence is close to a PCB-contaminated harbour, age perinatal and 8 years (range, 7–11 years); n = 393 (50% female)	THg in maternal hair: mean 0.6 µg/g, range, 0.3–5.1	These results support an adverse relationship between low-level prenatal MeHg exposure and childhood memory and learning, particularly visual memory.

TABLE 5.2 **OVERVIEW OF PRIMARY STUDIES WITH NEUROLOGICAL OUTCOMES FOR THE REVIEW OF "TOXIC EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Cao *et al.*, 2010 the United States (Philadelphia, PA; Newark, NJ; Cincinnati, OH; and Baltimore, MD)	Cohort	Neurological, Neurodevelopment: Behaviour Intelligence/ cognition Mental and psychomotor development	Children, living in poverty, who had blood Pb levels between 20–44 mg/dL, age 2, 5 and 7 years; n = 531–767 (approx. 44% female)	THg in pre-, post-, treatment and placebo group blood means were between 0.52 and 0.65 µg/L, with 95% CIs ranging from 0.49 to 0.61	At the present postnatal MeHg exposure level of US children, adverse effects on children's cognition and behaviour were not detectable, since they did not appear in a longitudinal study among children living in poverty in the United States.
Yorifuji *et al.*, 2013 Faroe Islands	Pregnancy cohort	Neurological, Neurodevelopment: Nerve signalling	Children, age birth and 3.75 years; n = 139 (52% female)	THg in cord blood: GM 22.8 µg/L, IQR 13.7–41.2 THg in maternal hair: GM 4.6 µg/L, IQR 2.7–8.2	The present study found that higher mercury concentrations were associated with the prolonged latencies of visual-evoked potentials, in particular higher maternal hair mercury was associated with the prolonged N145 latency.
Llop *et al.*, 2020 Spain	Pregnancy cohort	Neurological, Neurodevelopment: Intelligence/ cognition Memory and learning Motor function Speech and language	Children, age 4.1–6.4 years; n = 1251 (53% female)	THg in hair: GM 0.98 µg/g, 95% CI 0.94–1.03, SD 1.42	There was a positive effect of Hg on the neurophysiological development for all measured scales. However, the effect was attenuated when adjusted by children's fish intake or theoretical scenarios of low precision in fish intake and Hg measurements.
Wang *et al.*, 2014 the United States (Philadelphia, PA; Newark, NJ; Cincinnati, OH and Baltimore, MD)	Cohort	Neurological, Neurodevelopment: Intelligence/ cognition Memory and learning Motor function Speech and language	Children, urban inner-city children exposed to lead, age 12 months through 7 years; n = 613–780 (45% female)	MeHg in blood: GM 0.56 µg/L, 95% CI 0.52–0.59	The relatively low MeHg exposure in US school-aged children from this population (lead exposed) had no detectable adverse effect on neuropsychological development. The positive associations observed between MeHg and neurodevelopment may reflect exposure to beneficial polyunsaturated fatty acids from seafood.

Notes: THg: total mercury; BSID II: Bayley Scales of Infant Development-Second Edition; IQR: interquartile range; IQ: intelligence quotient; DDST-II: Denver Developmental Screening Test, version II; PEDS: Parents' Evaluation of Developmental Status; PCB: polychlorinated biphenyl; Pb: Lead; CI: confidence interval; GM: geometric mean; SD: standard deviation.

5.2.1.2 Previous reports

In their 2012 report, EFSA summarized recent literature by the time of exposure. First, for prenatal exposures, findings were reported by region. In 14 years of data from the Faroe Islands, results consistently pointed to a detrimental effect of Hg on some neurological outcomes. In Seychelles, no consistent findings were found, although the newest reports do report a negative association between Hg and neurological endpoints, when maternal fish intake is included as a confounder. Among other regions, few studies found associations at Hg levels that were lower than those reported in the Faroe Islands or Seychelles. As such, no additional conclusions were drawn. EFSA did not reach any conclusions regarding postnatal Hg exposure and neurological effects in childhood, primarily because of inconsistent findings. Finally, studies addressing neurotoxicity in adults revealed no relevant associations with Hg exposures at low levels.

The 2022 VKM report considered two systematic reviews on autism and/or AHDH, and their associations with Hg. Both reviews (one of which – Yoshimasu *et al.*, 2014 – is summarized in Section 5.2.1.1 Systematic reviews) were inconclusive. A meta-analysis of inhibitory control in humans was also inconclusive for MeHg. The remaining reviews on neurological outcomes in VKM 2022 are summarized in the systematic reviews described previously.

5.2.2 CARDIOVASCULAR OUTCOMES

5.2.2.1 Systematic reviews

The literature search identified four systematic reviews related to Hg and cardiovascular disease (**Table 5.3**). Two of them (Chowdhury *et al.*, 2018 and Hu *et al.*, 2021) studied the association between Hg and various cardiovascular endpoints in a general adult population. The two other (Hu *et al.*, 2018 and Gallego-Vinas *et al.*, 2019) examined indicators related to cardiovascular disease, with one focusing on blood pressure and hypertension in a general adult population (Hu *et al.*) and the other focusing on blood pressure in children and adolescents (Gallego-Vinas *et al.*). Of the four reviews, three generally concluded that there was no association with Hg.

A systematic review by Chowdhury *et al.* (2018), which investigated the risk of cardiovascular disease in relation to exposure to toxic environmental metal contaminants, included 37 articles, of which nine were related to Hg. Three of the articles were cohort studies and six were case-control studies. The authors concluded that Hg exposure was not associated with cardiovascular disease. Hu *et al.* (2021) reviewed 14 studies to investigate the effects of Hg exposure on cardiovascular disease and mortality. Nine of these studies were cohort studies, four were case-control studies, and one was a cross-sectional study. The author concluded that exposure to Hg was associated with certain cardiovascular endpoints, which are summarized in **Table 5.3**.

Gallego-Vinas *et al.* (2019) reviewed eight articles in a systematic review on Hg and blood pressure among children and adolescents. The review comprised five cohorts, one cross-sectional study and one case-control study. The results of the studies were inconsistent, and the authors stated that no conclusion could be established. Hu *et al.* (2018) reviewed 29 studies, including 27 cross-sectional studies, one cohort study and one case-control study, in a meta-analysis assessing the effects of Hg exposure on blood pressure and hypertension. A significant positive association between Hg and hypertension and between Hg and blood pressure was identified.

TABLE 5.3 **OVERVIEW OF SYSTEMATIC REVIEWS WITH CARDIOVASCULAR OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Chowdhury *et al.*, 2018 Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis	Cardiovascular; Total cardiovascular and coronary heart disease	Total n = 9: n = 3 cohort studies and n = 6 case-control studies	Blood Hg ranging from 0.004 to 3.5 µg/L.	Meta-analysis: Cardiovascular disease (n = 11 410): RR (95% CI): 0.94 (0.66–1.36). Coronary heart disease (n = 9 169): RR (95% CI): 0.99 (0.65–1.49)	Mercury exposure was not associated with any cardiovascular risk.
Gallego-Viñas *et al.*, 2018 Chronic mercury exposure and blood pressure in children and adolescents: a systematic review	Cardiovascular; Blood pressure	Total n = 8: n = 6 cohort studies, n = 1 case-control studies, n = 1 cross-sectional study	Prenatal exposure (maternal): Arithmetic mean of total Hg: Range hair Hg: 565–700 µg/kg. Blood Hg: 1.86 µg/L Cord blood: 22.6–31.77 µg/L Postnatal exposure (child): Arithmetic mean of total Hg: Blood Hg: 0.10–8.1 µg/L Hair Hg: 960 µg/kg	4/7 studies found a positive association between chronic Hg exposure and blood pressure. Three of these studies assessed Hg exposure in prenatal life.	The results of the studies were inconsistent. As such, with the current available scientific evidence, it cannot be concluded that an association exists.

TABLE 5.3 **OVERVIEW OF SYSTEMATIC REVIEWS WITH CARDIOVASCULAR OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Hu *et al*., 2018 Mercury Exposure, Blood Pressure, and Hypertension: A Systematic Review and Dose–response Meta-analysis	Cardiovascular; Blood pressure and hypertension	Total n = 29: n = 1 cohort study n = 1 case-control study, and n = 27 cross-sectional studies	n = 11 studies were conducted at low to moderate mercury exposure levels (mean Hg concentration of the highest exposure group ≤ 2 µg/g in hair or equivalent). n = 18 studies were conducted at high mercury exposure levels (mean Hg concentration of the highest exposure group >2 µg/g in hair or equivalent).	Meta-analysis: The pooled OR for hypertension, comparing the highest and lowest mercury exposure categories, was 1.35 (95% CI: 0.99, 1.83) for populations with hair mercury ≥2 µg/g in comparison with the OR of 1.12 (95% CI: 0.82, 1.52) for populations with hair mercury <2 µg/g. A nonlinear dose–response relationship with an inflection point at 3 µg/g was identified, for both hypertension and systolic blood pressure. Hair Hg concentration higher than 2 µg/g is associated with a 59% increase in OR for hypertension, an increase of 2.20 mmHg and 1.24 mmHg in systolic blood pressure and diastolic blood pressure, respectively.	The association between Hg exposure and the prevalence of hypertension was non-linear, with no association in populations exposed to low-to-moderate mercury (hair Hg <2 µg/g) and evident association in populations exposed to high mercury (hair Hg ≥2 µg/g). However, the interpretation of a causal association of Hg exposure and hypertension is limited by the cross-sectional design of original studies. Current evidence suggests that hair Hg concentration of 2–3 µg/g might be considered the threshold of Hg's toxic effect on hypertension. Heterogeneity was observed for Hg species and exposure groups across different studies.
Hu *et al*., 2021 Mercury exposure, cardiovascular disease, and mortality: A systematic review and dose-response meta-analysis	Cardiovascular; Cardiovascular disease and mortality; Fatal/non-fatal ischemic heart disease, stroke, all cardiovascular disease, cardiovascular disease mortality, all-cause mortality.	Total n = 14: n = 9 cohort studies, n = 4 case-control studies, and n = 1 cross-sectional studies	Highest exposure levels in the studies varied from hair Hg concentrations of 1 to 30 µg/g.	Meta-analysis: Total cardiovascular disease (n = 10 351): RR = 0.93, 95% CI: 0.80, 1.08). Ischemic heart disease (n = 18 312): RR = 1.21, 95% CI: 0.98, 1.50. Stroke (n = 18,428): RR = 1.03, 95% CI: 0.87,1.23. All-cause mortality (n = 3 254): RR = 1.21, 95% CI: 0.90, 1.62. A J-shaped relationship between Hg exposure and fatal/non-fatal cardiovascular outcomes was observed, with turning points at 1 µg/g hair Hg for ischemic heart disease and 2 µg/g for stroke and all cardiovascular disease.	Chronic exposure to Hg was associated with an increased risk of all-cause mortality and fatal/non-fatal ischemic heart disease. The risk of multiple cardiovascular endpoints starts to increase consistently at a hair Hg concentration of 2 µg/g.

5.2.2.2 Primary studies

The search identified four primary studies assessing the effect of Hg on outcomes related to cardiovascular disease (**Table 5.4**). Of these studies, two (Tajik *et al.*, 2016 and Chan *et al.*, 2021) reported a significant association, while the other two (Chen *et al.*, 2018 and Tajik *et al.*, 2018) found no association. One study reported on the association between Hg and ischemic stroke, while the other three studies looked at indicators related to cardiovascular disease.

A cohort study conducted by Chen *et al.* (2018) did not support the posited hypothesis that Hg exposure at low-to-moderate levels was associated with incidence of ischemic stroke within a population of adults above 44 years of age.

Chan *et al.* (2021) found that in children, prenatal MeHg exposure, but not recent MeHg exposure, was adversely associated with cardiac autonomic function, as measured by heart-rate variability. No associations were found between postnatal MeHg exposure and heart-rate variability or postnatal MeHg exposure and blood pressure. Tajik *et al.* (2016) studied the association of serum long-chain n-3 PUFA and hair Hg with resting heart rate, peak heart rate during exercise and heart rate recovery after exercise in men of 42 to 60 years. Higher hair Hg content was associated with a trend towards lower peak heart rate after adjusting for the long-chain n-3 PUFA. Hair Hg concentration was not associated with resting heart rate or heart-rate recovery. Further, Tajik *et al.* (2018) found no association between hair Hg concentrations and exercise cardiac power in men 42 to 60 years.

TABLE 5.4 OVERVIEW OF PRIMARY STUDIES WITH CARDIOVASCULAR OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Chen *et al.*, 2018 the United States (southeastern states)	Case-cohort	Cardiovascular, Cardiovascular: Ischemic stroke	Adults, older than 44 years; Blacks were intentionally oversampled, age mean 65 years; SD 9.4; n = 2 494 (55% female)	THg in serum: median 0.03 µg/dL	The present study does not support the hypothesis that mercury exposure is associated with the incidence of ischemic stroke within a population with low-to-moderate level of exposure.
Chan *et al.*, 2021 Hong Kong	Pregnancy cohort	Cardiovascular, Cardiovascular: cardiac autonomic function and blood pressure	Children, age 8.1 years ± 0.9; n = 604 (45% female)	Cord blood Hg: mean 50.12 nmol/L, SD 23.9 Child blood Hg: mean 15.94 nmol/L, SD 9.94	Prenatal Hg exposure is adversely associated with cardiac autonomic function as measured by heart rate variability. In comparison, no associations were found between postnatal MeHg exposure and heart-rate variability and blood pressure.
Tajik *et al.*, 2016 Finland	Cohort	Cardiovascular, Cardiovascular: exercise cardiac power; VO2 max; maximal systolic blood pressure during exercise	Adults, men, age 42–60 years; n = 1 672 (0% female)	THg in hair: mean 1.94 µg/g, range 0 to 15.67	Hair Hg was not associated with the measured cardiac outcomes. Higher circulating concentrations of long-chain n-3 PUFA, mainly a marker of fish consumption in this study population, were associated with higher exercise cardiac power and VO2 max in middle-aged and older men.
Tajik *et al.*, 2018 Finland	Cohort	Cardiovascular, Cardiovascular: resting heart rate, peak heart rate during exercise and heart-rate recovery after exercise	Adults, men free of cardiovascular disease, age 42–60; n = 1 008 (0% female)	THg in hair: mean 1st quartile 1.09 µg/g, mean 4th quartile 2.74.	Higher hair Hg content showed a trend towards lower peak heart rate after adjusting for the long-chain n-3 PUFA (P trend = 0·05), but this only slightly attenuated the associations of the serum long-chain n-3 PUFA with heart rate.

5.2.2.3 Previous reports

EFSA, 2012 included ten articles on Hg and cardiovascular disease. Two studies (Guallar *et al.*, 2002 and Virtanen *et al.*, 2005) found an increased risk of acute coronary event or myocardial infarction with higher Hg concentrations. Two studies (Ahlqwist *et al.*, 1999 and Yoshizawa *et al.*, 2002) did not find a statistically significant association between myocardial infarction and Hg concentrations. Two newer studies (Wennberg *et al.*, 2007 and Mozaffarian *et al.*, 2011) did not indicate any association between stroke and Hg exposure. Three studies (Hallgren *et al.*, 2001; Wennberg *et al.*, 2011 and Bergdahl *et al.*, 2013) showed associations between Hg and decreased risk of myocardial infarction. Finally, one study (Mozaffarian *et al.*, 2011) showed no association between Hg and the risk of cardiac disease.

The 2012 EFSA assessment included 17 articles on indicators related to cardiovascular disease: Dórea *et al.*, 2005; Pedersen *et al.*, 2005; Vupputuri *et al.*, 2005; Fillion *et al.*, 2006; Valera *et al.*, 2008; Bautista *et al.*, 2009; Choi *et al.*, 2009; Valera *et al.*, 2009; Lim *et al.*, 2010; Yaginuma-Sakurai *et al.*, 2010; Valera *et al.*, 2011a; Valera *et al.*, 2011b; Nielsen *et al.*, 2012; Olsén *et al.*, 2012 and Valera *et al.*, 2013. Of these, 14 articles focused on blood pressure, 1 on hypertension, 7 on hearth-rate variability, 1 on vasodilating function, 1 on brainstem auditory-evoked potentials, 1 on carotid intima-media thickness, and 1 on vasodilation function. EFSA concluded that the observations related to myocardial infarction, heart-rate variability and possible blood pressure were of potential importance; however, the results were not conclusive. EFSA specified that it is important to take the beneficial effects of fish consumption into account when studying the associations between Hg and cardiovascular outcomes.

The 2022 VKM assessment identified one systematic review on Hg and cardiovascular disease (Hu *et al.*, 2021). This study was also included in the systematic reviews and has been summarized in a prior section. The 2022 VKM assessment identified two reviews on blood pressure and hypertension, which were also included in the review and are summarized in a prior section (Hu *et al.*, 2018 and Gallego-Vinas *et al.*, 2019). The 2022 VKM assessment identified two reviews on heart rate variability (Gribble *et al.*, 2015 and Karita *et al.*, 2018). Neither of these was included in the present literature analysis due to being rated "low" and "very low" confidence in the risk-of-bias assessment (Appendix 5, **Table A5.6**). According to the 2022 VKM report, neither of these two studies found associations between autonomic heart control and MeHg exposure.

5.2.3 GROWTH

5.2.3.1 Systematic reviews

The literature search conducted identified one recent systematic review (Dack *et al.*, 2021) (**Table 5.5**) on Hg and prenatal growth (birth weight, birth length and head circumference), including 11 prospective and 16 cross-sectional studies, comprising participants from 17 countries. According to the authors, many of the

studies included showed no strong evidence of an effect. Inverse associations with birth weight were reported in a significant minority with the highest mean Hg concentrations. Overall, the systematic review by Dack *et al.* did not identify strong evidence that Hg exposure led to impaired prenatal growth, but some evidence of a negative association with Hg was noted.

TABLE 5.5 **OVERVIEW OF SYSTEMATIC REVIEWS WITH GROWTH OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Dack *et al.*, 2021 Mercury and Prenatal Growth: A Systematic Review	Growth; Birth outcomes; Foetal growth outcomes: Birth weight, birth length, and head circumference	Total n = 27: n = 11 prospective studies, and n = 1 cross-sectional studies	Blood levels: Range mean Hg: 0.91–4.9 µg/L. Hair levels: Range mean Hg: 320–607 µg/kg Umbilical cord: Range mean Hg: 0.91-21.0 µg/L	Birth weight: A total of 27 studies with inconsistent results, but populations with high Hg exposure and high-quality studies were more likely to report a negative association. Birth length: 10/14 studies found no evidence of association. Head circumference: 13/14 studies found no evidence of association.	Most studies showed no strong evidence of an effect, but a significant minority report inverse associations with birth weight, particularly studies of populations with the highest mean mercury concentrations.

5.2.3.2 Primary studies

Six articles considering the association of Hg exposure with growth were identified (**Table 5.6**). Three cross-sectional studies assessed measurements at birth only (García-Esquinas *et al.*, 2013; Miyashita *et al.*, 2015 and Tang *et al.*, 2016). Two of the three cohort studies addressed prenatal growth using ultrasound measurements (Drouillet-Pinard *et al.*, 2010 and Ballester *et al.*, 2018), and one of these (Drouillet-Pinard *et al.*) combined it with measurements at birth. The third cohort study (Papadopoulou *et al.*, 2021) followed the participating children from one month to eight years of age. Among all six growth studies, four report at least one association between Hg and a growth outcome.

Among the three cross-sectional studies on newborns, one reported an association between Hg and growth (Tang *et al.*, 2016), while two did not (García-Esquinas *et al.*, 2013 and Miyashita *et al.*, 2015). No associations were observed between Hg concentrations in cord, maternal and paternal blood and weight, length or Apgar scores in newborns in Spain (García-Esquinas *et al.*, 2013). In newborns in Japan, no associations between Hg concentrations and birth weight, length, chest circumference and head circumference were observed (Miyashita *et al.*, 2015). For newborns from certain areas of China, Tang *et al.* (2016) concluded that their results suggested that Hg exposure had potential adverse effects on birth outcomes, as they found that birth weight was significantly reduced in the second tertile of Hg concentration in umbilical cord serum after adjusting for all covariates. No association was found in multivariable linear regression for Hg.

Regarding prenatal growth in the cohort studies, Ballester *et al.* (2018) followed a Spanish pregnancy cohort and found that prenatal Hg exposure did not affect foetal parameters investigated at 12, 20 and 34 weeks of gestation, except for being associated with a small reduction of biparietal diameter early in pregnancy. Drouillet-Pinard *et al.* (2010) assessed prenatal and growth measurements at birth in a pregnancy cohort in France. In this study, a negative association was observed between maternal Hg exposure and biparietal diameter, measured at 20 to 24 weeks of gestation. Otherwise, no association between maternal level of total hair Hg and ultrasound measures or newborn anthropometric measures were found.

In the only cohort study identified following postnatal growth (Papadopoulou *et al.*, 2021), Norwegian mother–child pairs were enrolled. High Hg exposure (top decile) was associated with a reduction in children's weight growth trajectory, compared to lower exposure, especially for girls.

In summary, two studies found no association between prenatal exposure and growth in newborns, while one study suggested a potential association of Hg in cord serum with birth weight in newborns. For prenatal growth, both studies found a small reduction of biparietal diameter in early to mid-pregnancy but no association with other measured foetal growth parameters. The only longitudinal study on post-natal growth found an association between high Hg exposure and the weight-growth trajectory in children. However, for seafood consumption, the authors concluded that no detrimental effects were found. The results of the individual studies overall were similar to those reported in the systematic review included in this section.

TABLE 5.6 **OVERVIEW OF PRIMARY STUDIES WITH GROWTH OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Garcia-Esquinas *et al.*, 2013 Spain (Madrid)	Cross-sectional	Growth, Foetal and child growth: newborn size and health status	Children, of mother/father/ newborn sets, where the birth occurred at a public hospital, age at birth; n = 112 (gender not provided)	THg in cord blood: GM 6.7 µg/L, IQR 5–11 THg in maternal blood: GM 3.9 µg/L, IQ range 2.4–6.8 THg in paternal blood: mean 5.4 µg/L, IQ range 3.5–9.1	No associations were observed between [mercury] levels and newborn's weight, length or Apgar (appearance, pulse, grimace, activity, respiration) scores. The findings do not support an association between total mercury in cord blood and foetal health.
Miyashita, *et al.*, 2015 Japan (Hokkaido)	Cross-sectional	Growth, Foetal and child growth: newborn anthropometric measurements, babies born small for gestational age (SGA)	Children, newborn, age at birth; n = 367 (53% female)	THg in maternal hair: range 0.24–4.73 µg/g	There were no associations between the concentrations of hair Hg and newborn anthropometric measurements of birth weight, length, chest circumference and head circumference in the multiple linear regression models, with or without adjustment for factors. Although, the incidence of babies born small for gestational age by weight may reduce with higher concentrations of Hg in hair.
Tang, *et al.*, 2016 China (Shengsi Island)	Cross-sectional	Growth, Foetal and child growth: infant anthropometric measurements, including birth weight, length and head circumference	Children, Chinese and fish consuming, age at birth; n = 103 (42% female)	THg in cord blood serum: median 21.94 µg/L, IQR: 15.10, 27.64	Results suggested that Pb and Hg exposure has potential adverse effects on birth outcomes in Chinese fish consumers from Yangtze River outlet and Hangzhou Bay estuary regions. The second tertile Hg concentration in the umbilical cord serum was significantly correlated with birth weight after adjusting for all covariates, but not the third tertile. From multivariable linear regression for Hg, no significant associations were found between exposure and birth weight, height, head circumference, and gestation age in both models adjusted for different covariates
Ballester, *et al.*, 2018 Spain	Pregnancy cohort	Growth, Foetal and child growth: longitudinally measured foetal biometry (foetal growth)	Children, age: prenatal at 12, 20 and 34 weeks gestation; n = 1 552-1 560 (48% female)	THg in cord blood: GM 8.2 µg/L	The longitudinal assessment of the association of prenatal Hg exposure with foetal growth showed a small reduction of biparietal diameter early in pregnancy, but no significant changes were observed in other foetal parameters.

TABLE 5.6 **OVERVIEW OF PRIMARY STUDIES WITH GROWTH OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Drouillet-Pinard *et al.*, 2010 France (Nancy and Poiters)	Pregnancy cohort	Growth, Foetal and child growth: foetal growth	Children, age 20–24 and 30–34 weeks of gestation, and birth; n = 109–156 (45% female	THg in maternal hair: median 0·52 µg/g, IQR 0.30–0.82, SD 2.6 THg in child hair: median 0·38 µg/g, IQR 0.30–0.43, SD 0.32	In conclusion, the data do not support a detrimental effect of low maternal Hg contamination on birth weight or other newborn anthropometric measurements. In the whole sample of women, there was no association between maternal level of total hair Hg and ultrasound measures as well as newborn anthropometric measures.
Papadopoulou *et al.*, 2021 Norway	Pregnancy cohort	Growth, Foetal and child growth: child body mass index trajectories	Children, age 1 month to 8 years; n = 2277 (49% female)	THg in maternal blood: median 1.03 mg/L, 0.96 IQR, range 0.003–12.68	High prenatal mercury exposure (top decile compared to the rest) was associated with a reduction in the child's weight–growth trajectory (Estimates ranging from -130 g (95% CI = -247, -12 g) at 18 months to -608 g (95% CI = -1.102, -113 g) at 8 years. Overall, the findings do not provide evidence of detrimental effects of seafood consumption on child growth from birth to childhood.

Notes: THg: total mercury; GM: geometric mean, IQR: interquartile range, IQ: intelligence quotient, SD: standard deviation.

5.2.3.3 Previous reports

In the 2012 EFSA report, growth was addressed under "Developmental toxicity other than neurotoxicity and immunotoxicity". Of the six studies identified by EFSA, three did not find an association between birth outcomes and Hg: Lucas *et al.*, 2004; Lederman *et al.*, 2008 and Drouillet-Pinard *et al.*, 2010. Of the three studies that did find an association, one (Lee *et al.*, 2010) found an association only for a certain genotype of the mother; one (Cace *et al.*, 2011) found an association for cerebellum width, but not length; and one (Ramon *et al.*, 2009) found an association for birth weight and size for gestational age.

The 2022 VKM assessment included two systematic reviews on "Foetal growth and birth outcomes" in their report. These reviews were also identified in the literature search. However, one of the reviews, Saavedra *et al.*, 2022, was graded "low" in confidence in the risk-of-bias analysis and was excluded for further assessment and, thus, was not mentioned earlier (Appendix 5, **Table A5.6**). This review concluded, based on four studies, that Hg exposure was associated with lower birth weight. The authors noted that Hg toxicity may sometimes be mitigated, for instance through PUFAs in the maternal diet.

5.2.4 OTHER HEALTH OUTCOMES

5.2.4.1 Systematic reviews, primary studies and previous reports

For the topics described in the following sections (5.2.4.1.1 through 5.2.4.1.11), only a limited number of articles could be identified for any one outcome in the literature review. Therefore, original articles, reviews and findings from earlier reports are described together, categorized by outcome. The main results from the group of "other health outcomes" are summarized in **Table 5.7** for the systematic reviews and in **Table 5.8** for the primary studies.

5.2.4.1.1 Diabetes and metabolic syndrome

The literature search identified one systematic review considering diabetes and metabolic syndrome together, one systematic review on metabolic syndrome, and two primary studies on T2D and metabolic syndrome.

In the systematic review by Roy *et al.* (2017), on both diabetes and metabolic syndrome, the associations found in the 24 articles included were weak to moderate, ranging from no association to an OR of 7.35 (1.73–31.1). Several of the studies included found an association between increased Hg exposure and risk of diabetes and metabolic syndrome. However, the associations were reported not to be consistent between studies and the results from the longitudinal studies were conflicting. The authors stated that, based on a weight of evidence approach, an association between total Hg concentration in various matrices and the development of either diabetes mellitus or metabolic syndrome seems to exist, but sufficient evidence for a causal relationship was not found.

Reviewing studies on metabolic syndrome, Xu *et al.* (2021) performed a meta-analysis on the results of 11 studies and found that exposure to Hg was associated with a higher prevalence of metabolic syndrome.

Tsai *et al.* (2019) conducted a cross-sectional study entitled Nutrition and Health Survey in Taiwan on T2D and Hg exposure in the general population. The authors' findings showed a significant association between elevated Hg concentration in red blood cells and T2D prevalence. It was stated that future research, particularly longitudinal cohort studies with suitable specimens, were needed in order to verify the findings.

Stratakis *et al.* (2020) assessed the association between maternal Hg exposure and metabolic syndrome in children. An aggregate metabolic syndrome score (a metric considering waist circumference; systolic and diastolic blood pressures; and levels of triglyceride, high-density lipoprotein cholesterol and insulin) was put in association with maternal Hg exposure and high maternal Hg exposure was found to be associated with an unfavourable metabolic profile in children.

In summary, one original article (Tsai *et al.*, 2019) suggested an association between Hg and diabetes and another (Stratakis *et al.*, 2020) suggested an association with metabolic syndrome. In addition, the existing systematic reviews identified several studies that found an association. However, in one review it was stated that the associations were not consistent and did not provide sufficient evidence for a causal relationship to be established, and the other review argues for more studies in order to be able to adjust adequately for appropriate confounders.

The 2012 EFSA assessment identified one original article (Park *et al.*, 2009) on metabolic syndrome, which found an association with Hg exposure.

5.2.4.1.2 Immune system

Four primary studies were identified on the possible association of Hg exposure and immune system functions. Two of the studies (Emeny *et al.*, 2019 and Kindgren *et al.*, 2019) found no association of Hg exposure with endpoints connected to the immune function, while two others (Miyake *et al.*, 2011 and Carrasco *et al.*, 2021) found indications for an association in some endpoints.

Miyake *et al.* (2011) assessed the occurrence of wheeze and eczema symptoms related to allergic disorders in children of Japan in a pregnancy cohort study, finding that neither maternal nor children's hair Hg levels were related to the risk of wheeze or eczema. Carrasco *et al.* (2021) investigated prenatal and postnatal Hg exposure and respiratory health in a pregnancy cohort study in Spain and reported that no association was found.

Emeny *et al.* (2019) investigated endpoints. including respiratory infections and symptoms, eczema and occurrence of allergies in infants in the United States, and related the parameters investigated to THg in the mothers' toenails. Higher toenail Hg in fish-consuming mothers was reported to be related to a greater RR of lower-tract respiratory infections and respiratory symptoms of their child at 9–12 months

of age, while a reduced RR was reported to be observed among infants 0 to 4 months of age. The authors also reported that there was little to no evidence of an association between toenail Hg and upper-respiratory infection, allergy or eczema at any age interval.

To assess the association of heavy metal exposure with autoimmunity and the development of juvenile idiopathic arthritis, Kindgren *et al.* (2019) conducted a prospective birth cohort study in Sweden. The authors found that Hg in cord blood was significantly higher in the juvenile idiopathic arthritis group than in the controls, but not in the antinuclear antibodies group, and concluded that moderate exposure to heavy metals during pregnancy and early childhood may affect the immune system.

The 2012 EFSA assessment identified seven original articles on "immunotoxicity". These include Miyake *et al.*, 2011 and Carrasco *et al.*, 2021 (described earlier in this section). Three further articles found no adverse association of Hg in relation to antinuclear antibodies (Alves *et al.*, 2006), antibodies against vaccine toxoids (Heilmann *et al.*, 2010), and asthma and atopic dermatitis (Grandjean *et al.*, 2010). One study investigating immunological status (Belles-Isles *et al.*, 2002) found an association for a subset of naive T-cells, and another study (Nyland *et al.*, 2011b) found an association with total immunoglobulins, but not with IgG. Finally, one study (Park *et al.*, 2011) provided evidence for an association of Hg with atopic dermatitis.

5.2.4.1.3 Reproduction

One systematic review and one original article were identified considering the effect of Hg exposure on reproduction generally. The systematic review (Sirohi *et al.*, 2021) investigated the association between environmental exposures to endocrine-disrupting chemicals and endometriosis. Only one study within this review was identified to report on the association between serum Hg levels and endometriosis, and no association was found. Mocevic *et al.* (2013) conducted a cross-sectional study on male partners of pregnant women in Greenland, Poland and Ukraine, evaluating the association between serum levels of reproductive hormones and THg in blood. The authors reported that no evidence was found that environmental Hg exposure had effects on biomarkers of male reproductive health in the considered population and exposures.

The 2012 EFSA assessment identified five studies on "reproductive toxicity". Three of these – investigating pre-term birth (Xue *et al.*, 2007), reproductive hormones and anovulation (Pollack *et al.*, 2011) and endometriosis and uterine myomas (Jackson *et al.*, 2008) – reported not to have found any association. The remaining two studies assessed semen parameters, and while one reported to not have found evidence for an association with Hg exposure (Rignell-Hydbom *et al.*, 2007), the second one reported an association with particularly head and midpiece defects and some motion characteristics (Choy *et al.*, 2002).

5.2.4.1.4 Vision

In a cross-sectional study on visual acuity, and its association with Hg exposure, Fillion *et al.* (2011), investigated adults from fish-eating communities in Brazil (the Caruso project). According to the authors, the concentration of Hg in hair may be associated with visual acuity loss in older people, but not in younger people.

The 2012 EFSA assessment identified one article (Lemire *et al.*, 2010) that looked at vision as an outcome. The study found that individuals with a blood Hg above the 25th percentile had a higher prevalence of age-related cataracts, compared to individuals below the 25th percentile, though the finding was not statistically significant for the oldest age group (>65 years of age). Further, it was stated that the results needed to be interpreted with caution due to the low number of participants and cases included in said article.

5.2.4.1.5 Osteoporosis

Two articles were identified in the present literature review which assessed the association between Hg exposure and osteoporosis by measuring bone mineral density and THg in blood in participants of the Korea National Health and Nutrition Examination Survey. Cho *et al.* (2012) studied postmenopausal women in said cohort, Kim *et al.* (2016) considered middle-aged men. According to both studies, the risk for osteoporosis was reduced with higher blood Hg concentrations.

5.2.4.1.6 Multiple sclerosis

The literature search identified one systematic review (Sarihi *et al.*, 2021) on heavy metal concentrations (including Hg) in multiple sclerosis patients. Of the 16 articles included in the systematic review, data from six studies (one cohort and five case-control studies, all from Italy or Iran) were subjected to a meta-analysis focusing on Hg. The authors reported that no differences in Hg exposure between multiple sclerosis patients and healthy controls were found.

5.2.4.1.7 Hypertension and renal disease

The literature search identified one original study (Sanders *et al.*, 2019 – a cross-sectional study on children from the United States) investigating the association of exposure to different metals, including Hg, on hypertension and renal disease. Survey-weighted single chemical analyses showed an increase in the estimated glomerular filtration of 0.6 percent (95% CI: 0.1, 1.0) with each decile increase in urine Hg. No significant association with blood Hg was observed. The authors concluded that metals, including As, Pb, Hg, Cd and their combinations, may affect renal parameters, but stated that potential reverse causation cannot be ruled out due to the cross-sectional study design.

5.2.4.1.8 Thyroid hormones

The literature search identified a meta-analysis addressing the association between Hg exposure and thyroid hormone levels (Hu *et al.*, 2021). The analysis included

13 studies, 6 of which were prospective cohort studies and 7 of which were cross-sectional studies. The meta-analysis indicated that exposure to Hg in blood could significantly correlate with the levels of TSH, T4, and FT4 in the general population. However, the authors did not state if the observed changes might cause adverse effects.

5.2.4.1.9 Pulmonary function

Pan *et al.* (2020) conducted a cross-sectional study among Chinese children to assess the association between blood Hg levels and pulmonary function. After adjusting for confounders, no association was found.

5.2.4.1.10 Cancer

Two articles, Zidane *et al.*, 2019 and Rhee *et al.*, 2020, considered the association between Hg exposure and cancer. Zidane *et al.* conducted a case-control study on thyroid cancer in French Polynesia measuring THg in fingernails and reported that the concentrations were not associated with thyroid cancer risk. Rhee *et al.* investigated skin cancer in adults in the United States in a cross-sectional study, reporting higher blood THg and MeHg levels to be associated with a higher prevalence of non-melanoma skin cancer.

5.2.4.1.11 Sexual maturation

One article was identified in the literature search (De Craemer *et al.*, 2017), which assessed the association between Hg exposure and sexual maturation in Belgian adolescents participating in the Flemish Environment and Health Study. The authors reported that no significant effect of Hg exposure on hormone levels in blood was observed. Among several other physical maturation endpoints assessed in this study, it was reported that only female breast development was significantly associated with hair Hg, and the authors stated that the results for Hg should be interpreted with caution.

TABLE 5.7 **OVERVIEW OF SYSTEMATIC REVIEWS WITH OTHER HEALTH OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Hu *et al.*, 2021 Association between mercury exposure and thyroid hormones levels: A meta-analysis	Other; thyroid hormones; thyroid stimulating hormone (TSH), triiodothyronine (T3) and free T3, thyroxine (T4) and free T4	Total n = 13: Prospective cohort studies (n = 6) and cross-sectional studies (n = 7)	The Hg content of most studies included was defined as low by reported evidence, which indicated a blood exposure threshold of approximately equivalent to 4–5 µg/L.	Meta-analysis: TSH (n = 10 930): Effect size (ES) (95% CI): 0.48 (0.18, 0.78). T3 (n = 8 216): ES (95% CI): 0.20 (-0.37, 0.77). fT3 (n = 8 821): ES (95% CI): 0.20 (-0.40, 0.80). T4 (n = 6 809): ES (95% CI): -0.02 (-0.02, -0.01). fT4 (n = 8,726): ES (95% CI): 0.47 (0.11, 0.82)	This meta-analysis indicates that exposure to Hg in blood could significantly correlate with the levels of TSH, T4 and FT4 in the general population.
Roy *et al.*, 2017 Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature	Other; diabetes; type 2 diabetes, gestational diabetes, insulin resistance and metabolic syndrome	Total n = 24: Prospective cohort studies (n = 4, nested case-control studies (n = 3) and cross-sectional studies (n = 17)	Not mentioned	The associations found in the articles were weak to moderate, ranging from no association at all to an OR of 7.35 (1.73–31.1). Several of the studies found an association between increased Hg exposure and risk of diabetes and metabolic syndrome, but the associations were not consistent between studies and the results from the longitudinal studies were conflicting.	Increased total Hg exposure may augment the risk of diabetes and metabolic syndrome, but the lack of consistency of the epidemiological evidence prevents the inference of a causal relationship.
Sarihi *et al.*, 2021 Toxic heavy metal concentrations in multiple sclerosis patients: A systematic review and meta-analysis	Other; multiple sclerosis	Total n = 6: Cohort study (n = 1) and case-control studies (n = 5)	See results from meta-analysis.	Meta-analysis: Cases (n = 296) vs. controls (n = 361) in pooled estimates of the weighted mean differences on Hg concentrations: Weighted mean differences (95% CI): -0.14 (-0.77, 0.49).	No clear differences in Hg concentrations in multiple sclerosis patients vs. healthy controls.
Sirohi *et al.*, 2021 Environmental exposures to endocrine disrupting chemicals (EDCs) and their role in endometriosis: a systematic literature review	Other; endometriosis	Total n = 1: Cohort study (n = 1)	Not mentioned	Only one study (Pollack *et al.*, 2014) reported an association between serum Hg levels and endometriosis. The study did not find a statistically significant positive association between serum and urinary levels of Hg	No association between Hg exposure and endometriosis was found.

TABLE 5.7 **OVERVIEW OF SYSTEMATIC REVIEWS WITH OTHER HEALTH OUTCOMES FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR TITLE	HEALTH OUTCOME	NUMBER OF STUDIES	LEVEL OF Hg DETECTED	RESULTS	OVERALL CONCLUSION
Xu *et al.*, 2021: Associations between metabolic syndrome and four heavy metals: A systematic review and meta-analysis	Other; metabolic syndrome	Total n = 11: Study type not given	Blood Hg ranging from 0.50 to 65.0 µg/L	Meta-analysis: Hg concentrations were higher in metabolic syndrome patients compared to controls: Pooled estimated effect sizes = 1.26 (95% CI: 1.06, 1.48).	Exposure to Hg was associated with prevalence of metabolic syndrome.

Notes: CI: confidence interval; OR: odds ratio.

TABLE 5.8 OVERVIEW OF PRIMARY STUDIES WITH OTHER HEALTH OUTCOMES (N = 15) FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg"

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Tsai, *et al.*, 2019 Taiwan Province of China	Cross-sectional	Other outcomes, type 2 diabetes: plasma glucose levels after fasting and/or treatment with hypoglycaemic medication	Adults, age for non-type 2 diabetes: 41.13 ± 14.64 years and for type 2 diabetes: 55.37 ± 12.87 years; n = 646 (51% female)	THg red blood cells in non-type 2 diabetes: GM 13.21 ppb, 95% CI 12.42–14.04 THg red blood cells in type 2 diabetes: GM 18.95 ppb, 95% CI 15.66–22.93	Findings showed that elevated Hg in red blood cells is significantly associated with type 2 diabetes prevalence.
Stratakis, *et al.*, 2020 France, Greece, Norway, Spain, the United Kingdom of Great Britain and Northern Ireland	Pregnancy cohort	Other outcomes, metabolic health and inflammation: metabolic syndrome score for children	Children, age at birth until age 6 to 12 years; n = 805 (44% female)	THg in maternal blood: median 2.5 µg/L, IQR 1.5-4.2	High maternal mercury exposure was associated with a metabolic profile in children. However, moderate fish intake was associated with improvements in the metabolic health of children.
Miyake, *et al.*, 2011 Japan (Osaka)	Pregnancy cohort	Other outcomes, immune system: allergic disorders, wheeze and eczema	Children, age prenatal 2–9 months gestation; and 16–24 months and 29–39 months; n = 582 (47% female)	THg in maternal hair: median 1.52 µg/g, range 0.26–6.05 THg in child hair: median 1.38 µg/g, range 0.13–9.51	Neither maternal nor children's hair mercury levels were related to the risk of wheeze or eczema after adjustment for potential confounding variables.
Carrasco, *et al.*, 2021 Spain	Pregnancy cohort	Other outcomes, immune system: respiratory health	Children, age at birth and 4.4 years ± 0.2; n = 1 347–1 868 (48% female)	THg in cord blood: GM 8.23 µg/L, IQR 9.00 THg in child hair: GM 0.97 µg/L, IQR 1.04	No associations were found between prenatal and postnatal Hg exposure and respiratory and allergy problems, although these associations could be modulated by diet and other pollutants, especially during prenatal period.

TABLE 5.8 **OVERVIEW OF PRIMARY STUDIES WITH OTHER HEALTH OUTCOMES (N = 15) FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Emeny, *et al.*, 2019 the United States (New Hampshire)	Pregnancy cohort	Other outcomes, immune system: respiratory infections or respiratory symptoms, atopic dermatitis (eczema) or allergy in the preceding four months	Infants, of women in gestational week 24–28 if they reported using water from a private, unregulated well in their home since their last menstrual period and were not planning a change in residence prior to delivery, age 4–12 months; n = 706 (49% female)	THg in maternal toenails: GM 0.02 µg/g, range 0.00007–1.19	In-utero exposure to MeHg might increase the risk of lower (but not higher) respiratory infections and respiratory symptoms in the first year of life. There was little to no evidence of associations of toenail Hg with upper respiratory infection, allergy or eczema at any interval.
Kindgren, *et al.*, 2019 Sweden	Pregnancy cohort and retrospective case-control	Other outcomes, immune system: juvenile idiopathic arthritis, and antinuclear antibodies (ANA)	Children, age 16 years; n = 40 controls, and 42 cases of juvenile idiopathic arthritis	THg in cord blood Hg (µg/L): median (range) Controls: 0.20 (0.20–0.53) Antinuclear antibodies: 0.29 (0.20–0.65) juvenile idiopathic arthritis: 0.30 (0.20–1.01)	Concentrations of Hg (and Al, Cd, Li) in cord blood were significantly higher in the juvenile idiopathic arthritis-group than in controls. Concentrations of Hg in cord blood were not significantly higher in the antinuclear antibodies-group compared to controls. Moderate exposure to heavy metals, including Hg, associated with fish consumption, during pregnancy and early childhood may cause effects on the immune system of the offspring.
Mocevic, *et al.*, 2013 Greenland, Poland and Ukraine	Cross-sectional	Other outcomes, reproduction: semen quality and serum levels of reproductive hormones	Adults, male partners of pregnant women, age mean (range): 29.5 (18.0–51.3); n = 529 (0% female)	THg in blood (ng/mL): median (range) Greenland: 9.2 (0.2–385.8) Poland: 1.0 (0.2–6.4) Ukraine: 1.0 (0.2–4.9)	Results show evidence that environmental mercury exposure in Greenlandic and European men with median whole blood concentration up to 10 ng/ml has adverse effects on biomarkers of male reproductive health.

TABLE 5.8 OVERVIEW OF PRIMARY STUDIES WITH OTHER HEALTH OUTCOMES (N = 15) FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Fillion, *et al.*, 2011 Brazil (Lower Tapajos River basin)	Cross-sectional	Other outcomes, vision: visual acuity	Adults, in fish-eating communities, age mean (range): 35.8 (15–66); n = 243 (female 52%)	THg in hair: median 11.5 mg/g, range 1.0–57.9 THg in blood: median 41.8 mg/L, range 1.7–179.3 THg in plasma: median 6.9 mg/L, range 0.2–30.9	Hair Hg may be associated with visual acuity in older persons. No association was observed between Log Hair Hg and near visual acuity loss in younger people, whereas for older persons, there was a highly significant association. Log Hair Hg showed positive association with distant visual acuity loss, but did not reach significance level (P <0.05).
Cho, *et al.*, 2012 South Korea	Cross-sectional	Other outcomes, osteoporosis: bone mineral density	Adults, postmenopausal women, age mean between 60 and 64 years; n = 481 (100% female)	THg in blood: median 3.74 µg/L, IQR <2.67–5.23	High blood Hg levels were associated with a lower risk of having osteoporosis in postmenopausal women.
Kim, *et al.*, 2016 South Korea	Cross-sectional	Other outcomes, osteoporosis: one mineral density	Adults, men, age 61 years ±0.2; n = 1 190 (0% female)	THg in blood: median 5.337 µg/L, IQR 3.347–8.104	Data showed that high blood Hg levels may be positively associated with increased total hip and femur neck bone mineral density, but do not offer significant protection against fragility-associated fractures.
Sanders, *et al.*, 2019 the United States	Cross-sectional	Other outcomes, hypertension and renal disease: kidney function	Children, age mean 15.4 (SD 2.3); n = 2709 (48% female)	THg in blood: mean 0.68 µg/L, SD 1.56 THg in urine: mean 0.41 µg/L, SD 0.94	The findings suggest metals, including As, Pb, Hg, Cd and their combinations, may affect renal parameters. Survey-weighted single chemical analyses showed estimated glomerular filtration rate was 0.6% (95% CI: 0.1, 1.0) higher with each decile increase in urine Hg. There was no significant association with blood Hg.
Pan, *et al.*, 2020 China (Wuxi City)	Cross-sectional	Other outcomes, pulmonary function: forced expiratory volume in 1 s and forced vital capacity	Children, local and native-born, age mean 12.5; n = 221 (47% female)	THg in blood: mean 1.41 µg/L, 10th percentile 0.77, 95th percentile was 2.95	There was no association between blood Hg concentrations and pulmonary function in children.

TABLE 5.8 **OVERVIEW OF PRIMARY STUDIES WITH OTHER HEALTH OUTCOMES (N = 15) FOR THE REVIEW OF "HEALTH EFFECTS OF MeHg" (cont.)**

AUTHOR, YEAR COUNTRY	STUDY DESIGN	HEALTH OUTCOME	STUDY PARTICIPANTS	MERCURY CONCENTRATIONS	RESULTS AND CONCLUSIONS
Zidane, *et al.*, 2019 French Polynesia	Case-control	Other outcomes, cancer: thyroid cancer risk	Cases of thyroid cancer and a control group (closest in terms of date of birth, otherwise random), -, age younger than 56; n = 229 cases, 249 controls (gender not provided)	THg in fingernails, cases: mean 1.10 µg/g, 95% CI 0.96-1.24 THg in fingernails, control: mean 1.20 µg/g, 95% CI 0.90-1.30	Hg (and other non-essential trace elements) fingernail concentrations were not associated to differentiated thyroid cancer risk.
Rhee, *et al.*, 2020 the United States	Cross-sectional	Other outcomes, cancer: skin cancer	Adults, age >20 years; n = 29413 (52% female)	THg in blood: mean 1.6 µg/L, SD 2.4 IHg in blood: mean 0.3 µg/L, SD 0.4 MeHg in blood: mean 1.3 µg/L, SD 2.4	Higher blood THg and MeHg levels were associated with a higher prevalence of nonmelanoma skin cancer.
De Craemer, *et al.*, 2017 Belgium	Cross-sectional	Other outcomes, sexual maturation: sex hormone levels in males and genital development in males and females	Adolescents, age 14–15 years; n = 138–311 (balanced gender ratio)	THg in hair: mean 0.169 µg/g, 95% CI 0.157–0.181 MeHg in hair: mean 0.112 µg/g, 95% CI 0.104–0.121	No significant effect on hormone levels in blood was observed. For the other maturation endpoints, only female breast development was significantly associated with H-MeHg (OR= 0.635, 95% CI: 0.411, 0.951) and H-THg (OR= 0.744, 95% CI: 0.527, 0.973). Authors are cautious to draw conclusions.

Notes: THg: total mercury; GM: geometric mean, CI: confidence interval, ppb: parts per billion, IQR: interquartile range, SD: standard deviation, OR: odds ratio.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CHAPTER 6

RESULTS AND SUMMARIZATION OF THE LITERATURE REVIEW "THE ROLE OF SE WITH REGARD TO THE HEALTH EFFECTS OF MeHg"

6.1 LITERATURE AND QUALITY ASSESSMENT

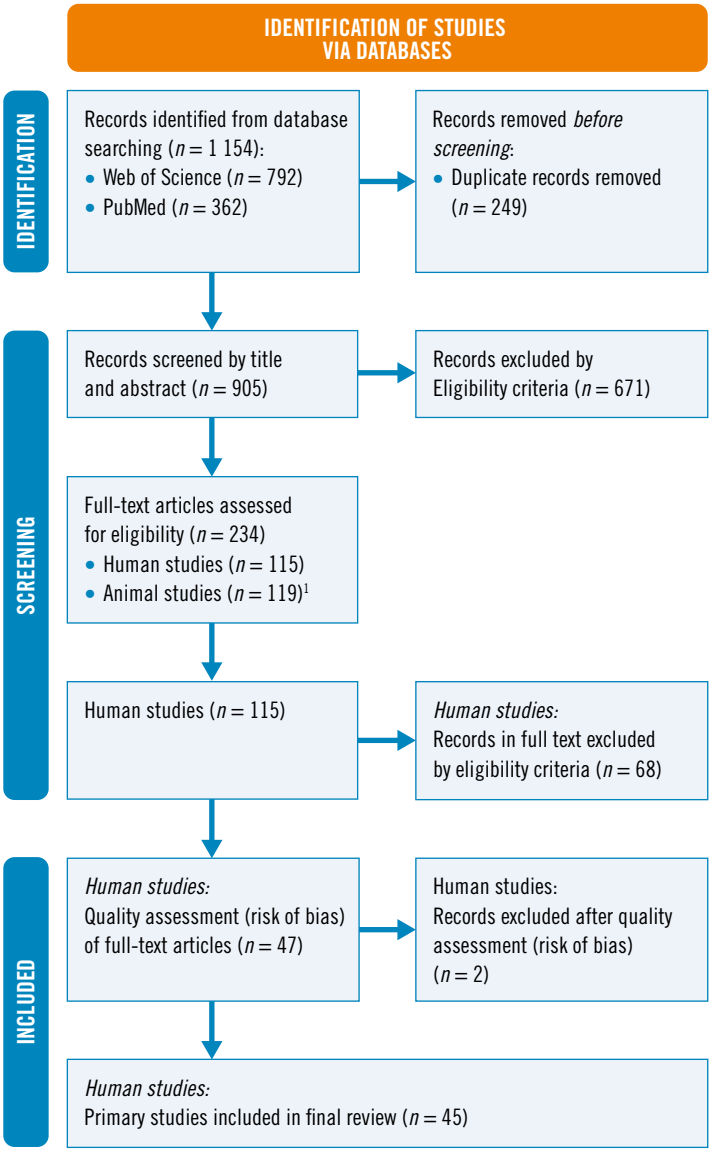
Literature searches for the review on "The role of Se with regard to the health effects of MeHg" were performed in the databases PubMed and Web of Science. A flow diagram of the results from the literature searches is given in **Figure 6.1**.

The parallel literature searches performed in Web of Science and PubMed resulted in 1 154 records. Of these, 249 were found to be duplicate records. Following duplicate removal in Endnote, 905 records were subjected to title and abstract screening using Rayyan. Based on the predefined inclusion and exclusion criteria (**Table 2.12**), 671 records were excluded and 234 records (comprising 115 human studies and 119 animal studies) were retained for full-text screening.

6.1.1 HUMAN STUDIES

A total of 115 records of the human studies were assessed in full text. Of these, 68 were excluded based on the inclusion and exclusion criteria (Appendix 6, **Table 6.2**). Thus, 47 records were assessed for risk of bias with the OHAT tool. Of the 47 articles included for full-text quality assessment, 28 articles were rated Tier 1, 17 articles were rated Tier 2, and 2 articles were rated Tier 3 (Appendix 6, **Table 6.3**). The studies graded Tier 3 were excluded, leaving 45 records for further assessment.

FIGURE 6.1. **FLOW DIAGRAM FOR THE REVIEW "THE ROLE OF SE WITH REGARDS TO THE HEALTH EFFECTS OF MeHg"**



Notes: [1]Animal studies were included in the literature search and further used for background information for mechanistic and biologically plausible evidence in the context of the included human studies. However, the animal studies were not quality assessed or included in the weighing of the evidence of the studies.
Source: Prepared by authors based on Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L. *et al.* 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71

6.1.2 ANIMAL STUDIES

A total of 119 animal studies were included and found relevant from the literature search. These studies were further used for background information for mechanistic and biologically plausible evidence. However, they were not quality assessed (risk-of-bias assessment) nor was their evidence included in the weight-of-evidence assessment.

6.2 RESULTS AND SUMMARIZATION OF THE LITERATURE INCLUDED

6.2.1 DESCRIPTION OF THE LITERATURE

Forty-five human primary studies were included in the final review investigating the role of Se with regard to the health effects of MeHg. A detailed description of the human studies included is given in Appendix 6, **Table A6.4**, including study design, study participants, measurements and exposure of Hg and Se, outcome assessment, and results and conclusions regarding the effect of Se on MeHg toxicity.

The 45 articles comprised 34 different studies (some studies were published in several articles) from 12 countries in Asia, Europe, North America and South America (**Table 6.1**). Of the 45 included articles, 23 studies were cohort studies, 6 were case-control studies, and 16 were cross-sectional studies.

TABLE 6.1 DISTRIBUTIONS OF THE STUDIES AND PUBLICATIONS INCLUDED PER INVESTIGATED COUNTRY

COUNTRY	NUMBER OF STUDIES	NUMBER OF ARTICLES
Brazil	2	6
Canada	6	7
China	1	1
Faroe Islands	1	2
Japan	4	4
Korea	1	2
Poland	1	2
Slovenia and Croatia	1	1
Sweden	5	3
Taiwan Province of China	2	2
the United Kingdom of Great Britain and Northern Ireland	1	4
the United States	9	11

The reported results and the information given in the 45 articles varied. Although all the studies measured Se and Hg levels in different human tissues, not all studies could assess the potential effect of Se on Hg toxicity. Fifteen of the studies did not find any association between Hg and the investigated health outcome. Thus, although Se was measured, the studies could not assess the potential effect of Se on Hg toxicity. In addition, four of the studies had not specifically studied the effects of Se on Hg toxicity, even though they had measured both Se and Hg concentrations. (A summary of the studies is given in Appendix 6, **Table A6.4**). This section does not describe in detail the studies that could not assess the potential role of Se on MeHg exposure. Thus, 26 studies (13 cohort studies, 1 case-control study, and 12 cross-sectional studies) are described in further detail in the following results sections.

The health outcomes measured in the studies varied, and the results from the studies are summarized within the following health outcomes:

- cardiovascular outcomes
- oxidative stress
- immune system
- reproduction
- thyroid hormones
- prenatal somatic development
- neurodevelopment and cognition
- vision function
- motor function

The results from the animal studies are communicated briefly with the goal of coupling human findings to mechanisms, but those studies were not quality assessed and are therefore not used for weighing the evidence.

6.2.2 CARDIOVASCULAR OUTCOMES

Five studies investigated the effects of Se on MeHg toxicity for cardiovascular outcomes. A general summary of the studies is given in Table 6.2. The five studies included three cohort studies (in four publications) (Bélanger *et al.*, 2008b; Park *et al.*, 2016; Hu *et al.*, 2017 and Park *et al.*, 2017) and one cross-sectional study (Ayotte *et al.*, 2011).

Of these, two cohort studies (in three publications) (Park *et al.*, 2016; Hu *et al.*, 2017 and Park *et al.*, 2017) and the cross-sectional study (Ayotte *et al.*, 2011) showed an effect of Se on MeHg toxicity for cardiovascular outcomes, while one cohort study (Bélanger *et al.*, 2008b) showed unclear effects (see **Table 6.2**).

In addition to the five studies that found an effect of Hg on cardiovascular outcomes and measured the potential effect of Se, eight additional studies were found in the literature search including cardiovascular outcomes (Appendix 6 **Table A6.4**). One study did not study effects of Se on MeHg toxicity (Emanuele *et al.*, 2017), and seven studies (Engström *et al.*, 2011; Mozaffarian *et al.*, 2011; Wennberg *et al.*, 2011; Mozaffarian *et al.*, 2012; Park *et al.*, 2013; Gregory *et al.*, 2016 and Chen *et al.*, 2018) did not show toxicity of Hg on the investigated parameters and thereby could not investigate the modification of such toxicity by Se. As Se may alleviate cardiovascular toxicity of Hg, the studies that did not find an effect of Hg could have had Se as a confounder. Of those studies reporting no Hg toxicity, some had reported lower mean levels of Hg in blood and toenails than reported in the four studies shown in **Table 6.2**: For toenails, the concentration range was 0.21–0.31 µg/g as median (Mozaffarian *et al.*, 2011 and Mozaffarian *et al.*, 2012) and for blood the geometric mean was 1.03 µg/L (Park *et al.*, 2013). The other studies could not be compared for Hg concentrations, as they measured Hg in other matrices, namely erythrocytes, urine, serum or hair.

TABLE 6.2 **STUDIES INCLUDED FOR THE HEALTH OUTCOME "CARDIOVASCULAR OUTCOMES" FOR THE REVIEW "SE AND MeHg"**

AUTHOR, YEAR	TIER, STUDY DESIGN,	Hg AND Se EXPOSURE	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON MeHg TOXICITY*[1]
Ayotte *et al.*, 2011	Tier 1, cross-sectional study, n = 869, 37 years, 45%	Blood geometric mean: Hg 11 µg/L Se 300 µg/L	Canadian Inuit, Nunavik, high seafood diet Regression analysis	Se intake offsets Hg exerted inhibition of PON1 activity, a predictor for coronary heart disease. *Effect*
Hu *et al.*, 2017	Tier 2, cohort study, n = 2169, 42 years 39%	Blood median Hg, 7.8 µg/L Se 280 µg/L	Canadian Inuit, Nunavut ++, aged >18 years Two concentrations for each Hg and Se	High Se and low Hg had the lowest prevalence of cardiovascular outcomes (except stroke). *Effect*
Park *et al.*, 2016; Park *et al.*, 2017[2]	Tier 1, cohort study, n = 501, 45 years 47%	Toenail mean Hg 0.4 µg/g mean/median Se 0.7/1.0 µg/g	Koreans from Yeungnam area >35 years Regression analysis	Positive association between toenail Hg and > metabolic syndrome, which was weaker at higher Se concentrations; > higher risk of hyper-LDL-cholesterolemia and dyslipidemia, non-significant at high toenail selenium levels >0.685 µg/g. *Effect*
Bélanger *et al.*, 2008 b	Tier 2, cohort study, n = 31, 47 years 100%	Blood mean Hg 21.9 nmol/L before fishing season	Canadian sports fishermen Two different doses of seafood in same population	Fishing season improved cardiovascular health, not homocysteine. Role of Se unclear. Likely dominating confounder: Seasonal lifestyle with more exercise and fresh air. Not designed to investigate effect of Se. *Unclear effect*

Notes: PON1: paraoxonase-1; LDL: low-density lipoprotein. [1]The effects of Se on MeHg toxicity were assessed and categorized as: "effect", "indirect effect", "unclear effect" and "no effect". [2]These two articles are about the same study, but refer to different outcomes.

6.2.2.1 Weight of evidence for "Cardiovascular outcomes"

Although some studies showed an effect of Se on the toxic effects of Hg on cardiovascular outcomes, only a small number of studies were found, and different outcomes were investigated in specific population groups. In addition, the potential risk of confounding factors cannot be ruled out. Therefore, in conclusion, when weighing the evidence according to the criteria from the WRCF, there is "limited, suggestive" evidence of the effect of Se on MeHg toxicity on cardiovascular outcomes.

This conclusion was based on:

> There is evidence from at least two independent cohort studies (Park *et al.*, 2016; Hu *et al.*, 2017 and Park *et al.*, 2017).

> There is evidence from more than one study type, though one study (Ayotte *et al.*, 2011) was a cross-sectional study, and therefore was not weighed heavily compared to the cohort studies.

> There is low unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect. The studies were deemed low risk of bias (one cohort study ranked Tier 1), and included both males and females and different ethnic groups.

> The presence of a plausible biological gradient ("dose–response") in the association: One study was a small two-factorial study investigating high and low Se combined with high and low Hg. Most of the difference was found between high Se/low Hg and low Se/high Hg (Hu *et al.*, 2017), while another study (Ayotte *et al.*, 2011) found that metabolic syndrome was associated positively with Hg, but that this was dependent on the concentration of Se.

6.2.2.2 Animal studies on "Cardiovascular outcomes"

There were no animal studies with the outcome of cardiovascular diseases included in the literature search.

6.2.3 OXIDATIVE STRESS

Five studies investigated the effects of Se on MeHg toxicity for the outcome of oxidative stress. A general summary of the studies is given in **Table 6.3**. The studies included two cohort studies (Bélanger *et al.*, 2008b and Kuras *et al.*, 2019) and two cross-sectional studies (in three publications) (Bélanger *et al.*, 2006; Bélanger *et al.*, 2008a and Karimi *et al.*, 2016) (**Table 6.3**). One cross-sectional study (Karimi *et al.*) showed an effect of Se on Hg toxicity, while the remaining studies showed only indirect or less clear effects. Those with unclear results had a low number of participants (< n = 100 participants). Three studies were rated Tier 1, while one study was rated Tier 2. There was no directional heterogeneity between the studies, as there was no study that did not find effects of Se on Hg toxicity regarding oxidative stress (**Table 6.3**).

In addition to the five studies that found an effect of Hg on the oxidative stress outcomes and measured the potential effect of Se, two additional studies were found in the literature search including oxidative stress: Rocha *et al.*, 2016 and Kuras *et al.*, 2019. Rocha *et al.* did not find any toxicity of Hg and was not included for further assessment, while Kuras *et al.* did not investigate modulation of Hg effects by Se. Kuras *et al.*, however, did show correlations of Hg with selenoprotein-P and small oxidants in blood.

TABLE 6.3 **STUDIES INCLUDED FOR THE HEALTH OUTCOME "OXIDATIVE STRESS" FOR THE REVIEW "SE AND MeHg"**

AUTHOR, YEAR	TIER, TYPE, N, MEAN AGE, PERCENT MALE	Hg AND Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Karimi *et al.*, 2016	Tier 1, cross-sectional study, n = 268, 48 years, 42%	Blood mean Hg 8 µg/L median Se 240 µg/L	Long Island the United States, avid seafood eaters Regression analysis	Association of high Hg from fish consumption and GSH:GSSG (reduced glutathione:oxidized glutathione), which is indicative for oxidative stress, was slightly less pronounced in those with highest Se in blood. Possible slight alleviation of Hg-induced stress. *Effect*
Belanger *et al.*, 2006 Belanger *et al.*, 2008a[2]	Tier 1, cross-sectional study, n = 99, 43 years, 28%	Blood mean Hg 21 µg/L Se 636 µg/L	Inuit Regression analysis	> Concentration of plasma homocysteine was negatively predicted by Se, but dietary Hg showed no association. > Low LDL oxidation may be partly explained by high blood Se status, that might reduce the deleterious effects of MeHg on cardiovascular health. *Indirect effect*
Bélanger *et al.*, 2008b	Tier 2, cohort study, n = 31, 47 years, 100%	Blood mean Hg 4.4 µg/L before fishing season and 7.1 µg/L after (recalculated from molar to mass based) Se blood mean 243 µg/L before and 248 µg/L after fishing season.	Canadian sports fishermen Two different doses of seafood in same population	Fishing season improved cardiovascular health, not homocysteine. Role of Se unclear. Not designed to investigate effect of Se. *Indirect effect*
Kuras *et al.*, 2019	Tier 1, cohort study, n = 67, 41 years, 100%	Blood median Hg 1 µg/L, hair 0.3 µg/g, urine 0.23 µg/L. Plasma median Se 82 µg/L; urine 17 µg/L.	Polish men Regression analysis	Both Hg and Se increase in an intervention with high fish intake. Increase in TBARS as an effect of fish intake but little evidence for direct action of Se on GSH-Px. No direct evidence for a protective effect of Se. Se and selenoproteins mainly investigated as biomarker of Hg effect. *Indirect effect*

Notes: LDL: low-density lipoprotein; TBARS: thiobarbituric acid-reactive substances; GSH-Px: glutathione peroxidase. [1]The effect of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect". [2]These two articles are about the same study, but refer to different outcomes.

6.2.3.1 Weight of evidence for "Oxidative stress"

In conclusion, when weighing the evidence according to the criteria from the WCRF, this was found to be "limited evidence, no conclusion" regarding the effect of Se on Hg toxicity outcomes on oxidative stress. This conclusion was based on:

> There is direct evidence from only one cross-sectional study, and only indirect evidence from more than one study type.

> There is no direct, only indirect, evidence from two independent cohort studies.

> The number of participants in the cohort studies was low (< n = 100).

The one cross-sectional study (Karimi *et al.*, 2016) with a moderate number of participants (n = 268), rated Tier 1, shows a slight effect, and four studies (Bélanger *et al.*, 2006; Bélanger *et al.*, 2008; Bélanger *et al.*, 2008b and Kuras *et al.*, 2018) indicate the same direction of effect, but without providing direct evidence.

6.2.3.2 Animal studies on "Oxidative stress"

Further corroboration on the outcomes of oxidative stress comes from animal studies (Grotto *et al.*, 2008; Grotto *et al.*, 2009; Joshi *et al.*, 2014; Orct *et al.*, 2015 and Moniruzzaman *et al.*, 2021). A mice study that was included in the literature search (Balthrop *et al.*, 1985) showed that intraperitoneal injections of Se produced an increase in glutathione and glutathione-S-transferase activity in Se-deficient animals only. However, when followed by MeHg injections, the negative effect of MeHg on glutathione-S-transferase was reduced by the administered Se. However, Se supplementation may either alleviate or augment the effects of MeHg, depending on their doses and combinations (Jin *et al.*, 2012).

6.2.4 IMMUNE SYSTEM

Five studies investigated the effects of Se on MeHg toxicity for the outcome of biomarkers of the immune system. A general summary of the studies is given in **Table 6.4**.

The five studies included two cross-sectional studies: Hui *et al.*, 2016 and Nyland *et al.*, 2011a. When investigating the effect of Se on Hg toxicity on the immune system, Hui *et al.* found an effect, while Nyland *et al.* did not. Both studies were rated Tier 2 in the quality assessment conducted with the OHAT risk-of-bias tool.

In addition to the two studies that found an effect of Hg on immune system outcomes and measured the potential effect of Se, an additional study was found in the literature search: Monastero *et al.* (2017). This study did not find an effect of Hg toxicity.

TABLE 6.4 **STUDIES INCLUDED FOR THE HEALTH OUTCOME "IMMUNE SYSTEM" FOR THE REVIEW "Se AND MeHg"**

AUTHOR, YEAR	TIER, TYPE, N, MEAN AGE, PERCENT MALE	Hg and Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Hui *et al.*, 2016	Tier 2, cross-sectional study, n = 608, 8 years 54%	Median Hg cord blood: 9 µg/L blood: 3 µg/L Median Se blood: 92 µg/L	Chinese local birth cohort Regression analysis	Small but significant association between mercury and IL-10 concentration, more pronounced when selenium and cord blood mercury were low. Se seems to alleviate Hg toxicity. The clinical significance is unclear. *Effect*
Nyland *et al.*, 2011	Tier 2, cross-sectional study, n = 232, 15–78 years (no mean provided), 48%	Median Hg hair: 14 µg/g blood: 54 µg/L plasma: 9 µg/L urine: 3 µg/L Se concentrations not provided.	Brazil Tapajos River basin population, affected by MeHg from gold extraction. Regression analysis	Antinuclear (ANA) and antinucleolar (ANoA) autoantibody levels and eight cytokines in serum samples, e.g. (IL)-6, (IFN)-γ, (IL-4), and IL-17, were investigated. Se status was not associated with any changes in ANA and did not modify associations between Hg and ANA titers. *No effect*

Notes: IL: interleukin; IFN: interferon [1]The effect of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.4.1 Weight of evidence for "Immune system"

In conclusion, when weighing the evidence according to the WCRF criteria, very "limited evidence, no conclusion" was found of the effect of Se on Hg toxicity outcomes on the immune system. This conclusion was based on:

> There were no cohort studies investigating this hypothesis, both studies were cross- sectional and were graded Tier 2.

> There may be a countereffect of Se on the effect of Hg on IL-10, with uncertain clinical significance. Other immune system markers were not found to be associated.

The data on effects of Se on Hg toxicity on the immune system was too scarce for conclusions; however, there are animal studies that demonstrate effects and encourage further investigation in humans.

6.2.4.2 Animal studies on "Immune system"

In a study of mice (Li *et al.*, 2014a), proliferation of T and B lymphocytes was investigated upon administration of Hg and Se with drinking water, where – at low Hg concentration – Se exhibited protective effects on Hg-induced suppression, while – at greater Hg concentration – immunotoxicity induced by high concentrations of Se became evident, with protective effects at a Se/Hg molar ratio of 1:1, witnessing antagonistic effects between Se and Hg. Another mice study (Li *et al.*, 2014b) investigating redox-mediated immune suppression by MeHg found a protective effect of Se administered by diet.

6.2.5 REPRODUCTION

Two studies, a case-control study (Maeda *et al.*, 2019) and a cross-sectional study (Ai *et al.*, 2019), investigated the effects of Se on MeHg toxicity for the outcome of reproduction. A general summary of the studies is given in **Table 6.5**. Both studies were graded Tier 2. The cross-sectional study (Ai *et al.*, 2019) did not show an effect, while the case-control study (Maeda *et al.*, 2019) showed an effect. The study finding an effect bases this claim on a small difference in Se and Hg blood levels. Hg blood levels in these studies were compared between pregnant and infertile groups, where a higher level of Hg was found in the infertile group.

TABLE 6.5 STUDIES INCLUDED FOR THE HEALTH OUTCOME "REPRODUCTION" FOR THE REVIEW "Se AND MeHg"

AUTHOR, YEAR	TIER, TYPE, N, MEAN AGE, PERCENT MALE	Hg and Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Maeda *et al.*, 2019	Tier 2, case-control study, n = 141, 35 years infertile, 34 years fertile, 0%	Mean blood Hg infertile: 5.3 µg/L fertile: 5 µg/L Mean blood Se Infertile: 189 µg/L fertile: 200 µg/L	Women from northeast Japan Comparison of two groups	The Se and Se/Hg ratio were lower in the infertile group than in the control group. Hg levels were higher in the infertile group than in the control group (adjusted for age and Se). The authors concluded that Hg and Se exposures appear to have adverse and protective effects on female fertility, respectively. However, the difference in Hg and Se blood levels between the groups were small, and the fertile group was slightly younger than the control group. *Effect*
Ai *et al.*, 2019	Tier 2, cross-sectional study, n = 84, 37 years, 0%	Mean Hg blood: 9 µg/L semen: 1 µg/L. Mean Se blood: 205 µg/L semen: 82 µg/L	Men from Taiwan Comparison of two groups	Dose-dependent correlation between blood Hg and normal sperm count. High predatory fish intake had lower percentage of normal morphology in sperm. No significant difference between high- and low-quality semen for Se concentrations. *No effect*

Notes: [1]The effects of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.5.1 Weight of evidence for "Reproduction"

In conclusion, when weighing the evidence according to the WCRF criteria, "limited evidence, no conclusion" is found for the effect of Se on Hg toxicity outcomes on reproduction. This conclusion was based on:

> The one study (Maeda *et al.*, 2019) claiming to have found an effect based its claims on very small differences in the levels of Hg concentrations, where the infertile group had somewhat higher Hg.

> The other study investigating the hypothesis found no clear effect for the outcome of sperm count (Ai *et al.*, 2019).

> Both studies investigated very different outcomes and therefore cannot be compared.

> Non-significant trends in these studies may encourage better or larger studies.

6.2.5.2 Animal studies on "Reproduction"

An animal study that was included from the literature search (Beyrouty *et al.*, 2006) produced evidence for an alleviation of MeHg toxicity on body weight gain during lactation in mice by preceding feeding with Se-enriched diet. Reduced embryotoxicity of MeHg through selenite by concomitant exposure was also shown in another animal study (Nobunaga *et al.*, 1979). There is some evidence from animal studies pointing towards an effect of Se on Hg toxicity on reproduction, but different outcomes (weight gain of offspring, reduced embryotoxicity) from those in the human studies (female fertility, sperm count) were investigated.

6.2.6 THYROID HORMONES

Gustin *et al.* (2021) investigated the effects of Se on MeHg toxicity for the outcome of thyroid hormones. A general summary of the study is given in **Table 6.6**. This cohort study included the effects on the thyroid hormones free tri-iodothyronine (fT3), total T3 and free thyroxine (fT4). An association was found with Hg status, though no or a very slight effect was found of Se.

TABLE 6.6 STUDIES INCLUDED FOR THE HEALTH OUTCOME "THYROID HORMONES" FOR THE REVIEW "Se AND MeHg"

AUTHOR, YEAR	TIER, TYPE, N, MEAN AGE, PERCENT MALE	Hg and Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Gustin *et al.*, 2021	Tier 1, cohort study, n = 542, 30 years, 0%	Median Hg Erythrocytes: 1.5 µg/L Median Se Plasma: 67 µg/L	Mothers from northern Sweden Regression analysis	Erythrocyte Hg was non-linearly associated with fT3, TT3 and fT3:fT4 ratio. No or very slight effect of Se. The authors concluded that Hg can interfere with thyroid hormones, but that Se does not affect this interference. *No effect*

Notes: fT3: free triiodothyronine; TT3: total triiodothyronine; fT4: free thyroxine
[1] The effects of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.6.1 Weight of evidence for "Thyroid hormones"

In conclusion, when weighing the evidence according to the WCRF criteria, "limited evidence, no conclusion" is found of the effect of Se on Hg toxicity outcomes on thyroid hormones. There was only one study investigating only thyroid hormones, which found no effect.

6.2.6.2 Animal studies on "Thyroid hormones"

There were no animal studies with the outcomes within the research field of thyroid hormones included from the literature search.

6.2.7 BIRTH OUTCOMES

Two studies (Wells *et al.*, 2016 and Kobayashi *et al.*, 2019) investigated the effects of Se on MeHg toxicity on birth outcomes. A general summary of the studies is given in **Table 6.7**. Wells et al, a cross-sectional study, found a protective effect of Se on Hg toxicity on developmental early-life outcomes, while Kobayashi *et al.*, a cohort study, did not.

In summary, there is evidence from two different studies, one cohort study with a very high participant number (ranked Tier 1), finding no effect, and one cross-sectional study with a much lower participant number (ranked Tier 2), finding an effect. These studies originate from two different population groups (Japan and the United States) (**Table 6.7**).

TABLE 6.7 STUDIES INCLUDED FOR THE HEALTH OUTCOME "BIRTH OUTCOMES" FOR THE REVIEW "Se AND MeHg"

AUTHOR, YEAR	TIER, TYPE N, MEAN AGE, PERCENT MALE	Hg AND Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Wells *et al.*, 2016	Tier 2, cross-sectional study, n = 271, 0 years	Geometric mean cord blood: 1 µg/L Mean Se cord blood: 70 µg/L	the United States (Baltimore) mother–child pairs Regression analysis	The negative association of Hg with birth weight and ponderal index was influenced by Se. *Effect*
Kobayashi *et al.*, 2019	Tier 1, cohort study, n = 15 444, 31 years, 52%	Mean/median Hg blood: 4 µg/L Mean Se Blood: 171 µg/L	Japanese children Regression analysis	No effect of Hg on birth weight and "small for gestational age" as outcomes. Weak correlation with head circumference and blood Hg. Se did not give any protective effect. *No effect*

[1] The effect of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

In addition to the two studies that found an effect of Hg on the birth outcomes and measured the potential effect of Se, one additional study (Chen *et al.*, 2014) was found in the literature search which included birth outcomes (Appendix 6, **Table A6.4**). This study did not measure the effect of Se on Hg toxicity.

6.2.7.1 Weight of evidence on "Birth outcomes"

In conclusion, when weighing the evidence according to WCRF criteria, "limited evidence, no conclusion" was found regarding the effect of Se on Hg toxicity outcomes on birth outcomes. This conclusion was based on:

> There is only one study providing evidence of an effect.

> Two independent cohort studies have not yet been conducted.

> There was heterogeneity in the results.

6.2.7.2 Animal studies for "Birth outcomes"

There were no animal studies with the outcomes within the research field of birth outcomes included from our literature search.

6.2.8 NEURODEVELOPMENT AND COGNITION

Five studies investigated the effects of Se on MeHg toxicity for the outcome of neurodevelopment and cognition. A general summary of the studies is given in **Table 6.8**. All five studies were cohort studies. One cohort study (Tratnik *et al.*, 2017) found an indirect positive effect, while the other four cohort studies (Steuerwald *et al.*, 2000; Choi *et al.*, 2008; Golding *et al.*, 2017 and Tatsuta *et al.*, 2017) found no protective effect of Se for the neurotoxicological effects of Hg.

In conclusion, there is evidence from four cohort studies, two ranked Tier 2 and two ranked Tier 1, three of which had moderately high participant numbers, originated from different population groups (Japan, the Faroe Islands and the United Kingdom of Great Britain and Northern Ireland) reporting that Se had no protective effect on the neurotoxicological effects of Hg early in life, if cord blood Hg levels were rather high. The only study finding evidence for a protective effect of Se on Hg neurotoxicity showed this only for a genetic subgroup and had a participant group with relatively low levels of Hg in cord blood.

In addition to the five studies that found an effect of Hg on the birth outcomes and measured the potential effect of Se, five additional studies were found in the literature search including birth outcomes (Boucher *et al.*, 2014b; Golding *et al.*, 2016a; Golding *et al.*, 2016b; Oken *et al.*, 2016 and Mao *et al.*, 2019) (Appendix 6 **Table A6.4**). These studies did not measure the effect of Se on Hg toxicity.

TABLE 6.8 **STUDIES INCLUDED FOR THE HEALTH OUTCOME "NEURODEVELOPMENT AND COGNITION" FOR THE REVIEW "Se AND MeHg"**

AUTHOR, YEAR	TIER, TYPE N, MEAN AGE, PERCENT MALE	Hg and Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF SE ON Hg TOXICITY*[1]
Tratnik *et al.*, 2017	Tier 1, cohort study, n = 361, mother–child pairs	Cord blood mean Hg Croatia: Hg 3.4 µg/L Slovenia: Hg 1.6 µg/L Cord serum mean Se 40 µg/L (both countries)	Children from Croatia and Slovenia Regression analysis	Hg-related decrease in cognitive score only in children carrying at least one Apoeε4 allele, and general decrease in fine motor scores. Positive association between Se and the language score, but not in the subgroup of children carrying the ε4 allele. Unclear if effect of Se on Hg toxicity or just separate effects. Weak effect of Se for a genetic subgroup. *Indirect effect*
Choi *et al.*, 2008	Tier 2, cohort study, n = 1 022, 7 years, 0%	Geometric mean Hg cord blood 23 µg/L Geometric mean Se cord blood 112 µg/L	Children from Faroe Islands Regression analysis	No evidence that Se was an important protective factor against MeHg neurotoxicity. Increased Se levels were not associated with decreased mercury-related neuropsychological dysfunctions. *No effect*
Golding *et al.*, 2017	Tier 2, cohort study, n = 2 062, 8 years	Median Hg blood 2 µg/L Median Se blood 108 µg/L	UK children Regression analysis, fish eaters and non-fish eaters also treated separately	Selenium did not influence positive effect of fish eating on intelligence despite correlation of fish eating with Hg. *No effect*
Steuerwald *et al.*, 2000	Tier 1, cohort study, n = 182, 17 days, 51%	Geometric mean Hg cord blood 20 µg/L cord serum 3 µg/L hair 4 µg/g Geometric mean Se cord serum 103 µg/L	Infants from Faroe Islands Regression analysis	The authors found a significant decrease in the neonatal NOS connected to methylmercury from seafood. They also concluded that that there was no evidence that Se offered protection against mercury-associated decrease in NOS. *No effect*
Tatsuta *et al.*, 2017	Tier 1, cohort study, n = 566, 1.5 years, 50%	Mean Hg cord blood 15–17 µg/L hair 3 µg/g Mean Se cord plasma 66–67 µg/L	Japanese coastal children Regression analysis	Prenatal Hg negatively affected psychomotor performance as measured in BSID-II. Good correlation between cord blood Hg and hair Hg; small but significant negative effect of Hg on the psychomotor part of the BSID-II test. *No effect*

Notes: NOS: neurologic optimality score; BSID-II: Bayley Scales of Infant Development second edition
[1] The effect of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.8.1 Weight of evidence for "Neurodevelopment and cognition"

In conclusion, when weighing the evidence according to the WCRF criteria, "limited evidence, no conclusion" was found regarding the effect of Se on Hg toxicity outcomes on neurodevelopment and cognition. This conclusion was based on:

> Only cohort studies have been carried out, therefore there is no evidence from different study types.
> Four different independent cohort studies found no effect on this group of outcomes.
> There is heterogeneity in the results of the studies.

6.2.8.2 Animal studies on "Neurodevelopment and cognition"

Studies in mice and rats show evidence for an alleviation of MeHg toxicity by Se on average auditory startle response time and somatosensory sensitivity, grip strength, clasping reflex, flexion and voluntary wheel running and neuronal degeneration by preceding feeding with Se-enriched diet (Beyrouty *et al.*, 2006; Heath *et al.*, 2010 and Sakamoto *et al.*, 2013), on cerebellar damage by concomitant MeHg and Se exposure by gavage (Tu *et al.*, 2021), on neurotoxicity by concomitant injection with selenite (Chang, 1983), and on the development of reflexes by subcutaneous injection of selenite (Satoh *et al.*, 1985). Feeding pregnant mice different concentrations of Se and MeHg also showed increasingly negative neurobehavioral outcomes in the offspring in groups exposed to lower Se and higher MeHg (Watanabe *et al.*, 1999). Another study, where selenite was injected subcutaneously, found that inorganic selenium was ineffective in preventing most of the MeHg-induced brain biochemical alterations (Glaser *et al.*, 2010).

6.2.9 VISION FUNCTION

Four studies investigated the effects of Se on MeHg toxicity for the outcome of vision function. A general summary of the studies is given in **Table 6.9**. Two cross-sectional studies found positive effects of Se, one on colour vision in adult people (Fillion *et al.*, 2013) and one on cataract formation in older people (Lemire *et al.*, 2010). One cross-sectional study and one cohort study found no effects of Se on Hg toxicity, one investigated acuity in adult people (Fillion *et al.*, 2011) and one visual-evoked potential in children (Saint-Amour *et al.*, 2006).

In conclusion, there is evidence from two cross-sectional studies (rated Tier 1) that specific visual impairments caused by Hg exposure may be alleviated by Se. Since both studies investigated different outcomes, and two further studies investigating further different outcomes did not find an effect, the amount of evidence is scarce for the outcome of visual function.

TABLE 6.9 **STUDIES INCLUDED FOR THE HEALTH OUTCOME "VISION FUNCTION" FOR THE REVIEW "Se AND MeHg"**

AUTHOR, YEAR	TIER, TYPE N, MEAN AGE, PERCENT MALE	Hg AND Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF SE ON HG TOXICITY*[1]
Fillion *et al.*, 2013	Tier 1, cross-sectional study, n = 228, 35 years, 50%	Mean/median hair Hg 14/11.5 µg/g Mean/median plasma Se 182/145 µg/L Designed for Se interference analysis	Brazil Tapajos River basin population. Regression analysis	Increased Se associated with less colour confusion and more near visual contrast; might counteract colour vision loss associated with hair Hg. *Effect*
Lemire *et al.*, 2010	Tier 1, cross-sectional study, n = 211, 50/73 years 55%	Median Hg blood: 44 µg/L plasma: 6.4 µg/L Median Se blood: 222 µg/L plasma 133 µg/L	Brazil Tapajos River basin population. Regression analysis	Weak effect of Se on cataract formation, which may be caused by the effect of Se as an antioxidant. *Effect*
Fillion *et al.*, 2011	Tier 1, cross-sectional study, n = 243, 36 years 55%	Mean/median Hg hair: 14/11.5 µg/g blood: 52/42 µg/L plasma: 8/7 µg/L Mean/median Se blood: 313/251 µg/L plasma: 179/141 µg/L	Brazil Tapajos River basin population. Regression analysis	Hg is associated with worse acuity in older people, but Se did not change that. Blood Se was significantly lower in the group excluded for age-related cataracts. *No effect*
Saint-Amour *et al.*, 2006	Tier 1, cohort study, n = 110, 5 years, 38.5%	Mean Hg blood: 6 µg/L; cord blood: 17 µg/L Mean Se blood: 331 µg/L cord blood: 319 µg/L	Arctic Nunavik Regression analysis	Visual-evoked potentials. Designated N75 and P100, N150 were negatively impacted by Hg, while no significant interaction with Se was found. *No effect*

Notes: N75: negative deflection at ≈ 75 ms; P100: positive deflection at ≈ 100 ms; N150: negative deflection at ≈ 150 ms.
[1] The effects of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.9.1 Weight of evidence for "Vision function"

In conclusion, when weighing the evidence according to the WCRF criteria, "limited evidence, no conclusion" is found of the effect of Se on Hg toxicity outcomes on vision outcomes. This conclusion was based on:

> Only one cohort study was undertaken, finding no effect. All other studies were cross-sectional studies. Thus, there are no results showing effects from two independent cohort studies.

> The direction of effect is consistent, in that the studies concluding with "effect" and "no effect" have investigated different visual outcomes.

6.2.9.2 Animal studies on "Vision function"

There were no animal studies with the outcomes within the research field of vision function included from the literature search.

6.2.10 MOTOR FUNCTION

One study (Lemire *et al.*, 2011) investigated the effects of Se on MeHg toxicity for the outcome of motor function. This was a cross-sectional study investigating the effect of Se on Hg-induced impairments of motor function. A general summary of the study is given in **Table 6.10**. The study was rated Tier 1 in the risk-of-bias assessment. The study showed that high plasma Se was correlated positively with motor function outcomes, while Hg was a counteracting confounder.

TABLE 6.10 **STUDY INCLUDED FOR THE HEALTH OUTCOME "MOTOR FUNCTION" FOR THE REVIEW "Se AND MeHg"**

AUTHOR, YEAR	TIER, TYPE N, MEAN AGE, PERCENT MALE	Hg and Se	STUDIED GROUP, OTHER STUDY CHARACTERISTICS AND STATISTICAL APPROACH	CONCLUSIONS *EFFECT OF Se ON Hg TOXICITY*[1]
Lemire *et al.*, 2011	Tier 1, cross-sectional study, n = 319, 42 years 50%	Mean/median Hg blood: 51/44 µg/L plasma median: 6 µg/L Mean/median Se blood: 288/222 µg/L plasma median: 133 µg/L	Brazil Tapajos River basin population Regression analysis	Positive correlation between high plasma Se and motor function outcomes, more when including Hg as a counteracting confounder. *Effect*

[1] The effects of Se on MeHg toxicity were assessed and departed into the categories of "effect", "indirect effect", "unclear effect" and "no effect".

6.2.10.1 Weight of evidence for "Motor function"

In conclusion, when weighing the evidence according to the WCRF criteria, "limited evidence, no conclusion" is found regarding the effect of Se on Hg toxicity outcomes of motor function. There was only one study investigating motor function, which found an effect.

6.2.10.2 Animal studies on "Motor function"

MeHg was also shown in mice to cause a significant decrease in motor activity, which was reduced by selenomethionine co-exposure, both if administered by diet and via injection (Folven *et al.*, 2009).

6.3 FINAL WEIGHT OF EVIDENCE FOR THE REVIEW "THE ROLE OF Se WITH REGARD TO THE HEALTH EFFECTS OF MeHg"

A summarization of the final weight of evidence for the different outcomes included in "The role of Se with regard to the health effects of MeHg" is given in **Table 6.11**. The direction of the effect is given according to whether most studies showed "effect" or "no effect" regarding the effect of Se on MeHg toxicity. If the studies showed contradictory findings, this was depicted as "unclear".

As shown in **Table 6.11**, except for the health outcome "cardiovascular outcomes", which was graded "limited, suggestive", the remaining health outcomes were graded "limited, no conclusion".

TABLE 6.11 SUMMARY OF FINAL WEIGHT OF EVIDENCE FOR THE "ROLE OF Se WITH REGARD TO THE HEALTH EFFECTS OF MeHg"

HEALTH OUTCOME	DIRECTION OF AN EFFECT OF Se ON MeHg TOXICITY	CONCLUSION, WEIGHT OF EVIDENCE
Cardiovascular outcomes	Effect (protective)	Limited, suggestive
Oxidative stress	Effect (protective)	Limited, no conclusion
Immune system	No effect	Limited, no conclusion
Reproduction	Unclear	Limited, no conclusion
Thyroid hormones	Unclear	Limited, no conclusion
Birth outcomes	No effect	Limited, no conclusion
Neurodevelopment and cognition	No effect	Limited, no conclusion
Vision function	Effect (protective)	Limited, no conclusion
Motor function	Effect (protective)	Limited, no conclusion

Note: Final weight of evidence is based on the grading from the World Cancer Research Fund grading system (WCRF, 2018 and WCRF, 2018a).

It should be noted that even though, for most of the health outcomes, the evidence was graded "Limited, no conclusion", this was mostly related to the low number of studies published, the variability of the methodology used in the studies, the investigation of different population groups, and the fact that most of the studies were not methodologically designed to measure "The role of Se with regards to the health effects of MeHg". Thus, although the evidence on this topic is rather low, the weight of evidence might change if high quality studies designed to measure the interaction between Se and Hg toxicity are conducted.

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CHAPTER 7

RESULTS AND SUMMARIZATION OF "OCCURRENCE DATA FOR MeHg AND, DIOXINS AND dl-PCBs"

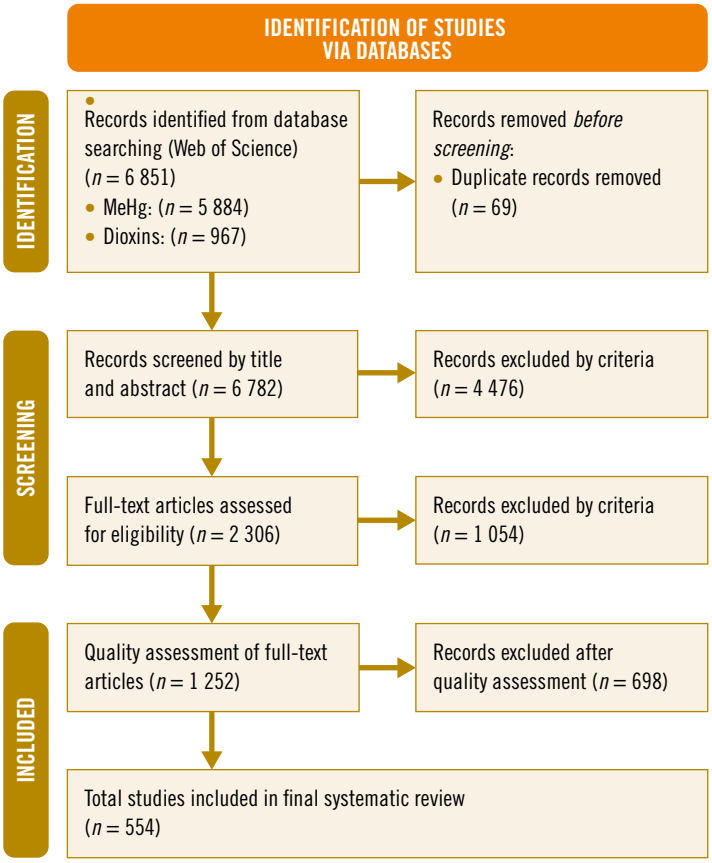
7.1 LITERATURE SEARCH

Literature searches for the systematic review on the "Occurrence data for MeHg and dioxins in fisheries and aquaculture products" were performed in Web of Science. A flow diagram of the results from the literature searches is given in **Figure 7.1**. The literature searches in Web of Science resulted in 6 851 records. Of these, 69 duplicate records were identified and removed, and 6 782 records were screened by title and abstract using the online screening tool Rayyan. A further 4 476 records were excluded based on inclusion and exclusion criteria during this title and abstract screening. The remaining 2 306 records were screened based on the full-text articles. Of these, 1 054 records were excluded based on exclusion criteria: 20 articles because the language of the article was not English and 1 034 articles because of sampling before 2011 or sampling year missing. The remaining 1 252 full-text articles were subjected to quality assessment.

7.2 QUALITY ASSESSMENT OF THE LITERATURE INCLUDED FROM THE LITERATURE SEARCH

Quality assessment of full-text articles was performed using the quality-assessment template described in Section 2.5.4 with questions assessing the quality of the article with respect to food description, component identification, sampling plan, number of analytical samples, sample handling and analytical method and performance.

FIGURE 7.1. **FLOW DIAGRAM FOR THE REVIEW "OCCURRENCE DATA OR MeHg, AND DIOXINS AND dl-PCBs IN FISHERIES AND AQUACULTURE PRODUCTS"**



Source: Prepared by authors based on Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L. *et al.* 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372: n71. https://doi.org/10.1136/bmj.n71

Of the 1 252 articles eligible for quality assessment, 698 articles were excluded and 554 articles were included. Of the excluded articles, 383 articles were excluded due to inadequate food description, 46 due to inadequate component identification, 62 due to missing sample number, 103 due to inadequate analytical method or performance, and 104 articles were excluded for other reasons.

Details of the quality assessment for each article are given in Appendix 7, **Table A7.3**, which also provides the full reference for each article.

7.3 OVERVIEW OF CONCENTRATION DATA FOR TOTAL Hg, MeHg, DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

The data obtained from the literature review and the data from the EFSA database were treated separately and summarized in separate tables. This was done for several reasons. Most importantly, there was no way to control which data were

published both in articles and to EFSA, thus some of the data could be the same. Moreover, different levels of information were included in the two datasets. That is, in the literature data, the species or genus name was always included, while the EFSA data contained more generic names of species or species groups. There was also a difference with regard to sample origin. The EFSA database is primarily a European database with data from European laboratories analysing samples of European seafood or seafood imported from third-party countries, while the data from the literature search could represent seafood sampled and analysed anywhere in the world.

In the literature, except for a few articles, data were mostly presented as mean concentrations, where median values were given (Appendix 7, **Table A7.4**). In the following tables, results from the literature are presented as means of mean or median values. For consistency, the EFSA data are also presented as mean values in the tables.

7.3.1 OVERVIEW OF CONCENTRATION DATA FROM THE LITERATURE SEARCH

From the 554 articles included, concentration data for total Hg, MeHg or dioxins and dl-PCBs were extracted, along with necessary metadata, and compiled in an excel sheet as described in Section 1.1.4. Most of the articles reported data on total Hg, adding up to a total sample number of 68 998, while only 66 of the articles had results for MeHg (total n = 7 720). Forty-six articles reported results for either dioxins, dl-PCBs and/or the sum of dioxins and dl-PCBs, and of these 2 760 samples were analysed for either dioxins, dl-PCBs or both and/or their total sum.

An overview of concentration data from the literature search for total Hg and MeHg, in finfish and shellfish, from different regions around the world, is shown in **Table 7.1**, **Table 7.2**, **Table 7.3**, **Table 7.4**, **Table 7.5** and **Table 7.6** (finfish), and in **Table 7.12**, **Table 7.13**, **Table 7.14**, **Table 7.15** and **Table 7.16** (shellfish). An overview of the concentration data from the literature search for dioxins and dl-PCBs is presented in **Table 7.22**, **Table 7.23**, **Table 7.24** and **Table 7.25** (finfish), and in **Table 7.31**, **Table 7.32** and **Table 7.33** (shellfish).

7.3.2 OVERVIEW OF CONCENTRATION DATA FROM THE DATABASE OF THE EUROPEAN FOOD SAFETY AUTHORITY

The final dataset on total Hg and MeHg compiled from the EFSA data contained 24 628 samples of finfish and shellfish. Of these, 23 411 samples had results for total Hg, whereas only 1 217 samples had results for MeHg.

The final dataset on dioxins and dl-PCBs compiled from the EFSA data contained 9 797 samples of finfish and shellfish. Of these, 9 390 samples had results for both dioxins and dl-PCBs (all 29 congeners), 45 samples had results only for dioxins (17 congeners) and 362 samples had results only for dl-PCBs (12 congeners).

An overview of concentration data for total Hg and MeHg from the EFSA dataset, in finfish and shellfish, from different regions around the world, is given in **Table 7.7**, **Table 7.8**, **Table 7.9**, **Table 7.10** and **Table 7.11** (finfish), and in **Table 7.17**, **Table 7.18**, **Table 7.19**, **Table 7.20** and **Table 7.21** (shellfish). An overview of the concentration data from the EFSA dataset for dioxins and dl-PCBs is presented in **Table 7.26**, **Table 7.27**, **Table 7.28**, **Table 7.29** and **Table 7.30** (finfish) and in **Table 7.34**, **Table 7.35**, **Table 7.36**, **Table 7.37** and **Table 7.38** (shellfish).

7.4 MERCURY IN FINFISH AND SHELLFISH FROM DIFFERENT REGIONS AROUND THE WORLD

7.4.1 MERCURY IN FINFISH FROM THE LITERATURE REVIEW

In the literature, THg results were found for 57 189 analysed samples of finfish, while the number of MeHg results was much lower, 6 957. Of the analysed finfish, 1 340 and 122 samples for THg and MeHg, respectively, were from farmed fish, while the rest were from wild stocks (55 621 and 6 685) or unknown (for instance, sampled at market, with no information about geographic origin). More than half of the analysed finfish originated from marine waters (n = 33 035 and 4 819, for THg and MeHg, respectively), while 24 154 and 2 138 finfish samples analysed for THg and MeHg, respectively, were from inland waters.

7.4.1.1 Farmed finfish from inland waters

Farmed finfish from inland waters had generally low concentrations of Hg (**Table 7.1**). Only one species, Argyrosomus regius, meagre, from Europe, had a mean concentration higher than 0.2 mg/kg wet weight. The rest of the species in this category had mean concentrations of up to 0.053 mg/kg.

7.4.1.2 Farmed finfish from marine waters

Farmed fish species from the Mediterranean had higher Hg levels than farmed marine fish from other areas (**Table 7.2**). The farmed fish from the different areas did not include the same species. Farmed *Thunnus thynnus*, Atlantic bluefin tuna from the Mediterranean, had a mean concentration of 0.6 mg/kg. In area 61, only one species had a mean concentration of THg and MeHg of more than 0.2 mg/kg (n = 5). Samples with sample numbers less than 10 were usually excluded from the table, but in this case, they were kept because both THg and MeHg were analysed in a number of species with n < 10.

TABLE 7.1 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS (mg/kg WET WEIGHT) IN MUSCLE TISSUE OF SPECIES OF FARMED FINFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS)

FAO AREA/SPECIES LATIN NAME	N	THg	N	MeHg
01 AFRICA, INLAND WATERS				
Chanos chanos	12	0.012		
03 SOUTH AMERICA, INLAND WATERS				
Piaractus brachypomus	111	0.053		
04 ASIA, INLAND WATERS				
Misgurnus anguillicaudatus	15	0.050		
Monopterus albus	15	0.049		
Anguilla japonica	60	0.037		
Carassius auratus	13	0.031		
Aristichthys nobilis	35	0.027	23	0.002
Carassius carassius	47	0.023		
Ctenopharyngodon idella	197	0.022		
Pampus argenteus	87	0.015		
Cyprinus carpio	158	0.014		
Oreochromis mossambicus	73	0.014	1	0.002
Tinca tinca	23	0.010		
Pseudosciaena crocea	72	0.009		
Oncorhynchus mykiss	40	0.005		
05 EUROPE, INLAND WATERS				
Argyrosomus regius	16	0.251		
Tinca tinca	20	0.048		
Sparus aurata	24	0.044		
Dicentrarchus labrax	16	0.044		
Oncorhynchus mykiss	27	0.009		

Note: N is the number of analytical samples, including both individual and composite samples. Cases where N < 10 are excluded.

TABLE 7.2 TABLE 7.2 MEAN TOTAL Hg (THg) AND METHYLMERCURY (MeHg) LEVELS IN MUSCLE TISSUE OF SPECIES OF FARMED FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

FAO AREA/SPECIES LATIN NAME	N	THg	N	MeHg
27 ATLANTIC, NORTHEAST				
Salmo salar	14	0.019		
37 MEDITERRANEAN AND BLACK SEA				
Thunnus thynnus	40	0.600		
Dicentrarchus labrax	39	0.322		
Salmo trutta	30	0.238		
Sparus aurata	37	0.218		
61 PACIFIC, NORTHWEST				
Epinephelus octofasciatus	5	0.235	5	0.209
Epinephelus coioides	5	0.162	5	0.143
Hypoplectrus indigo	7	0.147	7	0.090
Genyonemus lineatus	5	0.134	5	0.087
Ephippus orbis	6	0.123	6	0.060
Lateolabrax japonicus	5	0.115	5	0.105
Pagrus major	10	0.086	10	0.076
Acanthopagrus latus	5	0.072	5	0.055
Epinephelus awoara	2	0.065	2	0.042
Acanthopagrus schlegelii	5	0.048	5	0.033
Larimichthys crocea	5	0.048	5	0.030
Anguilla japonica	5	0.047	5	0.031
Paralichthys olivaceus	5	0.041	5	0.016
Cynoscion nebulosus	6	0.034	6	0.022
Larimichthys polyactis	8	0.023	8	0.009
Sardinella jussieu	4	0.020	4	0.006
Siganus fuscescens	5	0.013	5	0.004

Note: N is the number of analytical samples, including both individual and composite samples.

7.4.1.3 Wild-caught finfish from inland waters

THg results for wild-caught finfish from inland waters are given per genus and inland region (FAO area) in **Table 7.3** and for MeHg in **Table 7.4**. The highest mean value, 2.89 mg/kg, was found in *Synodontis* from Africa. However, the mean value was particularly high due to an extreme value in *Synodontis* from one study from the Flag Boshielo Dam in South Africa (Sara *et al.*, 2017). Three genera from Africa had mean concentrations above 0.5 mg/kg. In South American inland waters, 16 genera had THg above 0.5 mg/kg, while in Europe and Asia, no genus had mean concentrations of THg above 0.5 mg/kg. In North America, only one genus, *Petromyzon*, had THg higher than 0.5 mg/kg. With regard to MeHg, two genera from North America and none in South America, Asia or Europe had mean concentrations above 0.5 mg/kg (**Table 7.4**). Higher MeHg concentrations than THg in North America could be due to a selective analysis of MeHg in fish species or areas expected to have higher Hg levels.

TABLE 7.3 MEAN TOTAL MERCURY (THg) LEVELS IN DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

FAO AREA/GENUS	N	THg
01 AFRICA INLAND WATERS		
Synodontis	75 (12[1])	2.89 (0.160[1])
Barbus	13	0.755
Hydrocynus	10	0.510
Schilbe	29	0.240
Marcusenius	26	0.204
Esox	10	0.175
Chrysichthys	109	0.165
Sander	12	0.151
Clarias	367	0.138
Bagrus	21	0.130
Lepomis	35	0.103
Ictalurus	10	0.092
Micropterus	26	0.088
Hemichromis	51	0.085
Labeobarbus	11	0.083
Distichondus	21	0.080
Sarotherodon	20	0.072
Scardinius	22	0.070
Citharinus	21	0.060
Labeo	22	0.058
Mugil	203	0.051
Auchenoglanis	21	0.040
Lates	205	0.038
Oreochromis	330	0.029
Cyprinus	11	0.024
04 ASIA INLAND WATERS		
Barbonymus	16	0.430
Chanodichthys	17	0.410
Hemibagrus	20	0.410
Puntioplites	17	0.310
Gerres	14	0.300
Cyclocheilichthys	111	0.275
Lota	29	0.209
Esox	65	0.206
Channa	23	0.194
Toxotes	23	0.190
Silurus	76	0.180
Leiognathus	24	0.170
Brachymystax	35	0.147
Gymnocypris	58	0.126
Pelteobagrus	96	0.123

FAO AREA/GENUS	N	THg
Parasilurus	13	0.120
Erythroculter	112	0.117
Leuciscus	79	0.114
Sperata	10	0.110
Hemibarbus	31	0.109
Carassius	259	0.106
Thymallus	33	0.103
Cyprinus	123	0.079
Liza	35	0.074
Puntius	35	0.073
Mystus	25	0.073
Glyptothorax	11	0.070
Pangasius	67	0.069
Coptodon	40	0.066
Lethrinus	61	0.063
Pseudobagrus	44	0.062
Hypophthalmichthys	230	0.060
Spinibarbus	20	0.056
Aristichthys	77	0.053
Lutjanus	21	0.051
Coreius	35	0.050
Hemiculter	28	0.046
Epinephelus	26	0.046
Squaliobarbus	20	0.046
Leiocassis	14	0.045
Lates	30	0.040
Rhinogobio	22	0.035
Chondrostoma	46	0.030
Oncorhynchus	40	0.026
Ctenopharyngodon	70	0.019
Parabramis	12	0.019
Culterichthys	18	0.011
Oreochromis	15	0.010
Siganus	21	0.009
Rhynchocypris	30	0.008
Hypomesus	13	0.008
05 EUROPE INLAND WATERS		
Perca	1922	0.333
Aspius	24	0.312
Silurus	184	0.276
Esox	143	0.241
Sander	151	0.222

TABLE 7.3 MEAN TOTAL MERCURY (THg) LEVELS IN DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Osmerus	99	0.220
Anguilla	314	0.178
Scardinius	60	0.163
Cyprinus	197	0.158
Carassius	92	0.155
Abramis	457	0.135
Stizostedion	20	0.134
Alburnus	94	0.129
Hypophthalmichthys	17	0.129
Squalius	276	0.118
Rutilus	305	0.110
Leucos	80	0.099
Leuciscus	150	0.096
Alosa	21	0.090
Salvelinus	136	0.089
Salmo	44	0.073
Coregonus	119	0.070
Eleginus	10	0.063
Chondrostoma	89	0.044
Lota	10	0.035
Oncorhynchus	15	0.021
02 NORTH AMERICA INLAND WATERS		
Petromyzon (w+m)	116	1.39
Sander (w+m)	908	0.425
Esox (w+m)	983	0.406
Rhinichthys	223	0.400
Hiodon	205	0.314
Micropterus	652	0.304
Lota	92	0.293
Pomoxis	100	0.229
Salvelinus (w+m)	1516	0.214
Acantharchus (w)	18	0.213
Moxostoma	123	0.200
Ictalurus	295	0.192
Catostomus (w+m)	154	0.172
Cyprinus	56	0.168
Ameiurus (w+m)	80	0.165
Prosopium	30	0.160
Aphredoderous (w)	40	0.156
Notropis	40	0.150
Porogonias	10	0.150
Gasterosteus	360	0.147
Gambusia (w)	34	0.144
Morone (w+m)	84	0.136
Oncorhynchus (w+m)	398	0.122
Chirostoma	16	0.113
Lepomis (w+m)	312	0.110
Perca (w+m)	269	0.105
Coregonus (w+m)	548	0.105
Eupomotis	10	0.076
Alosa	31	0.072
Neogobius (w+m)	93	0.067
Semotilus	88	0.061
Osmerus (w+m)	80	0.058
Notomigonus	50	0.050
Oreochromis	99	0.050
Cottus	10	0.048
03 SOUTH AMERICA INLAND WATERS		
Pseudopimelodus	25	1.40
Hydrolycus/Raphiodon	21	1.20
Calophysus	43	0.949
Rhaphiodon	181	0.868
Acestrorhynchus	73	0.848
Pellona	173	0.790
Salminus	53	0.783
Pygocentrus	47	0.739
Cichla	464	0.679
Ageneiosus	120	0.670
Phractocephalus	42	0.630
Sternopygus	25	0.623
Hoplias	253	0.583
Pinirampus	28	0.576
Plagioscion	119	0.568
Pseudoplatystoma	87	0.530
Hypophthalmus	163	0.486
Sorubim/Hemisorubim	10	0.480
Odontesthes	11	0.465
Anodus	58	0.430
Serrasalmus	215	0.415
Ctenolucius	28	0.385
Rhamdia	99	0.383
Potamorhina	225	0.331
Caquetaia	160	0.330
Trachelyopterus	25	0.320

TABLE 7.3 MEAN TOTAL MERCURY (THg) LEVELS IN DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Triportheus	92	0.275
Centropomus	14	0.265
Potamotrygon	14	0.260
Hoplerythrinus	36	0.255
Tocantinsia	17	0.240
Boulengerella	36	0.230
Astronotus	14	0.216
Pimelodus	106	0.210
Schizodon	81	0.174
Hemiodus	68	0.172
Psectrogaster	90	0.156
Megalonema/Pimelodus	21	0.150
Semaprochilodus	32	0.141
Spatuloricaria	16	0.120
Arius	15	0.120
Hassar	15	0.120
Andinoacara	41	0.117
Curimata	38	0.109
Leporinus	95	0.109
Mylossoma	261	0.106
Pimelodella	21	0.100
Astyanax	172	0.097
Pachyurus	37	0.092
Prochilodus	508	0.092
Mugil	20	0.081
Bivibranchia	13	0.080
Brycon	73	0.074
Geophagus	63	0.065
Hypostomus	115	0.064
Hemiancistrus	14	0.060
Oligosarcus	30	0.059
Cyphocharax	42	0.056
Baryancistrus	10	0.030
Pterygoplichthys	13	0.029
Myloplus	34	0.023
Tometes	15	0.010
Hypomasticus	10	0.010

Notes: N is the number of analytical samples, including both individual and composite samples. All analysed edible tissues are included. When whole fish (w) or both whole fish and muscle (w+m) were analysed, this is marked after the genus name. When nothing is specified, muscle tissue was analysed. Cases where N < 10 are excluded.
[1] Excluding fish from one study (N = 63, mean THg 11.1 mg/kg).

TABLE 7.4 MEAN METHYLMERCURY (MeHg) LEVELS IN GENUS OF WILD-CAUGHT FINFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

FAO AREA/GENUS	N	MeHg
02 SOUTH AMERICA INLAND WATERS		
Rhinichthys	223	0.230
Perca	44	0.229
Acipenser	35	0.180
Aphredoderous	40	0.150
Esox	49	0.131
Neogobius	20	0.107
Catostomus	35	0.095
Semotilus	19	0.074
Cyphocharax	12	0.050
Salvelinus	20	0.038
Lepomis	50	0.032
03 NORTH AMERICA INLAND WATERS		
Pseudopimelodus	13	1.06
Ageneiosus	50	0.789
Trachelyopterus	17	0.423
Sternopygus	15	0.409
Ctenolucius	20	0.347
Hoplias	58	0.272
Caquetaia	57	0.268
Rhamdia	46	0.261
Astyanax	53	0.175
Leporinus	34	0.174
Andinoacara	25	0.117
Pimelodus	16	0.093
Prochilodus	106	0.078
Hypostomus	55	0.064

FAO AREA/GENUS	N	MeHg
04 ASIA INLAND WATERS		
Gymnocypris	58	0.109
Carassius	48	0.049
Erythroculter	49	0.033
Coreius	12	0.026
Cyprinus	27	0.023
Aristichthys	48	0.023
Hypophthalmichthys	120	0.017
Squaliobarbus	20	0.017
Ctenopharyngodon	23	0.005
05 EUROPE INLAND WATERS		
Sander	13	0.399
Esox	17	0.348
Aspius	24	0.309
Perca	17	0.243
Abramis	39	0.125
Rutilus	14	0.092
Leuciscus	143	0.088
Cyprinus	12	0.083

Notes: N is the number of analytical samples, including both individual and composite samples. All analysed edible tissues are included. When whole fish (w) or both whole fish and muscle (w+m) were analysed, this is marked after the genus name. When nothing is specified, muscle tissue was analysed. Cases where N < 10 are excluded.

7.4.1.4 Wild-caught finfish from marine waters

Finfish sampled from wild stocks (or from unknown source) in marine waters made up the largest volume of results published in the literature for both THg and MeHg.

Table 7.5 and **Table 7.6** provide results per FAO area and genus.

Almost all FAO areas included several genera with mean concentrations higher than 0.5 mg/kg, exceptions being 18 Arctic Sea; 58 Indian Ocean, Antarctic and Southern; 88 Pacific, Antarctic; 61 Pacific, Northwest; and 67 Pacific, Northeast. The highest mean THg concentration was 4.15 mg/kg, measured in *Makaira nigricans* (blue marlin), from Mexico, with only 16 samples analysed. *Makaira* from the Caribbean (n = 62) had a lower mean value of 0.91 mg/kg. Several areas included a number of genera with mean THg concentrations higher than 1 mg/kg. The genera included a number of sharks (*Carcharinus*, *Rhizopronodon*, *Galeus*, *Triakis*, *Alopias*, *Squalus*, *Scylorhinus*, *Deania*), the infamous predator barracuda (*Sphyraena*) as well as the genera *Lophius* (anglers or monkfishes), *Helicolenus* (blackbelly rosefish), *Micropterus* (bass) and *Johnius* (croaker). It is also worth noticing that swordfish (only one species, *Xiphias gladius*) had relatively high mean concentrations in a number of different FAO areas, and the same applies to tuna species (*Thunnus* spp.). However, tunas generally had lower mean concentrations than swordfish in areas where both were analysed. As mentioned earlier, fewer samples and genera by far were analysed for MeHg than for THg (**Table 7.6**). Only two genera from area 27, *Anguilla* (eel) and *Brosme* (tusk or cusk), and one genus from area 31, *Epinephelus* (groupers), had mean MeHg concentrations above 0.5 mg/kg. These species had higher mean levels of MeHg than of THg, but a lower number of samples were analysed, and these may have been sampled specifically in areas known for high Hg levels.

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

FAO AREA/GENUS	N	THg
04 ASIA INLAND WATERS (CASPIAN SEA)		
Clupeonella (w)	1050	0.014
18 ARCTIC SEA		
Gadus	10	0.140
Myoxocephalus	56	0.095
Stenodus	50	0.081
Coregonus	125	0.056
Microgadus	14	0.032
Boreogadus	40	0.030
Platichthys	28	0.026
Oncorhynchus	22	0.024
Ammodytes	13	0.020
Mallotus	11	0.010
Clupea	29	0.005
21 ATLANTIC, NORTHWEST		
Rhizoprionodon	10	1.64
Thunnus	519	0.650
Pomatomus	80	0.323
Caulolatilus	64	0.300
Squalus	159	0.284
Cottunculus	10	0.270
Catostomus	10	0.143
Gadus	30	0.134
Coregonus	27	0.122
Myoxocephalus	35	0.121
Lopholatilus	484	0.092
Gasterosteus (w)	14	0.078
Osmerus (w+m)	25	0.074
Salmo	12	0.073
Pleuronectoide	20	0.068
Salvelinus	170	0.066
Reinhardtius	10	0.048
Menidia (w)	193	0.040
27 ATLANTIC, NORTHEAST		
Deania	21	1.80
Mora	30	0.900
Lamna	33	0.840
Molva	150	0.796
Isurus	48	0.740
Etmopterus	10	0.700
Brosme	433	0.596
Prionace	40	0.520

FAO AREA/GENUS	N	THg
Xiphias	25	0.475
Anguilla	111	0.424
Thunnus	47	0.338
Mullus	17	0.338
Galeorhinus	124	0.315
Esox	21	0.296
Leucoraja	44	0.280
Merluccius	124	0.229
Platichthys	215	0.221
Perca	205	0.166
Reinhardtius	475	0.142
Pelecus	60	0.127
Trachurus	79	0.121
Solea	41	0.118
Anarhichas	93	0.115
Stizostedion	14	0.111
Scyliorhinus	11	0.108
Diplodus	10	0.105
Limanda	379	0.089
Abramis	26	0.085
Gadus	535	0.083
Capros	11	0.080
Rutilus	11	0.077
Scophthalmus	22	0.071
Zoarces	18	0.060
Salmo	12	0.056
Katsuwonus	16	0.050
Micromesistius	85	0.048
Pleuronectes	51	0.047
Pollachius	22	0.046
Clupea	167	0.032
Myoxocephalus	58	0.028
Neogobius	90	0.025
Sprattus (w)	45	0.015
31 ATLANTIC, WESTERN CENTRAL		
Carcharhinus	46	1.96
Micropterus	44	1.35
Rhizoprionodon	188	1.22
Sphyraena	27	1.06
Makaira	62	0.910
Anisotremus	15	0.769
Bagre	24	0.730

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Seriola	43	0.575
Lepomis	33	0.542
Sciaenops	30	0.508
Genidens	18	0.450
Epinephelus	245	0.399
Scomberomorus	18	0.394
Caulolatilus	62	0.380
Rhinoptera	25	0.370
Kajikia	45	0.350
Haemulon	23	0.316
Acathocybium	23	0.300
Centropomus	92	0.296
Cynoscion	12	0.274
Caranx	32	0.251
Squatina	94	0.240
Mycteroperca	326	0.239
Ariopsis	18	0.239
Istiophorus	38	0.220
Coryphaena	91	0.200
Lutjanus	452	0.164
Ocyurus	12	0.162
Elops	58	0.161
Mobula	15	0.158
Archosargus	17	0.158
Thunnus	11	0.150
Lachnolaimus	12	0.132
Pterois	366	0.103
Mugil	91	0.076
Brevoortia	10	0.063
Poecilia	11	0.055
Trinectes	12	0.054
Eugerres	53	0.054
Fundulus	19	0.053
Eucinostomus	23	0.036
Acanthurus	20	0.036
Anchoa	13	0.032
Cyprinodon	11	0.030
Cathorops	35	0.018
34 ATLANTIC, EASTERN CENTRAL		
Thunnus	36	0.777
Xiphias	17	0.672
Pseudotolithus	14	0.410
Sphyraena	13	0.194
Trichiurus	13	0.178
Brachydeuterus	51	0.150
Pseudupeneus	10	0.080
Lutjanus	16	0.057
Chloroscombrus	10	0.026
Trachurus	10	0.025
Sardinella	51	0.024
Solea	45	0.016
37 MEDITERRANEAN AND BLACK SEA		
Galeus	15	2.06
Scyliorhinus	27	1.84
Helicolenus	14	1.15
Lophius	18	1.14
Lepidorhombus	13	0.860
Euthynnus	89	0.740
Xiphias	125	0.694
Diplodus	153	0.688
Phycis	24	0.606
Thunnus	552	0.594
Trachinus	26	0.524
Pagellus	215	0.482
Zosterisessor	209	0.434
Scorpaena	43	0.420
Microchirus	29	0.397
Sarda	48	0.369
Chelidonichthys	35	0.362
Squalus	68	0.330
Raja	94	0.315
Mullus	1 270	0.294
Sparus	258	0.216
Micromesistius	42	0.207
Epinephelus	10	0.185
Arnoglossus	30	0.184
Scomber	292	0.170
Trachurus	375	0.160
Boops	40	0.141
Scophthalmus	28	0.137
Katsuwonus	26	0.137
Upeneus	23	0.130
Dicentrarchus	26	0.126
Merluccius	135	0.112

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Sardina	718	0.108
Spicara	13	0.104
Trisopterus	12	0.101
Etrumeus	30	0.100
Gobius	24	0.096
Lithognathus	89	0.087
Nemipterus	26	0.080
Saurida	41	0.070
Solea	96	0.067
Sprattus	120	0.059
Merlangius	362	0.059
Engraulis	1 204	0.057
Belone	50	0.050
Mugil	106	0.042
Sardinella	41	0.040
Platichthys	10	0.039
Psetta	67	0.033
Liza	29	0.031
Sepia	23	0.030
Marsupenaeus	39	0.027
Loligo	35	0.020
Spondylus	30	0.018
Siganus	10	0.017
Myctophidae	19	
41 ATLANTIC, SOUTHWEST		
Squalus	32	1.37
Cynoscion	139	1.24
Carcharhinus	21	0.719
Rhizoprionodon	47	0.695
Xiphias	23	0.680
Centropomus	17	0.655
Ramnogaster	51	0.540
Sphyrna	26	0.485
Thunnus	88	0.381
Genidens	45	0.353
Trichiurus	10	0.239
Hypanus	29	0.178
Micropogonias	90	0.173
Mustelus	83	0.156
Cathorops	26	0.126
Lycengraulis	28	0.106
Eugerres	45	0.106

FAO AREA/GENUS	N	THg
Umbrina	12	0.104
Odontesthes	46	0.101
Atherinella	16	0.097
Diapterus	11	0.078
Orthopristis	62	0.074
Percophis	43	0.074
Priacanthus	39	0.061
Merluccius	12	0.046
Sardinella	29	0.033
Brevoortia	10	0.032
Prochilodus	16	0.028
Mugil	34	0.028
Paralonchurus	12	0.026
Paralichthys	23	0.024
Aetobatus	12	0.006
47 ATLANTIC, SOUTHEAST		
Xiphias	17	0.816
Merluccius	10	0.630
Genypterus	10	0.580
Lophius	1 017	0.388
Sardinella	10	0.030
48 ATLANTIC, ANTARCTIC		
Dissostichus	39	0.680
51 INDIAN OCEAN, WESTERN		
Johnius	81	1.08
Xiphias	54	0.971
Acanthocybium	12	0.902
Sphyrna	12	0.727
Carcharhinus	89	0.724
Epinephelus	78	0.430
Thunnus	210	0.418
Sphyraena	56	0.378
Katsuwonus	37	0.363
Grammoplites	24	0.286
Alepes	20	0.282
Euthynnus	23	0.271
Cynoglossus	74	0.263
Platycephalus	16	0.255
Lethrinus	100	0.235
Scomberomorus	140	0.217
Lutjanus	39	0.215
Pampus	27	0.202

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Otolithes	34	0.182
Parastromateus	10	0.180
Pomadasys	11	0.170
Psettodes	10	0.151
Mugil	21	0.131
Coryphaena	30	0.109
Rhabdosargus	14	0.100
Auxis	18	0.092
Rhizoprionodon	12	0.089
Rastrelliger	26	0.084
Liza	70	0.075
Elagatis	16	0.062
Lobotes	10	0.061
Carangoides	15	0.050
Coilia	21	0.045
Canthidermis	18	0.028
Chiloscyllium	84	0.025
Uraspis	14	0.018
Kyphosus	32	0.007
Aluterus	10	0.007
Gerres	30	
57 INDIAN OCEAN, EASTERN		
Xiphias	94	0.612
Platycephalus	51	0.366
Thunnus	112	0.300
Mobula	15	0.190
Sphyraena	16	0.135
Mystus	10	0.121
Eleutheronema	72	0.077
Daysciaena	72	0.062
Mugil	75	0.041
Etroplus	75	0.040
Megalaspis	10	0.035
Caranx	17	0.014
Sardinella	15	0.013
Scomberomorus	10	0.011
Filimanus	13	0.005
Siganus	10	0.002
58 INDIAN OCEAN, ANTARCTIC		
Macrourus	15	0.336
Dissostichus	57	0.321

FAO AREA/GENUS	N	THg
61 PACIFIC, NORTHWEST		
Liza	27	0.492
Sebastes	14	0.452
Prionace	10	0.420
Sebastiscus	76	0.290
Nematalosa	15	0.267
Carcharhinus	17	0.250
Gadus	66	0.226
Pseudolabrus	11	0.209
Terapon	34	0.177
Acanthopagrus	69	0.118
Konosirus	36	0.117
Muraenesox	16	0.113
Pleuronectiformes	11	0.100
Lateolabrax	48	0.091
Epinephelus	166	0.091
Triaenopogon	62	0.089
Plectorhinchus	20	0.086
Trichiurus	42	0.083
Nemipterus	118	0.075
Priacanthus	25	0.075
Parargyrops	10	0.074
Paralichthys	26	0.071
Eupleurogrammus	30	0.070
Sparus	31	0.068
Branchiostegus	13	0.067
Sillago	56	0.064
Pholis	24	0.061
Callionymus	18	0.059
Megachasma	27	0.058
Thryssa	13	0.055
Inimicus	12	0.053
Lutjanus	28	0.051
Scomberomorus	50	0.049
Plotosus	12	0.048
Cynoglossus	129	0.044
	69	0.043
Synechogobius	19	0.042
Evynnis	18	0.042
Johnius	64	0.040
Saurida	33	0.036

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Siniperca	11	0.036
Argyrosomus	25	0.035
Pennahia	18	0.034
Larimichthys	29	0.034
Nibea	12	0.034
Trachurus	30	0.033
Trachinotus	140	0.032
Lagocephalus	11	0.031
Cirrhinus	12	0.031
Hexagrammos	16	0.031
Pseudopleuronectes	12	0.028
Morone	11	0.028
Leiognathus	39	0.028
Aristichthys	13	0.026
Setipinna	18	0.024
Pseudosciaena	27	0.023
Siganus	144	0.023
Dendrophysa	10	0.023
Thamnaconus	30	0.022
Repomucenus	18	0.022
Acanthogobius	12	0.022
Carassius	16	0.021
Gerres	32	0.021
Osteomugil	15	0.019
Chaeturichthys	24	0.018
Enchelyopus	12	0.016
Pampus	51	0.016
Engraulis	18	0.016
Lates	14	0.015
Mallotus	12	0.014
Sardinella	26	0.014
Salmonidae	13	0.014
Acipenser	10	0.014
Mugil	47	0.012
Pneumatophorus	10	0.008
Harpadon	62	0.007
Odontamblyopus	12	0.005
Pangasius	13	0.005
Miichthys	11	0.005
Collichthys	21	0.004
Ctenopharyngodon	14	0.004
Decapterus	13	

FAO AREA/GENUS	N	THg
Hapalogenys	12	
67 PACIFIC, NORTHEAST		
Raja	20	0.340
Hemilepidotus	75	0.340
Lepidopsetta	60	0.244
Malacoccottus	55	0.224
Atheresthes	128	0.152
Gadus	225	0.135
Sebastes	158	0.118
Beringraja	20	0.090
Pleurogrammus	221	0.045
71 PACIFIC, WESTERN CENTRAL		
Xiphias	20	0.646
Acanthopagrus	58	0.335
Toxotes	16	0.260
Decapterus	15	0.250
Gerres	10	0.173
Lates	17	0.101
Megalaspis	30	0.066
Thunnus	61	0.053
Siganus	10	0.030
Manta	15	0.009
77 PACIFIC, EASTERN CENTRAL		
Makaira	16	4.15
Triakis	10	1.27
Kajikia	17	0.880
Urolophus	12	0.770
Nezumia	43	0.748
Dasyatis	43	0.697
Sebastes	11	0.642
Sphyrna	156	0.590
Thunnus	363	0.566
Istiophorus	67	0.560
Alopias	63	0.560
Etelis	75	0.500
Lepophidium	14	0.490
Hydrolagus	140	0.490
Coelorinchus	26	0.487
Sebastolobus	19	0.466
Aprion	60	0.450
Seriola	11	0.437
Cephalurus	12	0.434

TABLE 7.5 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	THg
Prionace	30	0.390
Merluccius	241	0.334
Symphurus	20	0.305
Carcharhinus	30	0.280
Sciades	24	0.266
Platyrhinoidis	11	0.263
Haemulopsis	39	0.234
Zapteryx	88	0.226
Hoplopagrus	12	0.218
Caranx	25	0.217
Sphoeroides	15	0.203
Micropogonias	51	0.159
Pristipomoides	60	0.150
Gerres	15	0.145
Diapterus	110	0.135
Pseudupeneus	32	0.110
Coryphaena	79	0.103
Pseudobatos	97	0.082
Ancylopsetta	10	0.080
Pomadasys	57	0.079
Scomberomorus	22	0.072
Mustelus	163	0.068
Larimus	11	0.060
Myliobatis	83	0.058
Achirus	36	0.058
Caulolatilus	22	0.053
Lutjanus	36	0.052
Mugil	50	0.047
Hemicaranx	10	0.040
Trachinotus	30	0.030
Pronotogrammus	10	0.024
Rhincodon	72	0.022
Balistes	19	0.018
81 PACIFIC, SOUTHWEST		
Genypterus	120	0.530
Hoplostethus	101	0.510
Rexea	10	0.240
Pseudocyttus	20	0.150
Allocyttus	20	0.100
Thyrsites	10	0.060
87 PACIFIC, SOUTHEAST		
Carcharhinus	27	1.53
Sphyrna	19	1.28
Alopias	24	1.07
Prionace	132	0.985
Coryphaena	46	0.847
Thunnus	68	0.801
Isurus	22	0.608
Xiphias	42	0.551
Lampris	15	0.482
Mustelus	11	0.338
Brotula	10	0.276
Paralichthys	11	0.196
Cynoscion	14	0.195
Cilus	11	0.112
Macruronus	12	0.105
Sarda	15	0.097
Mugil	10	0.009
88 PACIFIC, ANTARCTIC		
Macrourus	15	0.365
Dissostichus	89	0.210
UNKNOWN FAO AREA		
Xiphias	90	0.869
Thunnus	17	0.420
Pagrus	20	0.310
Lates	12	0.300
Lutjanus	35	0.196
Macruronus	12	0.160
Platycephalus	22	0.160
Galeorhinus	10	0.130
Thunnus	7	0.101
Scomberomorus	36	0.088
Monacanthidae	20	0.070
Sillago	10	0.060
Scomberomorus	11	0.040
Merluccius	3	0.023

Notes: N is the number of analytical samples, including both individual and composite samples. THg: total Hg. When whole fish (w) or both whole fish and muscle (w+m) were analysed, this is marked after the genus name. When nothing is specified, muscle tissue was analysed.

TABLE 7.6 MEAN METHYLMERCURY (MeHg) LEVELS IN WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), BY GENUS, IN mg/kg WET WEIGHT

FAO AREA/GENUS	N	MeHg
18 ARCTIC SEA		
Gadus	10	0.140
Myoxocephalus	20	0.125
Stenodus	38	0.075
Coregonus	41	0.061
Boreogadus	40	0.030
Oncorhynchus	22	0.023
Platichthys	22	0.021
Ammodytes	13	0.020
Mallotus	11	0.010
Clupea	29	0.003
21 ATLANTIC, NORTHWEST		
Squalus	102	0.378
Cottunculus	10	0.260
Fundulus	290	0.037
27 ATLANTIC, NORTHEAST		
Anguilla	29	0.729
Brosme	137	0.616
Stizostedion	14	0.095
Rutilus	10	0.062
Gadus	10	0.054
Abramis	10	0.030
Clupea	10	0.015
Sprattus	10	0.006
Trachurus	40	
31 ATLANTIC, WESTERN CENTRAL		
Epinephelus	168	0.755
37 MEDITERRANEAN AND BLACK SEA		
Xiphias	45	0.495
Sardina	44	0.033
Myctophidae	19	0.019
41 ATLANTIC, SOUTHWEST		
Hypanus	11	0.019
47 Atlantic, Southeast		
Lophius	650	0.130
51 INDIAN OCEAN, WESTERN		
Lethrinus	45	0.320
Gerres	30	0.040
57 INDIAN OCEAN, EASTERN		
Xiphias	20	0.013
Caranx	11	0.005
Filimanus	13	0.004

FAO AREA/GENUS	N	MeHg
Macrourus	15	0.145
Dissostichus	50	0.106
61 PACIFIC, NORTHWEST		
Carcharhinus	17	0.164
Acanthopagrus	48	0.107
Terapon	34	0.102
Plectorhinchus	10	0.100
Muraenesox	12	0.086
Nemipterus	96	0.075
Sillago	45	0.067
Lateolabrax	14	0.060
Lutjanus	15	0.060
Argyrosomus	21	0.052
Hapalogenys	12	0.051
Inimicus	12	0.050
Parargyrops	10	0.047
Evynnis	18	0.046
Johnius	63	0.046
Decapterus	13	0.045
Sebastiscus	16	0.044
Konosirus	36	0.044
Sparus	24	0.043
Callionymus	12	0.043
Epinephelus	133	0.042
Pholis	24	0.042
Trichiurus	19	0.042
Paralichthys	16	0.042
Triaenopogon	62	0.038
Cynoglossus	99	0.036
Thryssa	13	0.036
Leiognathus	32	0.035
Platycephalus	62	0.035
Scomberomorus	37	0.035
Nibea	12	0.033
Synechogobius	18	0.032
Pennahia	18	0.030
Saurida	26	0.029
Lagocephalus	11	0.029
Hexagrammos	16	0.028
Pseudopleuronectes	12	0.026
Larimichthys	24	0.024
Trachinotus	18	0.023

TABLE 7.6 MEAN METHYLMERCURY (MeHg) LEVELS IN WILD-CAUGHT FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), BY GENUS, IN mg/kg WET WEIGHT (cont.)

FAO AREA/GENUS	N	MeHg
Setipinna	18	0.023
Repomucenus	18	0.021
Eupleurogrammus	24	0.019
Dendrophysa	10	0.019
Pampus	38	0.019
Liza	14	0.019
Osteomugil	14	0.018
Thamnaconus	26	0.017
Chaeturichthys	24	0.017
Nematalosa	13	0.016
Pseudosciaena	14	0.015
Harpadon	18	0.014
Enchelyopus	12	0.014
Siganus	129	0.014
Engraulis	18	0.011
Sardinella	25	0.011
Mugil	22	0.010

FAO AREA/GENUS	N	MeHg
81 PACIFIC, SOUTHWEST		
Genypterus	120	0.460
Hoplostethus	101	0.430
Rexea	10	0.220
Pseudocyttus	20	0.140
Allocyttus	20	0.100
Thyrsites	10	0.060
88 PACIFIC, ANTARCTIC		
Macrourus	15	0.184
Dissostichus	52	0.035
57 INDIAN OCEAN, E + 81 PACIFIC, SW		
Thunnus	17	0.410
Lates	12	0.260
Pagrus	20	0.250
Platycephalus	22	0.150
Galeorhinus	10	0.120
Macruronus	12	0.110
Monacanthidae	20	0.060
Sillago	10	0.050
Scomberomorus	11	0.030

Note: N is the number of analytical samples, including both individual and composite samples. Cases where N < 10 are excluded.

7.4.2 MERCURY IN FINFISH FROM DATA FROM THE EUROPEAN FOOD SAFETY AUTHORITY

In the data from EFSA, THg and MeHg values were reported using codes for species or species groups, rather than the less ambiguous Latin names (which are used in the literature data). Because of this, some species groups may include a wide range of species which may have very different Hg levels. Furthermore, some species may be present both with their specific species names and as part of a larger group of species. For instance, the species named Atlantic salmon could be included also in the species group "salmons". The EFSA data includes samples analysed in Europe, but includes both samples of fish of European origin and fish imported to Europe from other countries. In the EFSA data for finfish, only data for muscle tissue was included.

In the dataset for Hg in finfish reported to EFSA and included here, there are 17 799 results for THg and 1 006 results for MeHg. The majority of the samples reported for THg (n = 15 602), were from marine waters, while 1 755 were from inland waters. For 412 samples of finfish, it was not clear whether the samples were of marine or inland origin, and these were grouped together with the marine fish in the tables.

Most of the fish samples (n = 11 038) originated from wild stocks, whereas 1 276 samples were from aquaculture production. For 5 485 samples, it was not specified whether the samples originated from wild stocks or aquaculture, and these were included with the wild-caught fish in the results tables.

7.4.2.1 Farmed and wild finfish from inland waters

The samples were classified as farmed, wild-caught or "unspecified", and the latter constituted the largest group. In **Table 7.7**, results are given for species or species groups of freshwater finfish, independent of area or whether produced by farming, wild capture or unknown. Barbs had the highest mean THg concentration with 0.621 mg/kg, followed by pike, with a mean of 0.424 mg/kg. The analysed barbs were all from wild stocks or unspecified in Europe (**Table 7.8**), whereas pike included both wild, farmed and unspecified in Europe. The unspecified pike samples had the highest mean THg concentration, analysed in very few samples (mean 1.12 mg/kg, n = 7). In general, fewer numbers by far were reported for MeHg than for THg, and mean concentrations were mostly lower for MeHg than for THg (**Table 7.7**).

TABLE 7.7 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF FARMED AND WILD-CAUGHT FINFISH FROM INLAND WATERS (ALL REGIONS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg	N	MeHg
Barbs	32	0.621		
Pike	44	0.424	1	0.078
Freshwater bream, Europe	172	0.198		
Eel, European	17	0.159		
Roaches	42	0.141		
Perch	154	0.138	8	0.101
Pike-perch	23	0.130		
River eels	125	0.114	5	0.065
White crappie	13	0.101		
Carps, barbels and other cyprinids	555	0.096	105	0.021
Pangas catfishes	275	0.090	29	0.023
Catfishes (freshwater)	48	0.078	1	0.045
Salmons, trouts, smelts	170	0.028	25	0.021
African catfish	13	0.026		
Char	13	0.023	10	0.018
Tilapias and similar	42 (41[1])	0.103 (0.006[1])	6	0.020

Note: N is the number of analytical samples and may include both individual and composite samples. For THg, cases where N < 10 are excluded.

[1] Excluding one sample with THg-concentration of 4.1 mg/kg ww.

TABLE 7.8 MEAN TOTAL MERCURY (THg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF WILD-CAUGHT, FARMED OR UNSPECIFIED FINFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS), IN MG/KG WET WEIGHT

SPECIES/SPECIES GROUP	WILD		FARMED		UNSPECIFIED		TOTAL SUM	
	N	THg	N	THg	N	THg	N	THg
01 AFRICA INLAND WATERS								
Freshwater bream, Europe					15	0.502	15	0.502
Perch					55	0.107	55	0.107
04 ASIA INLAND WATERS								
Pangas catfishes	1	0.010	5	0.022	190	0.118	196	0.115
River eels	10	0.061					10	0.061
Perch	5	0.029			10	0.044	15	0.039
Tilapias and similar					33	0.004	33	0.004
05 EUROPE INLAND WATERS								
Barbs	15	0.884			15	0.423	30	0.654
Pikes	34	0.282	3	0.402	7	1.12	44	0.424
Perch	25	0.157	2	0.073	47	0.201	74	0.183
Eel, European	16	0.158			1	0.164	17	0.159
Freshwater bream, Europe	71	0.197	7	0.089	67	0.121	145	0.157
Pike-perch	4	0.252	1	0.174	12	0.103	17	0.142
Roaches	13	0.136	1	0.085	28	0.146	42	0.141
River eels	113	0.117	4	0.066			117	0.116
White crappie	1	0.125			11	0.099	12	0.101
Carps, barbels and other cyprinids	112	0.173	306	0.047	136	0.142	554	0.096
Catfishes (freshwater)	7	0.361	4	0.018	36	0.032	47	0.080
Salmons, trouts, smelts	12	0.043	64	0.023	93	0.029	169	0.027
Char			13	0.023			13	0.023
Pangas catfishes					21	0.005	21	0.005
SPAIN, UNSPECIFIED								
Freshwater bream	3	0.106			8	0.223	11	0.191
Perch					12	0.130	12	0.130
Pangas catfishes					26	0.039	26	0.039
UNKNOWN AREA								
Pangas catfishes					28	0.027		0.027

Note: N is the number of analytical samples and may include both individual and composite samples. Cases where N < 10 are excluded.

7.4.2.2 Farmed finfish from marine waters

The data on Hg in farmed marine finfish reported to EFSA included much fewer samples than the data on marine finfish from wild stocks. The results for THg and MeHg are given in **Table 7.9**. All species or species groups had low concentrations of THg and MeHg (well below 0.2 mg/kg). Sea bream from area 27 Northeast Atlantic had the highest mean THg and MeHg levels, while Atlantic salmon had the lowest.

TABLE 7.9 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF FARMED FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg	N	MeHg
27 ATLANTIC, NORTHEAST				
Sea bream	17	0.128	9	0.127
Sea bass	10	0.103	1	0.050
Salmons	23	0.044		
Trouts	49	0.027	3	0.021
Rainbow trout	53	0.024	6	0.026
Atlantic salmon	528	0.019	96	0.020
37 MEDITERRANEAN AND BLACK SEA				
Sea bass	34	0.081		
Gilthead seabream	14	0.068		
Trouts	20	0.047		
FRANCE, UNSPECIFIED				
Rainbow trout	20	0.048		
Salmons	35	0.038		

Notes: N is the number of analytical samples and may include both individual and composite samples. Cases where N < 10 for THg are excluded.

7.4.2.3 Wild-caught finfish from marine waters

The highest mean THg concentration in wild-caught finfish was reported in sharks from Spain (FAO area not specified), at 1.74 mg/kg (**Table 7.10**). In many areas, however, swordfish was the species or species group with the highest mean THg level, varying between 0.574 mg/kg in Morocco (FAO area unspecified) and 1.55 mg/kg in area 87 Southeast Pacific. Other species or species groups with mean THg concentrations above 0.5 mg/kg included sharks from Northeast Atlantic (FAO area 27); anglerfish, monkfish and stargazers (FAO area 37); European conger from the Mediterranean and Black Sea (also FAO area 37); butterfish from Western Central Pacific; yellowfin tuna from Eastern Central and Southeast Pacific (FAO areas 77 and 87); and blue shark from Spain (FAO area unspecified). Tunas were classified as "tuna" or "yellowfin tuna", and for several areas results for both groups were reported. Mean THg concentrations in the diverse species group "tuna" varied between 0.14 and 0.81 mg/kg, perhaps because different tuna species were analysed. However, yellowfin tuna, a large and globally migrating tuna species, also showed large variations between FAO

areas, from 0.21 mg/kg in Western-Central Pacific (FAO area 71, n = 22) to 0.66 mg/kg in Southeast Pacific (FAO area 87, n = 14). The number of samples analysed in each of these areas was relatively low and the geographic differences should be regarded cautiously.

Results for both THg and MeHg in species where both analytes were included are shown in **Table 7.11** (with all sampling areas pooled together). Mean MeHg concentrations exceeding 0.5 mg/kg were reported for swordfish, bonito, European conger, northern bluefin tuna and anglerfish, monkfish and stargazers. For swordfish, the mean MeHg concentration was lower than for THg, while for the rest of the species or species groups, MeHg values were mostly higher than THg values. Because many more samples were analysed for THg than for MeHg, the THg results are likely more representative than the MeHg results of the actual MeHg concentrations in marine fish.

One species group, river eels, included in **Table 7.10**, appear to be freshwater fish, but in the EFSA data these samples were reported as coming from the Mediterranean Sea and they are therefore included here.

TABLE 7.10 MEAN TOTAL MERCURY (THg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

SPECIES/ SPECIES GROUP	N	THg
27 ATLANTIC, NORTHEAST		
Swordfish	120	1.02
Sharks	38	0.835
Blue ling	50	0.448
Bluefish	44	0.448
Tusk	1461	0.339
Albacore	23	0.315
Tuna	199	0.303
Anglerfish, monkfish and stargazers	345	0.256
Sea bass	48	0.234
Halibut, Atlantic	797	0.206
Common ling	827	0.185
Hakes	330	0.138
Rays	29	0.131
Whiting	40	0.130
Eel, European	23	0.126
Halibut	11	0.121
Pollack	330	0.113
Ocean perch	57	0.109
Coalfish	43	0.105
Flounders	33	0.104
River eels	28	0.103
Grenadiers	22	0.101
Dab or common dab	25	0.098
Mullets	11	0.098
Beaked redfish	524	0.093
Pangas catfishes	85	0.090
Cod, Atlantic	779	0.090
Golden redfish	223	0.089
Perch	19	0.085
Sole	54	0.085
Mackerel, Atlantic	43	0.076
Cods, hakes, haddocks	488	0.074
haddock	235	0.071
Mackerel	402	0.066
Sardines and sardine-type fishes	90	0.062
Herrings	249	0.060
Plaice, European	458	0.057
Anchovies	66	0.056
Plaice	269	0.053
Herring, Atlantic	105	0.048
Rainbow trout	36	0.040
European sardine	27	0.039
Atlantic salmon	83	0.034
Trouts	90	0.033
Salmons	319	0.032
Salmons, trouts, smelts	153	0.026
Sprat	61	0.020
31 ATLANTIC, WESTERN CENTRAL		
Tuna, yellowfin	13	0.404
34 ATLANTIC, EASTERN CENTRAL		
Swordfish	24	1.06
Tuna, yellowfin	32	0.495
Tuna	67	0.404
Groupers	36	0.082
37 MEDITERRANEAN AND BLACK SEA		
Tuna	59	0.807
Anglerfish, monkfish and stargazers	24	0.616
Conger, European	21	0.563
Sole	19	0.223
Hakes	35	0.210
Scorpion fishes	23	0.193
Mullets	20	0.114
Anchovies	25	0.092
Sea bream	14	0.071
Gilthead seabream	28	0.067
Sea bass	109	0.065
Sardines and sardine-type fishes	29	0.060
Trouts	33	0.015
Salmons, trouts, smelts	35	0.013
41 ATLANTIC, SOUTHWEST		
Swordfish	33	0.676
Tuna	10	0.494
Hakes	77	0.052
47 ATLANTIC, SOUTHEAST		
Swordfish	57	1.01
Hakes	164	0.180
Cods, hakes, haddocks	15	0.056

TABLE 7.10 MEAN TOTAL MERCURY (THg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

SPECIES/ SPECIES GROUP	N	THg
51 INDIAN OCEAN, WESTERN		
Swordfish	57	1.34
Tuna	82	0.363
Tuna, yellowfin	42	0.261
57 INDIAN OCEAN, EASTERN		
Swordfish	46	0.642
Tuna	37	0.427
Tuna, yellowfin	17	0.232
61 PACIFIC, NORTHWEST		
Swordfish	11	1.11
Hakes	16	0.097
Grenadiers	12	0.088
Anglerfish, monkfish and stargazers	15	0.079
Cods, hakes, haddocks	82	0.037
Alaska pollock	17	0.027
Salmons, trouts, smelts	31	0.026
Salmons	66	0.025
67 PACIFIC, NORTHEAST		
Hakes	37	0.344
Salmons	26	0.031
Cods, hakes, haddocks	25	0.020
71 PACIFIC, WESTERN CENTRAL		
Swordfish	10	0.925
Butterfish	11	0.743
Tuna, yellowfin	22	0.211
Tuna	204	0.140
77 PACIFIC, EASTERN CENTRAL		
Tuna, yellowfin	29	0.635
87 PACIFIC, SOUTHEAST		
Swordfish	108	1.55
Tuna, yellowfin	14	0.663
Tuna	48	0.314
Hakes	20	0.096
Trouts	10	0.064
Salmons, trouts, smelts	13	0.017
Salmons	60	0.013
Atlantic salmon	11	0.010
FRANCE, UNSPECIFIED		
Swordfish	14	1.06
Tuna	12	0.362
Hakes	13	0.194
Sea bass	22	0.135
Dolphinfishes	13	0.107
Mackerel	23	0.070
Cods, hakes, haddocks	23	0.065
Trouts	24	0.059
Sardines and sardine-type fishes	12	0.042
GREENLAND, UNSPECIFIED		
Halibut, Greenland	16	0.045
INDIA, UNSPECIFIED		
Swordfish	11	0.591
Tuna	11	0.210
INDIAN OCEAN, UNSPECIFIED		
Swordfish	47	1.13
Tuna	102	0.361
MOROCCO, UNSPECIFIED		
Swordfish	14	0.574
Anchovies	11	0.044
Sardines and sardine-type fishes	24	0.032
PACIFIC OCEAN, UNSPECIFIED		
Swordfish	46	0.757
Tuna	21	0.347
Cods, hakes, haddocks	17	0.026
Salmons	11	0.021
RUSSIA, UNSPECIFIED		
Grenadiers	12	0.044
SPAIN, UNSPECIFIED		
Sharks	40	1.74
Swordfish	238	1.08
Blue shark	23	1.05
Bonito	37	0.480
Tuna	256	0.423
Tuna, yellowfin	20	0.410
Albacore	18	0.273
Blue whitings	15	0.138
Perch	10	0.133
Mackerel	70	0.117
Hakes	104	0.110
Sea bass	21	0.105

TABLE 7.10 MEAN TOTAL MERCURY (THg) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

SPECIES/ SPECIES GROUP	N	THg
Horse mackerels	20	0.092
Anglerfish, monkfish and stargazers	50	0.091
Anchovies	120	0.073
Cods, hakes, haddocks	51	0.071
Sole	13	0.068
Sardines and sardine-type fishes	35	0.060
Salmons, trouts, smelts	40	0.056
European sardine	13	0.055
THE UNITED STATES, UNSPECIFIED		
Cods, hakes, haddocks	15	0.030
Salmons, trouts, smelts	10	0.028
Salmons	13	0.025

SPECIES/ SPECIES GROUP	N	THg
VIET NAM, UNSPECIFIED		
Swordfish	18	1.10
Mackerel	27	0.255
Tuna	81	0.172
Wolffishes	11	0.004
UNKNOWN AREA		
Tuna	15	0.277
Hakes	25	0.055
Mackerel	10	0.053
Cods, hakes, haddocks	31	0.040
Herrings	15	0.037
Char	39	0.033
Trouts	31	0.024
Salmons, trouts, smelts	79	0.022

Note: N is the number of analytical samples and may include both individual and composite samples. Cases where N < 10 are excluded.

TABLE 7.11 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (K) LEVELS IN MUSCLE TISSUE OF SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM MARINE OR UNSPECIFIED AREAS AROUND THE WORLD (ALL REGIONS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg	N	MeHg
Swordfish	899	1.06	195	0.796
Bonito	43	0.424	15	0.691
Conger, European	21	0.563	11	0.682
Northern bluefin tuna	17	0.696	10	0.567
Anglerfish, monkfish and stargazers	448	0.250	20	0.548
Tuna, yellowfin	228	0.390	17	0.443
Tuna	1 247	0.340	137	0.363
Albacore	75	0.324	24	0.332
Sole	102	0.107	11	0.243
Hakes	853	0.144	44	0.159
Mackerel	579	0.091	20	0.119
Gilthead seabream	53	0.069	15	0.071
Plaice	306	0.054	15	0.064
Cods, hakes, haddocks	800	0.063	84	0.045

Notes: Results are shown only for species or species groups where both THg and MeHg were analysed. Cases where N < 10 are excluded.

7.4.3 MERCURY IN FINFISH, SUMMARY

Data on THg and MeHg from both the literature search and from the EFSA database showed that, in general, farmed finfish had lower Hg concentrations than wild finfish and farmed freshwater finfish had lower Hg levels than farmed marine finfish. Fish captured from wild stocks in marine waters had the highest concentrations, although the differences between marine and freshwater fish were not very large. The EFSA data exhibited a larger difference between average THg concentrations in marine and freshwater fish than what was found in the literature, with overall mean values for marine and freshwater fish in the EFSA data of 0.27 and 0.19 mg/kg, respectively, and mean values in the literature of 0.26 and 0.23 mg/kg, respectively. While the mean values for marine fish were remarkably similar in the two datasets, the results for fish from inland waters in the two datasets were quite different. Freshwater fish from the EFSA database included very few species, mostly from European inland waters, and most of them had low Hg levels. On the other hand, data from the literature included data on fish from inland waters of most continents, including a wide range of fish species with relatively high Hg levels, particularly from South America.

Within the category marine finfish from wild capture, certain species or species groups had particularly high Hg levels according to both the literature data and the data from EFSA. These included swordfish (*Xiphias gladius*) and many different sharks (**Table 7.5** and **Table 7.10**). Also, large tuna species in the genus *Thunnus* from literature and tuna or yellowfin tuna (*Thunnus albacares*) from the EFSA database, were among the groups with relatively high Hg levels throughout different regions of the world's oceans. However, large variations were observed within the groups. In addition, there were some genera or species groups more specific to the different areas that had relatively high mean Hg concentrations. It appears from a superficial look at the data and without statistical analyses, that the differences in Hg levels among species or species groups were more important than differences between geographical areas.

7.4.4 MERCURY IN SHELLFISH FROM THE LITERATURE REVIEW

In the literature, THg results were found for 11 809 analysed samples of shellfish, while MeHg results were found for only 763 analysed samples. Of the analysed shellfish, 1 752 and 7 samples for THg and MeHg, respectively, were from aquaculture, while the rest were from wild stocks (10 057 and 756, respectively) or unknown (including, for example, sampled at market with no information about origin). The majority of the analysed shellfish samples originated from marine waters (n = 9 850 and 689, respectively), while 1 959 and 74 shellfish samples analysed for THg and MeHg, respectively, were from inland waters.

7.4.4.1 Farmed shellfish from inland and marine waters

In the literature, results for Hg in farmed shellfish from inland waters were limited to three species, all from Asia (**Table 7.12**). These all had very low THg concentrations, with Chinese mitten crab (*Eirocheir sinensis*), having the highest mean level, at 0.05 mg/kg. Methylmercury was only reported from seven samples of whiteleg shrimp (*Litopenaeus vannamei*), and mean values of both THg and MeHg in this species were very low.

Farmed shellfish from marine regions included nine different species, distributed between three different FAO areas (**Table 7.13**). These also had very low THg levels, with the great Mediterranean scallop (*Pecten jacobaeus*) having the highest mean concentration, at 0.12 mg/kg (n = 10). No MeHg results were reported in the literature for farmed shellfish from marine areas.

TABLE 7.12 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN SPECIES OF FARMED SHELLFISH FROM INLAND WATERS, IN mg/kg WET WEIGHT

FAO AREA/SPECIES LATIN NAME	N	THg	N	MeHg
04 ASIA INLAND WATERS				
Eriocheir sinensis	36	0.050		
Meretrix lusoria	1 021	0.003		
Litopenaeus vannamei	7	0.002	7	0.001

Notes: Only FAO area 04 Asia inland included shellfish from inland aquaculture. N is the number of analytical samples, including both individual and composite samples.

TABLE 7.13 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OF FARMED SHELLFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

FAO-AREA/SPECIES LATIN NAME	N	THg
37 MEDITERRANEAN AND BLACK SEA		
Pecten jacobaeus	10	0.120
Ostrea edulis	96	0.054
Mytilus galloprovincialis	261	0.052
Venus verrucosa	12	0.020
47 ATLANTIC, SOUTHEAST		
Mytilus galloprovincialis	30	0.004
Choromytilus meridionalis	30	0.003
61 PACIFIC, NORTHWEST		
Ostrea plicatula	60	0.016
Tegillarca granosa	60	0.008
Sinonovacula constricta	60	0.008
Ruditapes philippinarum	69	0.007

Notes: No farmed shellfish from marine waters were analysed for methylmercury. N is the number of analytical samples, including both individual and composite samples.

7.4.4.2 Wild-caught shellfish from inland waters

The results for THg and MeHg in shellfish species sampled from wild stocks in different FAO areas are shown in **Table 7.14**. The table also includes samples whose origin (aquaculture or wild stocks) is not known. The THg concentrations were low in most species, except two bivalve species from Africa, *Aspatharia senegalensis* and *Etheria elliptica*, which had mean Hg levels above 0.5 mg/kg, but where the numbers of analysed samples were very low (n = 5 and n = 2, respectively). Apart from these two, red swamp crayfish (Procambarus clarkii), from Europe was the only shellfish species with a mean THg concentration higher than 0.1 mg/kg.

7.4.4.3 Wild-caught shellfish from marine waters

Most shellfish species from marine waters had low Hg concentrations, with a few exceptions (**Table 7.15)**. The mud crab genus *Scylla* had a high mean THg concentration due to one sample from a closed saltwater pond in China, at the site of a former chloralkali factory. When this sample was excluded, the mean THg concentration in *Scylla* was very low. Apart from this, Norway lobster (*Nephrops norvegicus*) and blue and red shrimp (*Aristeus antennatus*) had mean concentrations close to 0.5 mg/kg. For Norway lobster the samples from Mediterranean and Black Sea had a considerably higher mean concentration (0.537 mg/kg) than those from the Northeast Atlantic (0.2 mg/kg) (**Table 7.16**). The shrimp genus *Penaeus* had higher THg concentrations in Mediterranean and Black Sea than in Eastern Central Atlantic (FAO area 34) and Western Indian Ocean (FAO area 51). The genus *Homarus* had a higher mean concentration in Northeast Atlantic (FAO area 27) than in Northwest Atlantic (FAO area 21) and in Northwest Pacific (FAO area 61). The samples from Northeast Atlantic were European lobsters (*Homarus gammarus*), while the others were American lobster (*H. americanus*).

The mean MeHg concentration in Norway lobster was higher than the THg concentration, but only three samples were analysed for MeHg (Table 7.15). Genera with mean THg above 0.2 mg/kg included lobsters, shrimps, cephalopods and gastropods, as well as the Atlantic bay scallop (*Argopecten irradians*).

TABLE 7.14 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN TISSUES OF DIFFERENT SPECIES OF WILD-CAUGHT (OR UNKNOWN) SHELLFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

SPECIES	N	THg	N	MeHg
01 AFRICA, INLAND WATERS				
Aspatharia senegalensis	5	0.790		
Etheria elliptica	2	0.600		
Macrobrachium rosenbergii	50	0.010		
02 NORTH AMERICA, INLAND WATERS				
Cambarus carinirostris	20	0.050		
Corbicula fluminea	5	0.018		
Dreissena bugensis	2	0.005		
03 SOUTH AMERICA INLAND WATERS				
Macrobrachium amazonicum	349	0.018		
05 EUROPE INLAND WATERS				
Procambarus clarkii	105	0.113		
Mytilus galloprovincialis	4	0.026	4	0.010
04 ASIA INLAND WATERS				
Eriocheir sinensis	3	0.081		
Portunus pelagicus	5	0.075		
Scylla olivacea	12	0.072		
Crassostrea sp.	23	0.071		
Meretrix lusoria	27	0.065		
Anodonta woodiana[1]	8	0.052		
Thalamita crenata	6	0.048		
Polymesoda expansa	21	0.021		
Sinanodonta woodiana	9	0.020		
Chlamys farreri[1]	5	0.017		
Pilsbryoconcha compressa	3	0.014		
Perna viridis[1]	5	0.013		
Argopecten irradians[1]	5	0.012		
Paphia undulata[1]	5	0.010		
Ruditapes philippinarum[1]	5	0.010		
Crassostrea ariakensis[1]	5	0.008		
Babylonia areolata[1]	5	0.007		
Sinonovacula constricta[1]	5	0.007		
Corbicula leana[1]	52	0.005		
Haliotis discus[1]	5	0.004		
Cipangopaludina japonica[1]	71	0.002		
Penaeus monodon	1	0.0002	1	0.0002
Prawn, unknown			1	0.0021
Bellamya javanica			61	0.260

Notes: N is the number of analytical samples, including both individual and composite samples. All analysed edible tissues are included.
[1] Unknown whether farmed or wild.

TABLE 7.15 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT SHELLFISH FROM MARINE WATERS (ALL REGIONS), IN mg/kg WET WEIGHT

GENUS	N	THg	N	MeHg
Scylla	71 (70[1])	0.93 (0.048[1])	2	0.001
Nephrops	350	0.495	3	0.664
Aristeus	16	0.465		
Eledone	12	0.257		
Busycon	38	0.250		
Parapenaeus	753	0.249		
Hexaplex	20	0.245		
Argopecten	34	0.233		
Austramacoma	24	0.195		
Squilla	78	0.182		
Palaemon	38	0.180	32	0.185
Cancer	20	0.170		
Dosinia	15	0.169		
Maja	22	0.164		
Penaeus	465	0.161		
Homarus	197	0.160		
Chlamys	24	0.146	8	0.139
Eriphia	634	0.144		
Haliotis	81	0.128		
Sepia	148	0.118		
Pandalus	19	0.113	10	0.200
Callinectes	235	0.105		
Chionoecetes	227	0.101	39	0.020
Thysanoteuthis	24	0.101		
Concha	47	0.095		
Panulirus	124	0.083		
Nototodarus	30	0.080		
Litopenaeus	50	0.079		
Achelous	32	0.076		
Pinna	15	0.074	1.16	
Lithophaga	58	0.073		
Megapitaria	89	0.070		
Crassostrea	183	0.062	1	0.028
Octopus	302	0.062	14	0.036
Mytilus	605	0.054	15	0.015
Solen	54	0.053	12	0.011
Metapenaeus	197	0.052		
"Sea prawns"	2	0.003	2	0.003
Macrobrachium	24	0.048		
Anadara	232	0.044	42	0.009
Rapana	41	0.043	14	0.034

TABLE 7.15 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT SHELLFISH FROM MARINE WATERS (ALL REGIONS), IN mg/kg WET WEIGHT (cont.)

GENUS	N	THg	N	MeHg
Sinonovacula	63	0.041	6	0.002
Todarodes	113	0.041		
Donax	24	0.041		
Charybdis	160	0.040	9	0.031
Pachygrapsus	13	0.040		
Doryteuthis	23	0.039		
Berryteuthis	97	0.038		
Diplodonta	12	0.037		
Loligo	105	0.033	20	0.018
Callista	98	0.032		
Paralithodes	43	0.031		
Portunus	221	0.030	17	0.014
Senilia	30	0.030		
Osilinus	10	0.029		
Neptunea	51	0.029	24	0.003
Ruditapes	786	0.029	79	0.012
Fenneropenaeus	256	0.028	30	0.005
Patella	35	0.028		
Paracentrotus	136	0.025		
Farfantepenaeus	51	0.024		
Oratosquilla	32	0.021	24	0.021
Enteroctopus	16	0.021		
Paroctopus	99	0.020		
Cerithium	27	0.017		
Holothuria	42	0.016		
Mactra	12	0.016	12	0.012
Meretrix	117	0.015	42	0.007
Cyclina	12	0.014	12	0.010
Perna	103	0.014		
Cassidula	37	0.013		
Thais	12	0.012	6	0.019
Dosidicus	18	0.010		
Acetes	78	0.010		
Paphia	25	0.010		
Alpheus	43	0.009	36	0.006
Crangon	44	0.009	38	0.005
Ostrea	28	0.006	24	0.002
Trachypenaeus	43	0.006	36	0.006
Chamelea	14	0.005		
Nordotis	12	0.004		
Monetaria	12	0.004	12	0.002

TABLE 7.15 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT SHELLFISH FROM MARINE WATERS (ALL REGIONS), IN mg/kg WET WEIGHT (cont.)

GENUS	N	THg	N	MeHg
Harpiosquilla	36	0.00005		
"Pacific octopus"	21	0.095		

Note: [1]1 sample removed: THg 3.6 mg/kg, n = 1.

TABLE 7.16 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT SHELLFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

GENUS	N	THg
21 ATLANTIC, NORTHWEST		
Homarus	105	0.162
Pandalus	19	0.113
27 ATLANTIC, NORTHEAST		
Homarus	26	0.273
Nephrops	10	0.200
Cancer	20	0.170
Lithophaga	46	0.126
Ruditapes	484	0.031
Mytilus	34	0.027
Patella	15	0.012
31 ATLANTIC, WESTERN CENTRAL		
Callinectes	15	0.125
Thysanoteuthis	24	0.101
Crassostrea	17	0.009
Litopenaeus	31	0.033
34 ATLANTIC, EASTERN CENTRAL		
Austramacoma		
24	0.195	
Penaeus	48	0.092
Diplodonta	12	0.037
Senilia	30	0.030
Crassostrea	62	0.025
Perna	36	0.011
37 MEDITERRANEAN AND BLACK SEA		
Nephrops	340	0.537
Aristeus	16	0.465
Parapenaeus	748	0.277
Eledone	12	0.257
Hexaplex	20	0.245
Penaeus	98	0.223
Squilla	78	0.182
Maja	22	0.164

GENUS	N	THg
Sepia	42	0.153
Chlamys	16	0.146
Eriphia	634	0.144
Octopus	79	0.134
Crassostrea	73	0.131
Solen	42	0.091
Mytilus	239	0.086
Ruditapes	19	0.040
Portunus	39	0.080
Anadara	15	0.051
Donax	24	0.041
Patella	20	0.036
Pachygrapsus	13	0.040
Pinna	15	0.074
Rapana	18	0.034
Callista	98	0.032
Paracentrotus	130	0.031
Osilinus	10	0.029
Lithophaga	12	0.020
Holothuria	42	0.016
Cerithium	23	0.015
Haliotis	60	0.012
Chamelea	14	0.005
41 ATLANTIC, SOUTHWEST		
Callinectes	210	0.094
Achelous	32	0.076
Doryteuthis	17	0.056
Farfantepenaeus	45	0.027
Macrobrachium	20	0.025
Perna	30	0.024
47 ATLANTIC, SOUTHEAST		
Loligo	35	0.029

TABLE 7.16 MEAN TOTAL MERCURY (THg) LEVELS IN TISSUE OF DIFFERENT GENERA OF WILD-CAUGHT SHELLFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

GENUS	N	THg
51 INDIAN OCEAN, WESTERN		
Metapenaeus	104	0.131
Fenneropenaeus	60	0.116
Penaeus	300	0.085
Panulirus	120	0.076
57 INDIAN OCEAN, EASTERN		
Mytilus	298	0.047
Portunus	13	0.014
Cassidula	37	0.013
61 PACIFIC, NORTHWEST		
Busycon	38	0.250
Haliotis	21	0.243
Argopecten	34	0.233
Chionoecetes	227	0.101
Concha	47	0.095
Sinonovacula	45	0.059
Rapana	23	0.047
Charybdis	153	0.047
Homarus	66	0.045
Todarodes	113	0.041
Ruditapes[1]	18	0.016
Acetes[1]	78	0.01
Meretrix[1]	36	0.007
Metapenaeus[1]	86	0.007
Sinonovacula[1]	18	0.006
Paphia[1]	18	0.005
Fenneropenaeus[1]	161	0.003

Note: [1]Unknown whether farmed or wild.

7.4.5 MERCURY IN SHELLFISH FROM DATA FROM THE EUROPEAN FOOD SAFETY AUTHORITY

In the data from EFSA, THg and MeHg values were reported using codes for species or species groups, rather than the less ambiguous Latin names (which are used in the literature data). Because of this, some species groups may include a wide range of species which may have very different Hg levels. Also, some species may be present both with its specific species name and as part of a larger group of species. For instance, blue mussel could be included also in the species group "mussels". The EFSA data includes samples analysed in Europe, but includes both samples of fish of European origin and fish imported to Europe from other countries.

Shellfish data reported to EFSA included 5 610 results for THg and 211 results for MeHg. Of the THg results, as many as 4 124 were reported without information about whether the samples were from shellfish farming or wild stocks. It was assumed that they were most likely from wild stocks, but they may also have been farmed. Of the shellfish for which the origin was given, 495 samples analysed for THg were reported as farmed and 891 were reported as being from wild stocks. The majority of the reported samples (THg n = 3 630) were from marine waters, while only 174 samples were from inland areas. A large portion of the samples (THg n = 1 806) were reported without indications of the origin, and these were included together with the results for marine shellfish. Analysed tissue for shellfish was not specified in the dataset, but it is assumed that edible tissue was used, either muscle tissue (for instance, for crustaceans) or the whole soft part of the animal (for instance, for bivalves).

7.4.5.1 Farmed shellfish from inland and marine waters

The dataset received from EFSA's database included only four samples of shellfish from inland aquaculture (**Table 7.17**). All were freshwater shrimps or prawns with very low mean THg concentrations. No results were reported for MeHg.

TABLE 7.17 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OR SPECIES GROUPS OF FARMED SHELLFISH FROM INLAND AND MARINE WATERS, IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg
03 SOUTH AMERICA INLAND WATERS		
Freshwater shrimps or prawns	3	0.022
05 EUROPE INLAND WATERS		
Freshwater shrimps or prawns	1	0.032
27 ATLANTIC, NORTHEAST		
Oysters	80 (71)	0.025
Mussels	103 (98)	0.022
Oyster, European	28	0.013
Blue mussel	297	0.013
Scallop, great	34	0.012
Scallops, pectens	23	0.012

Note: N is the number of analytical samples and may include both individual and composite samples.

7.4.5.2 Wild-caught shellfish from inland waters

Overall mean concentrations of THg and MeHg in shellfish species groups sampled from wild stocks (or unspecified origin) in inland waters, included 127 samples of shrimps and prawns, 37 samples of freshwater crayfish, 5 oyster samples and 1 clam sample (**Table 7.18**). All these groups had low concentrations of THg. One sample of the group "shrimps and prawns" was analysed for MeHg. This sample had relatively high MeHg, with 0.349 mg/kg. Of the different areas, freshwater shrimps or prawns from Spain (FAO area not specified), had the highest mean concentration of THg, with 0.115 mg/kg, except a single sample of crayfish from FAO area 06 Oceania with a THg level of 0.120 mg/kg (**Table 7.19**).

TABLE 7.18 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM INLAND WATERS (ALL REGIONS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	THg N	THg	MeHg N	MeHg
Clams	1	0.100		
Shrimps and prawns[1]	127	0.072	1	0.349
Freshwater crayfishes	37	0.052		
Oysters	5	0.031		

Notes: N is the number of analytical samples and may include both individual and composite samples.
[1]Includes "Freshwater shrimps and prawns" (n = 118) and "Shrimps and prawns" (n = 9).

TABLE 7.19 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg
01 AFRICA INLAND WATERS		
Freshwater shrimps or prawns	5	0.070
02 NORTH AMERICA INLAND WATERS		
Freshwater shrimps or prawns	2	0.030
03 SOUTH AMERICA INLAND WATERS		
Freshwater shrimps or prawns	7	0.038
04 ASIA INLAND WATERS		
Freshwater shrimps or prawns	27	0.048
Freshwater crayfishes	3	0.043
Shrimps and prawns	9	0.009
05 EUROPE INLAND WATERS		
Clams	1	0.100
Freshwater crayfishes	33	0.051
Freshwater shrimps or prawns	26	0.070
Oysters	5	0.031
06 OCEANIA INLAND WATERS		
Freshwater crayfishes	1	0.120
Freshwater shrimps or prawns	1	0.010
CANADA, UNSPECIFIED		
Freshwater shrimps or prawns	2	0.054
GREENLAND, UNSPECIFIED		
Freshwater shrimps or prawns	1	0.050
SPAIN, UNSPECIFIED		
Freshwater shrimps or prawns	48	0.115

Note: N is the number of analytical samples and may include both individual and composite samples.

7.4.5.3 Wild-caught shellfish from marine waters

The data received from EFSA contained THg in 4 529 samples of marine shellfish originating from wild stocks, belonging to 39 different species or species groups, where 32 had a sample number of 10 or greater (**Table 7.20**). MeHg was analysed in 209 samples of 19 species or groups. All groups had mean THg concentrations below 0.2 mg/kg. Tissue samples include muscle (most crustaceans), whole body or soft or edible parts (most bivalves). Edible crab, common octopus and Norway lobster had the highest mean THg concentrations, with mean concentrations around 0.14 mg/kg. When comparing species or species groups in different areas, common octopus from Spain (FAO area not specified) had the highest mean THg concentration, with 0.26 mg/kg (**Table 7.21**), followed by shrimps and prawns from the Mediterranean and Black Sea area, with 0.20 mg/kg. Shrimps and prawns from the Mediterranean and Black Sea area had higher mean THg than shrimps and prawns from all other areas where this group was included.

Results for MeHg included much fewer samples than the results for THg, and mean concentrations of MeHg where higher than THg for Norway lobster, common shrimp and shrimps and prawns, but lower for most species (**Table 7.20**).

TABLE 7.20 MEAN TOTAL MERCURY (THg) AND METHYLMERCURY (MeHg) LEVELS IN SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM MARINE WATERS (ALL REGIONS), IN mg/kg WET WEIGHT

SPECIES/SPECIES GROUP	N	THg	N	MeHg
Edible crab	100	0.141		
Octopus, common	68	0.137	4	0.121
Lobster, Norway	169	0.137	5	0.160
Crabs, sea-spiders	281	0.123		
Lobsters	33	0.102		
Freshwater shrimps or prawns	36	0.096	1	0.020
Spiny and rock lobsters	12	0.081		
Cuttlefish, common	32	0.081	8	0.034
Freshwater crayfishes	36	0.071		
Crustaceans	20	0.061		
Cuttlefishes	157	0.055	15	0.016
Clams, cockles, arkshells	21	0.050		
Squids	238	0.049	15	0.036
Razor clam	22	0.048	13	0.010
Shrimps and prawns	628	0.045	29	0.138
Octopus, curled	106	0.043		
Cockles	153	0.039		
Water snails, conches and whelks	23	0.039		
Clams	314	0.038	22	0.011
Shrimps, common	312	0.036	20	0.083
Squids, cuttlefishes, octopuses	18	0.036		
Oysters	500	0.035		
Scallops, pectens	257	0.030		
Mussels	950	0.030	71	0.012
Octopuses	37	0.026		
Scallop, queen	93	0.025		
Prawn, northern	84	0.024		
Blue mussel	44	0.022		
White shrimp	11	0.021	2	0.015
Metapenaeus shrimps	27	0.012		
Oyster, European	20	0.011		
Scallop, great	20	0.011	4	0.020

Notes: N is the number of analytical samples and may include both individual and composite samples. Cases where N < 10 are excluded.

TABLE 7.21 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT

SPECIES/ SPECIES GROUP	N	THg
21 ATLANTIC, NORTHWEST		
Scallops, pectens	17	0.038
Oysters	23	0.017
27 ATLANTIC, NORTHEAST		
Edible crab	79	0.143
Crabs, sea-spiders	187	0.136
Lobsters	13	0.133
Lobster, Norway	156	0.127
Freshwater crayfishes	35	0.073
Crustaceans	20	0.061
Octopus, curled	17	0.058
Shrimps, common	91	0.053
Squids	38	0.051
Cuttlefishes	16	0.051
Water snails, conches and whelks	16	0.042
Octopus, common	18	0.041
Oysters	181	0.039
Scallops, pectens	156	0.038
Cockles	99	0.037
Shrimps and prawns	81	0.036
Clams	118	0.033
Mussels	515	0.028
Scallop, queen	52	0.028
Blue mussel	38	0.023
Oyster, European	20	0.011
Scallop, great	20	0.011
31 ATLANTIC, WESTERN CENTRAL		
Shrimps and prawns	23	0.046
34 ATLANTIC, EASTERN CENTRAL		
Cuttlefishes	17	0.045
37 MEDITERRANEAN AND BLACK SEA		
Shrimps and prawns	21	0.201
Freshwater shrimps or prawns	18	0.152
Octopus, curled	12	0.095
Mussels	19	0.038
Oysters	26	0.038
41 ATLANTIC, SOUTHWEST		
Squids	12	0.063
Shrimps and prawns	14	0.030
Scallops, pectens	12	0.023
51 INDIAN OCEAN, WESTERN		
Squids	13	0.056
57 INDIAN OCEAN, EASTERN		
Shrimps and prawns	53	0.013
Shrimps, common	29	0.012
61 PACIFIC, NORTHWEST		
Crabs, sea-spiders	19	0.064
Squids	40	0.035
Shrimps and prawns	16	0.023
71 PACIFIC WESTERN CENTRAL		
Squids	10	0.029
Shrimps and prawns	34	0.014
Shrimps, common	24	0.010
81 PACIFIC, SOUTHWEST		
Mussels	25	0.033
87 PACIFIC, SOUTHEAST		
Squids	16	0.044
Mussels	78	0.025
Scallop, queen	18	0.023
Scallops, pectens	15	0.023
Shrimps and prawns	39	0.022
CANADA, UNSPECIFIED		
Lobsters	12	0.074
France, unspecified		
Edible crab	10	0.150
Crabs, sea-spiders	10	0.122
Clams	11	0.046
Cockles	35	0.038
Oysters	255	0.032
Mussels	97	0.029
Scallop, queen	11	0.021
Shrimps and prawns	15	0.016
Shrimps, common	12	0.008
Greenland, unspecified		
Crabs, sea-spiders	15	0.046
Prawn, northern	58	0.027
Scallops, pectens	18	0.016

TABLE 7.21 MEAN TOTAL MERCURY (THg) LEVELS IN SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS), IN mg/kg WET WEIGHT (cont.)

SPECIES/ SPECIES GROUP	N	THg
INDIA, UNSPECIFIED		
Squids	25	0.034
Shrimps and prawns	43	0.020
Cuttlefishes	29	0.019
Octopuses	13	0.014
Shrimps, common	16	0.011
INDIAN OCEAN, UNSPECIFIED		
Shrimps and prawns	23	0.016
SPAIN, UNSPECIFIED		
Octopus, common	27	0.258
Shrimps and prawns	78	0.160
Crabs, sea-spiders	16	0.142
Shrimps, common	30	0.080
Cuttlefishes	65	0.074
Cuttlefish, common	12	0.067
Squids	45	0.066
Clams, cockles, arkshells	15	0.058
Clams	118	0.051
Razor clam	11	0.047
Mussels	186	0.038
Octopus, curled	44	0.034
Cockles	11	0.027
VIET NAM, UNSPECIFIED		
Clams	34	0.015
Prawn, northern	10	0.014
Metapenaeus shrimps	12	0.012
Shrimps and prawns	134	0.011
Shrimps, common	66	0.010
Mussels	10	0.010

Notes: N is the number of analytical samples and may include both individual and composite samples. Cases where N < 10 are excluded.

7.4.6 MERCURY IN SHELLFISH, SUMMARY

The data from both the literature and the EFSA database on Hg in farmed shellfish and in shellfish from inland waters was very limited and included few species or species groups. Farmed shellfish from inland waters all had very low Hg concentrations. In general, wild-caught shellfish from inland waters also had low concentrations. Two species with mean THg levels exceeding 0.5 mg/kg were represented with results from only two and five samples, which does not provide sufficiently conclusive evidence. Apart from these, only one species from the literature, red swamp crayfish (*Procambrus clarkii*) from Europe, and one group in the EFSA data, freshwater shrimps and prawns from Spain, had mean THg concentrations higher than 0.1 mg/kg.

According to data from both the literature and EFSA, farmed marine shellfish (all bivalves) also had very low Hg levels. Marine shellfish captured from wild stocks was the most diverse category of shellfish with the largest volume of Hg data and the largest number of species or species groups, both from the literature and from EFSA. Consequently, the range of Hg concentrations was also wider. However, Hg levels were generally low also in wild-caught marine shellfish, with only the Norway lobster from the Mediterranean and Black Sea area having a mean THg concentration slightly above 0.5 mg/kg.

Both the EFSA data and the data from the literature showed that, in general, in the different areas, the highest Hg levels were found in decapod crustaceans such as lobsters, crabs and shrimps and prawns, as well as in octopuses. In the literature data, some gastropod genera (abalone and whelk) from the Northwest Pacific and one gastropod from the Mediterranean (*Hexaplex*, murex) also had among the highest mean THg concentrations in those areas. Bivalves in general had very low THg concentrations.

It is difficult to compare geographical areas, since different species are represented in the different areas and very different amounts of data have been reported from the different areas. In the literature data, the Mediterranean and Black Sea area (FAO area 37) had the highest number of genera with Hg concentrations higher than 0.2 mg/kg, followed by Northwest Pacific (FAO area 61) and Northeast Atlantic (FAO area 27). In the EFSA data, this geographical trend was not as clear, having only one species group with THg > 0.2 mg/kg; but here the Hg concentrations in general were lower. At least part of the geographical differences may be due to different species analysed in the different areas. However, for some genera or species groups, including *Nephrops*, *Penaeus* and the group shrimps and prawns, mean THg concentrations in samples from the Mediterranean and Black Sea area were higher than in those from other parts of the world.

7.5 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN FINFISH AND SHELLFISH FROM DIFFERENT REGIONS AROUND THE WORLD

7.5.1 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN FINFISH FROM THE LITERATURE REVIEW

In the literature, results for dioxins and dl-PCBs were found for 2 408 analysed samples of finfish. Of these, 805 samples were from farmed fish, while the rest were from wild stocks (1 139 samples) or unknown (464 samples were sampled at market with no information about their origin). Most of the analysed finfish originated from marine waters (1 915 samples), while 461 finfish samples were from inland waters or unknown (32 finfish samples were sampled at market with no information about their origin).

7.5.1.1 Farmed finfish from inland and marine waters

Farmed finfish from inland and marine waters had generally low concentrations of dioxins and dl-PCBs (**Table 7.22**), and only one species, milk fish (*Chanos chanos*), from Asia inland waters, had a high mean value of sum dioxins of 4.36 ng TEQ/kg. The rest of the species in this category had mean concentrations of both sum dioxins and sum dioxins + dl-PCBs of 0.513 ng TEQ/kg or lower.

TABLE 7.22 MEAN CONCENTRATIONS OF SUM DIOXINS, SUM DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND SUM DIOXINS AND dl-PCBs IN FARMED FINFISH FROM DIFFERENT INLAND AND MARINE REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

FAO AREA/SPECIES LATIN NAME	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
04 ASIA INLAND WATERS				
Chanoschanos	4	4.36		
Oreochromis mossambicus	46	0.354		
Elops machnata	3	0.237		
27 ATLANTIC, NORTHEAST				
Salmo salar	738	0.273	0.247	0.513
37 MEDITERRANEAN AND BLACK SEA				
Salmo salar	2	0.117	0.390	0.507

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N =1 are excluded.

7.5.1.2 Wild-caught finfish from inland waters

For wild-caught finfish from inland waters, the literature review showed that the concentrations of dioxins and dl-PCBs were relatively low for most of the species investigated (**Table 7.23**). The highest mean values of dioxins+dl-PCBs were found in muscle of grass carp (*Ctenopharyngodon idella*) and goldfish (*Carassius aurata*) from Asia. The concentrations in these species, 38–49 ng TEQ/kg wet weight, were far above 6.5 ng TEQ/kg (maximum level in the European Union), but the results were based on very few samples and should be interpreted with caution. High levels of dioxins+dl-PCBs were also found in whole fish of lake trout (*Salvelinus namaycush*) and whole fish of walleye (*Sander vitreus*), from North America (12.6–29.5 ng TEQ/kg wet weight). In general, whole fish have higher levels than muscle tissue from the same species, and muscle of lake trout had a much lower mean concentration of dioxins than whole fish of this species. The difference between whole fish and muscle tissue could also be seen for chub (*Squalius cephalus*), from Europe, where whole fish had concentrations of dioxins+dl-PCBs more than two times higher than muscle tissue (**Table 7.23**). Apart from the species mentioned above, no other species had mean concentrations of dioxins and dl-PCBs above 6.5 ng TEQ/kg, and only one other species, wels catfish (Silurus glanis), from Europe, had mean concentrations of dioxins and dl-PCBs in muscle tissue above 3.0 ng TEQ/kg (**Table 7.23**).

7.5.1.3 Wild-caught finfish from marine waters

Finfish sampled from wild stocks (or unknown) in marine waters made up the largest volume of results published in the literature for dioxins and dl-PCBs. **Table 7.24** provides results for muscle tissue (per FAO area and genus). The highest mean values for dioxins in muscle tissue were found in five genera from FAO area 61 Pacific, Northwest – *Elops*, *Liza*, *Chanos*, *Nematolosa* and *Oreochromis*, with concentrations between 5.35 and 330 ng TEQ/kg. All these results came from the

TABLE 7.23 MEAN CONCENTRATIONS OF SUM DIOXINS, SUM DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND SUM DIOXINS AND dl-PCBs IN SPECIES OF WILD FINFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT/kg WET WEIGHT)

FAO AREA/SPECIES LATIN NAME	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
01 AFRICA INLAND WATERS				
Lates niloticus	31	0.030	0.063	
Oreochromis niloticus	31	0.027	0.030	
02 NORTH AMERICA INLAND WATERS				
Salvelinus namaycush (muscle)	12	2.02		
Salvelinus namaycush (whole)	71	4.93	23.6	29.5
Sander vitreus (whole)	4	2.77	9.86	12.6
04 ASIA INLAND WATERS				
Carassius auratus	5			49
Ctenopharyngodon idella	5			38
Cyprinus carpio	16	0.31	0.37	0.68
Silurus asotus	16	0.090	0.13	0.22
Carassius carassius	13	0.020	0.060	0.09
05 EUROPE INLAND WATERS				
Squalius cephalus (whole)	4	0.698	5.02	5.74
Silurus glanis	31	0.17	2.78	3.1
Abramis brama	26	0.89	1.19	2.4
Squalius cephalus (muscle)	10	0.37	2.12	2.3
Abramis bjoerkena	3	0.85	1.22	2.1
Oncorhynchus mykiss (whole)	4	0.230	1.53	1.74
Coregonus renke	2	0.26	0.69	0.940
Rutilus rutilus	32	0.20	0.56	0.763
Perca fluviatilis	45	0.13	0.36	0.495
Barbus barbus (whole)	2	0.125	0.28	0.41
Esox lucius	17	0.14	0.20	0.340
Stizostedion lucioperca	9	0.13	0.18	0.305
Anguilla anguilla	16			0.013

Notes: N is the number of analytical samples, including both individual and composite samples. The number of samples analysed for dioxins, dl-PCBs and dioxins+dl-PCBs may be different for some species. Cases where N = 1 are excluded. Where whole fish was analysed, this is indicated; otherwise, muscle tissue was analysed.

same study (Liao *et al.*, 2016) with samples collected from a closed saltwater pond in China at the site of a former chloralkali factory, which likely explains the high values of dioxins. Apart from these genera, the remaining species in this category had mean values of dioxins below 2.0 ng TEQ/kg and dioxins+dl-PCBs below 3.8 ng TEQ/kg (**Table 7.24**).

Results for whole body tissue of wild-caught finfish from marine waters published in the literature are given in **Table 7.25**. Results for whole fish were available for four different species from FAO area 27 (Atlantic, Northeast), with mean values of dioxins and dl-PCBs between 1.6 and 2.0 ng TEQ/kg.

TABLE 7.24 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF WILD FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), BY GENUS (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

GENUS OR OTHER DESCRIPTION	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
27 ATLANTIC, NORTHEAST				
Sprattus	30	1.79	1.95	3.74
Salmo	141	1.13	2.00	3.13
«Sea bass»	25	0.440	2.06	2.50
Clupea	45	0.990	0.920	1.91
Platichthys	23	0.870	0.940	1.82
Scomber	41	0.430	0.970	1.40
«Grey mullet»	26	0.140	0.530	0.670
Scophthalmus	16	0.170	0.500	0.670
«Sharks»	14	0.120	0.210	0.320
Gadus	40	0.105	0.151	0.257
Sebastes	2	0.157	0.388	
Zoarces	15	0.675		
37 MEDITERRANEAN AND BLACK SEA				
Sarda	3	0.458	3.23	3.69
Thunnus	26	1.90	0.700	2.60
«Sardine»	3	0.270	2.13	2.39
Scomber	5	0.366	1.81	2.17
Mullus	2	0.231	1.90	2.13
Boops	3	0.352	1.05	1.40
Xiphias	52	0.179	1.09	1.27
«Anchovy»	2	0.091	1.08	1.17
«Tuna»	2	0.042	0.58	0.622
Trachurus	6	0.332	0.27	0.602
Gadus	39	0.065	0.495	0.561
Merluccius	5	0.217	0.134	0.351
Solea	2	0.057	0.170	0.227
27 ATLANTIC NORTHEAST OR 37 MEDITERRANEAN AND BLACK SEA				
Thunnus	2	0.080	1.24	1.32
Solea	2	0.130	0.260	0.390
Sebastes	2	0.140	0.190	0.330
Mullus	2	0.100	0.170	0.270
Merluccius	2	0.040	0.140	0.180
41 ATLANTIC, SOUTHWEST				
Micropogonias	14	0.110		
48 ATLANTIC, ANTARCTIC				
Trematomus	10	0.360		
Chionodraco	11	0.089		
61 PACIFIC, NORTHWEST				
Pagrus	13	0.600	0.880	1.47

TABLE 7.24 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF WILD FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS), BY GENUS (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

GENUS OR OTHER DESCRIPTION	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
Okamejei	12	0.470	0.730	1.20
Scomber	15	0.410	0.700	1.12
Hippoglossus	5	0.140	0.830	0.970
Selachimorpha	15	0.210	0.720	0.930
Arctoscopus	11	0.260	0.610	0.870
Larimichthys	29	0.256	0.888	0.784
Theragra	33	0.135	0.420	0.555
Astroconger	15	0.122	0.100	0.444
Pleurogrammus	15	0.060	0.330	0.390
Cololabis	16	0.114	0.271	0.385
Pleuronectes	17	0.140	0.230	0.370
Mugil	11	0.148	0.200	0.369
Ostracion	14	0.060	0.300	0.360
Trichiurus	17	0.136	0.314	0.354
Clupea	17	0.210	0.095	0.305
Stephanolepis	16	0.060	0.240	0.300
Lophiomus	12	0.110	0.180	0.290
Scomberomorus	7	0.107	0.168	0.285
Paralichthys	2	0.152	0.200	0.276
Sebastes	17	0.040	0.210	0.250
Pampus	11	0.073	0.040	0.220
Miichthys	11	0.055	0.210	0.206
Gadus	15	0.063	0.092	0.155
Engraulis	9	0.046	0.010	0.150
Lateolabrax	14	0.074	0.192	0.128
Konosirus	10	0.030	0.080	0.110
Pleuronichthys	17	0.030	0.050	0.080
Cynoglossus	8	0.040	0.030	0.060
Thunnus	12	0.040	0.020	0.050
Misgurnus	16	0.030	0.020	0.040
Elops	7	330		
Liza	2	58.8		
Chanos	3	51		
Nematalosa	4	27		
Oreochromis	2	5.35		
«Hairtail»	5			0.946
«Flatfish»	5		1.28	
«Spanish mackerel»	10		1.65	

Notes: N is the number of analytical samples, including both individual and composite samples. The number of samples analysed for dioxins, dl-PCBs and dioxins+dl-PCBs may be different for some species. Cases where N = 1 are excluded.

TABLE 7.25 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN WHOLE BODY TISSUE OF SPECIES OF WILD FINFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

FAO AREA/ SPECIES LATIN NAME	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
27 ATLANTIC, NORTHEAST				
Maurolicus muelleri	4	1.10	0.97	2.00
Sprattus sprattus	25	0.910	1.09	2.00
«Sardine»	16	0.400	1.57	1.97
Benthosema glaciale	5	0.770	0.84	1.60

Note: N is the number of analytical samples, including both individual and composite samples.

7.5.2 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS FROM DATA FROM THE EUROPEAN FOOD SAFETY AUTHORITY

In the data from EFSA, values for dioxins and dl-PCBs were reported using codes for species or species groups, rather than the less ambiguous Latin names (which are used in the literature data). Because of this, some species groups may include a wide range of species which may have very different levels of dioxins and dl-PCBs. Also, some species may be present both with their specific species names and in terms of a larger group of species. For instance, the species named Atlantic salmon could be included also in the species groups "salmons" or "salmons, trouts, smelts". The EFSA data includes samples analysed in Europe, but includes both samples of fish of European origin and fish imported to Europe from other countries. Analysed tissue for finfish was muscle tissue ("fish meat"), and no data for dioxins and dl-PCBs in whole fish were available from the EFSA data.

The final dataset on dioxins and dl-PCBs compiled from the EFSA data contained 7 668 analysed samples of finfish. Of these, 7 438 samples had results for both dioxins and dl-PCBs (all 29 congeners), 42 samples had results only for dioxins (17 congeners) and 188 samples had results only for dl-PCBs (12 congeners). Of the analysed finfish, 1 142 samples were from farmed shellfish, 3 925 samples were from wild stocks, and the remaining 2 601 samples were reported without indications as to whether the samples were from farmed or wild-caught finfish. These unspecified samples were assumed to be from wild stocks and combined with the wild-caught finfish, even if they may have been farmed. Most of the analysed shellfish originated from marine waters (6 524 samples), while 1 033 samples were reported to be from inland waters. For the remaining 111 samples, this information was not given, and these unspecified samples were included together with the results for marine finfish.

7.5.2.1 Farmed finfish from inland waters

Farmed finfish from inland waters had generally low concentrations of dioxins and dl-PCBs (**Table 7.26**), but the number of samples in this category was limited. The highest mean value of dioxins and dl-PCB, 3.36 ng TEQ/kg, was found in European eel (only two samples), while the rest of the species and species groups in this category had mean concentrations of both sum dioxins and sum dioxins+dl-PCBs below 0.6 ng TEQ/kg.

TABLE 7.26 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF FARMED FINFISH FROM INLAND WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Eel, European	2	0.352	2	3.01	2	3.36
Freshwater bream, Europe	11	0.271	11	0.292	11	0.563
Carp, common	33	0.163	33	0.345	33	0.508
Carps	16	0.133	16	0.330	16	0.463
Salmons, trouts, smelts	2	0.116	2	0.325	2	0.441
Whitefishes or coregonus	3	0.110	4	0.407	2	0.404
Salmons	2	0.087	2	0.247	2	0.334
Trouts	9	0.039	9	0.140	9	0.179
Chum salmon	2	0.049	2	0.065	2	0.114
Tilapias and similar	7	0.035	7	0.008	7	0.044
Pangas catfishes	6	0.007	6	0.007	6	0.014

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.2.2 Farmed finfish from marine waters

Farmed finfish from marine (and unspecified) waters had low mean concentrations for dioxins and dl-PCBs for most species and species groups (**Table 7.27**). The highest mean values of dioxins and dl-PCBs were found in the species group "whitefishes or coregonus" with sum dioxins of 8.55 ng TEQ/kg and sum dioxins and dl-PCBs of 12.2 ng TEQ/kg. The results for this species group were, however, based on only four samples and should be interpreted with caution. The sample number was limited for most species/species groups in this category, except for Atlantic salmon, rainbow trout and trouts. Apart from the whitefishes or coregonus group, all species or species groups in this category had mean values of dioxins and dl-PCBs of 2.05 ng TEQ/kg or lower (**Table 7.27**).

7.5.2.3 Wild-caught finfish from inland waters

For wild-caught (or unspecified) finfish from inland waters, the EFSA data showed that the concentrations of dioxins and dl-PCBs were well below 6.5 ng TEQ/kg (maximum level in the European Union) for most species and species groups (**Table 7.28**). Only three species and species groups (river eels, European eel and barbs from FAO area 05 Europe), had higher mean values of dioxins and dl-PCBs, between 8.24 and 9.12 ng TEQ/kg. Dl-PCBs contributed most to the total sum for these three species and species groups, and the mean values for sum dioxins in these species groups were not particularly high (0.803-1.15 ng TEQ/kg). All other species and species groups had mean concentrations of sum dioxins and dl-PCBs below 2.0 ng TEQ/kg. Most of the samples originated from FAO area 05 Europe, and most of the species and species groups were different between the different FAO areas. Two species and species groups, perch and European perch, were reported from both FAO area 05 Europe and FAO area 01 Africa, and for these two species and species groups, the concentrations of dioxins and dl-PCBs were higher in Europe than in Africa.

TABLE 7.27 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF FARMED FINFISH FROM MARINE WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Whitefishes or coregonus	4	8.55	4	3.64	4	12.19
Brown trout	4	1.09	4	0.960	4	2.05
Herrings	2	0.891	2	1.05	2	1.94
River eels	5	0.317	5	1.06	5	1.37
Salmons, trouts, smelts	15	0.472	18	1.08	13	1.37
Halibut, Atlantic	10	0.313	10	0.666	10	0.980
Arctic char	8	0.206	8	0.557	8	0.764
Char	2	0.171	2	0.442	2	0.613
Atlantic salmon	675	0.247	675	0.315	675	0.563
Gilthead seabream	2	0.112	2	0.431	2	0.543
Turbot	7	0.153	7	0.340	7	0.493
Trouts	95	0.117	94	0.319	94	0.436
Rainbow trout	110	0.133	110	0.215	110	0.348
Sturgeon	13	0.161	13	0.179	13	0.340
Sea bass	30	0.047	30	0.279	30	0.326
Sea bream	39	0.062	38	0.221	37	0.280
Salmons	4	0.054	4	0.125	4	0.179
Cod	2	0.030	2	0.010	2	0.040

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.2.4 Wild-caught finfish from marine waters

Finfish sampled from wild stocks (or unknown) in marine waters made up the largest volume of results reported in the EFSA dataset for dioxins and dl-PCBs, and results for a wide range of species/species groups from several different geographical areas were reported (**Table 7.29** and **Table 7.30**). When the results were summarized independent of geographic origin (**Table 7.29**), mean values for all species/species groups were below 3.5 ng TEQ/kg for dioxins and below 6.5 ng TEQ/kg for dioxins and dl-PCBs (maximum levels in European Union). Nevertheless, several species/species groups, such as whitefishes or coregonus, smelt, shads, European eel and river eels had quite high mean concentrations of sum dioxins and sum dioxins and dl-PCBs, close to these levels. When the results were summarized for species/species groups within different areas (**Table 7.30**), the highest mean values of dioxins and dl-PCBs were found for tuna from FAO area 37 (Mediterranean and Black Sea), at 26.1 ng TEQ/kg, and shads from FAO area (27 Atlantic Northeast), 7.49 ng TEQ/kg. These results were, however, based on very few samples and should therefore be interpreted with caution. Tuna from several other areas around the world had much lower concentrations of dioxins and dl-PCBs. No other species/species groups had concentrations of dioxins and dl-PCBs above 6.5 ng TEQ/kg, but several species/species groups from FAO area 27 (Atlantic, Northeast) had

relatively high mean values of dioxins and dl-PCBs, up to 6.19 ng TEQ/kg (**Table 7.30**).

TABLE 7.28 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
01 AFRICA INLAND WATERS						
Perch	16	0.016	17	0.024	16	0.041
Nile perch	5	0.018	5	0.013	5	0.031
Perch, European	2	0.015	2	0.008	2	0.024
04 ASIA INLAND WATERS						
Pangas catfishes	44	0.056	45	0.013	44	0.069
Tilapias and similar	2	0.024	2	0.007	2	0.032
05 EUROPE INLAND WATERS						
River eels	245	0.804	248	8.24	245	9.12
Eel, European	60	0.803	60	7.93	60	8.74
Barbs	20	1.15	21	6.97	20	8.24
Brook trout	2	0.146	2	1.84	2	1.98
Freshwater bream - Europe	104	0.405	104	1.32	102	1.74
Whitefishes or coregonus	54	0.407	61	0.983	54	1.42
Salmons	5	0.294	5	0.995	5	1.29
Northern pike	45	0.158	45	0.686	45	0.844
Perch, European	15	0.129	15	0.673	15	0.801
Roaches	23	0.149	23	0.611	23	0.760
Perch	35	0.156	37	0.500	35	0.681
Pike	4	0.144	4	0.416	4	0.560
Pike-perch	13	0.149	13	0.314	13	0.463
Carp, common	56	0.105	57	0.347	56	0.457
Carps	43	0.206	42	0.239	41	0.456
River lamprey	3	0.068	3	0.373	3	0.441
Salmons, trouts, smelts	2	0.109	2	0.297	2	0.406
Brown trout	3	0.060	3	0.242	3	0.303
Trouts	37	0.047	37	0.217	37	0.264
Catfishes (freshwater)	5	0.057	5	0.160	5	0.217
Rainbow trout	18	0.042	18	0.170	18	0.212
Char	21	0.060	22	0.215	21	0.193
African catfish	3	0.014	3	0.039	3	0.053

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

TABLE 7.29 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD (OR UNSPECIFIED) FINFISH FROM MARINE OR UNSPECIFIED WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Whitefishes or coregonus	56	3.02	56	2.97	56	5.98
Smelt	3	2.67	3	2.61	3	5.27
Shads	5	0.865	5	3.92	5	4.78
Eel, European	39	0.715	39	3.84	39	4.56
River eels	57	1.24	58	2.92	57	4.19
Herring, Baltic	68	2.53	68	1.31	68	3.84
Sprat	97	1.45	98	1.74	97	3.18
Salmons, trouts, smelts	79	0.810	65	1.70	61	2.77
Atlantic salmon	202	1.03	202	1.68	202	2.71
Conger	2	0.326	2	2.19	2	2.52
Mackerel, Atlantic	110	0.515	110	1.72	110	2.24
Herrings	506	1.16	510	1.07	505	2.24
Herring, Atlantic	128	1.22	128	0.901	128	2.12
Mackerel, chub	2	0.164	2	1.75	2	1.91
Mackerel	309	0.621	328	1.30	309	1.88
Brown trout	4	0.768	4	0.953	4	1.72
Flounders	22	0.763	22	0.934	22	1.70
Garfish	3	0.337	3	1.30	3	1.64
European sardine	91	0.308	91	1.22	91	1.53
Halibut, Greenland	90	0.607	90	0.885	90	1.49
Trouts	225	0.603	228	0.785	223	1.41
Halibut, Atlantic	466	0.408	466	0.999	466	1.41
Sardines and sardine-type fishes	71	0.246	81	1.17	71	1.37
Herring, Pacific	3	0.622	3	0.604	3	1.23
Atlantic mackerel	30	0.357	30	0.820	30	1.18
Brook trout	6	0.087	6	1.079	6	1.17
Salmons	321	0.384	333	0.744	321	1.14
Mullets	8	0.209	10	0.692	8	1.07
Sea bream	4	0.223	4	0.735	4	0.958
Turbot	14	0.295	14	0.627	14	0.922
Herrings, sardines, anchovies	3	0.179	4	0.946	3	0.860
Sturgeon	6	0.372	6	0.430	6	0.802
Char	6	0.208	6	0.564	6	0.772
Tuna	207	0.063	214	0.722	197	0.740
Sea bass	160	0.113	165	0.571	160	0.685
Beaked redfish	525	0.199	525	0.416	525	0.615
Golden redfish	227	0.208	227	0.395	227	0.603
Halibut	4	0.172	4	0.395	4	0.567
Plaice	101	0.221	149	0.277	101	0.501
Brill	5	0.168	5	0.307	5	0.475

TABLE 7.29 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD (OR UNSPECIFIED) FINFISH FROM MARINE OR UNSPECIFIED WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Swordfish	35	0.066	35	0.387	35	0.453
Plaice, European	74	0.171	74	0.267	74	0.439
Anchovies	4	0.103	4	0.322	4	0.426
Gilthead seabream	7	0.103	7	0.315	7	0.418
Cod	385	0.105	404	0.236	385	0.349
Pangas catfishes	22	0.152	22	0.180	22	0.332
Rainbow trout	98	0.091	98	0.207	98	0.297
Hakes	79	0.073	84	0.221	79	0.293
Sole	39	0.118	41	0.157	39	0.278
Ocean perch	25	0.100	25	0.176	25	0.276
Horse mackerels	8	0.104	8	0.141	8	0.245
Whiting	15	0.109	15	0.135	15	0.244
Pink salmon	5	0.064	5	0.174	5	0.238
Wolffishes	4	0.129	4	0.102	4	0.231
Dab or common dab	7	0.092	7	0.125	7	0.217
Dolphinfishes	4	0.046	4	0.166	4	0.212
Tuna and bonito (generic)	2	0.089	2	0.115	2	0.204
Sharks	12	0.058	12	0.094	12	0.152
Rays	16	0.069	17	0.080	16	0.151
Haddock	95	0.068	96	0.054	95	0.122
Rat fish	2	0.077	2	0.040	2	0.117
Anglerfish, monkfish and stargazers	56	0.051	56	0.053	56	0.104
Pollack, pollock	2	0.058	2	0.035	2	0.093
Coalfish	50	0.026	51	0.053	50	0.078
Pollack	36	0.058	36	0.016	36	0.075
Cod, Atlantic	44	0.017	44	0.048	44	0.065
Tuna, bigeye	6	0.014	6	0.040	6	0.055
Bonito, Eastern Pacific	2	0.019	2	0.035	2	0.054
Tuna, yellowfin	2	0.015	2	0.025	2	0.039
Snappers	10	0.013	10	0.020	10	0.032
Freshwater bream - Europe	2	0.005	2	0.016	2	0.021
Pacific salmon (generic)	10	0.003	9	0.007	9	0.011

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

TABLE 7.30 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
18 ARCTIC SEA						
Halibut, Greenland	4	0.381	4	0.686	4	1.07
Atlantic salmon	2	0.061	2	0.163	2	0.225
21 ATLANTIC, NORTHWEST						
Mackerel, Atlantic	3	0.700	3	2.11	3	2.81
European sardine	3	0.464	3	2.06	3	2.53
Halibut, Atlantic	19	0.308	19	0.562	19	0.870
Mackerel	2	0.170	2	0.648	2	0.818
Halibut, Greenland	9	0.259	9	0.377	9	0.636
Atlantic salmon	4	0.098	4	0.202	4	0.300
Sea bass	2	0.030	2	0.236	2	0.266
Coalfish	2	0.028	2	0.106	2	0.135
Rays	4	0.054	4	0.063	4	0.117
Cod, Atlantic	2	0.014	2	0.101	2	0.115
Cod	8	0.021	8	0.040	8	0.061
Haddock	4	0.016	4	0.042	4	0.058
27 ATLANTIC, NORTHEAST						
Shads	2	1.26	2	6.22	2	7.49
Whitefishes or coregonus	54	3.12	54	3.07	54	6.19
Eel, European	29	0.910	29	4.81	29	5.72
Smelt	3	2.67	3	2.60	3	5.27
River eels	55	1.28	56	3.01	55	4.32
Herring, Baltic	68	2.53	68	1.31	68	3.84
Sprat	97	1.45	98	1.73	97	3.18
Salmons, trouts, smelts	70	0.894	57	1.90	53	3.12
Atlantic salmon	178	1.16	178	1.88	178	3.04
Herrings	499	1.17	500	1.08	498	2.25
Mackerel, Atlantic	86	0.511	86	1.64	86	2.15
Herring, Atlantic	127	1.22	127	0.897	127	2.12
Mullets	3	0.374	3	1.69	3	2.07
Halibut, Greenland	41	0.890	41	1.17	41	2.06
Mackerel	279	0.661	283	1.30	279	1.98
Brown trout	4	0.768	4	0.953	4	1.72
Flounders	22	0.763	22	0.934	22	1.70
Sea bass	32	0.255	33	1.40	32	1.69
Trouts	181	0.735	181	0.952	181	1.69
Garfish	3	0.337	3	1.30	3	1.64
European sardine	63	0.336	63	1.14	63	1.48
Halibut, Atlantic	428	0.411	428	1.03	428	1.44

TABLE 7.30 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Sardines and sardine-type fishes	44	0.278	44	1.05	44	1.33
Salmons	280	0.423	291	0.811	280	1.25
Herring, pacific	3	0.622	3	0.604	3	1.23
Atlantic mackerel	30	0.357	30	0.820	30	1.18
Brook trout	6	0.087	6	1.08	6	1.17
Sea bream	4	0.223	4	0.735	4	0.958
Turbot	14	0.295	14	0.627	14	0.922
Herrings, sardines, anchovies	3	0.179	3	0.681	3	0.860
Sturgeon	6	0.372	6	0.430	6	0.802
Char	6	0.208	6	0.564	6	0.772
Beaked redfish	525	0.199	525	0.416	525	0.615
Golden redfish	227	0.208	227	0.395	227	0.603
Plaice	82	0.264	127	0.309	82	0.601
Swordfish	3	0.104	3	0.418	3	0.522
Brill	5	0.168	5	0.307	5	0.475
Plaice, European	68	0.184	68	0.288	68	0.472
Cod	348	0.114	358	0.258	348	0.377
Sole	29	0.149	29	0.202	29	0.351
Hakes	54	0.082	54	0.268	54	0.350
Pangas catfishes	21	0.159	21	0.189	21	0.348
Ocean perch	21	0.114	21	0.203	21	0.316
Rainbow trout	92	0.093	92	0.209	92	0.301
Horse mackerels	7	0.104	7	0.147	7	0.251
Anchovies	2	0.078	2	0.161	2	0.239
Wolffishes	4	0.129	4	0.102	4	0.231
Dab or common dab	7	0.092	7	0.125	7	0.217
Whiting	14	0.114	14	0.101	14	0.215
Rays	9	0.086	9	0.089	9	0.175
Sharks	11	0.062	11	0.099	11	0.161
Haddock	76	0.080	77	0.058	76	0.139
Rat fish	2	0.077	2	0.040	2	0.117
Anglerfish, monkfish and stargazers	54	0.053	54	0.054	54	0.106
Tuna	43	0.032	37	0.053	35	0.093
Pollack, pollock	2	0.058	2	0.035	2	0.093
Coalfish	40	0.024	40	0.055	40	0.080
Pollack	36	0.058	36	0.016	36	0.075
Cod, Atlantic	39	0.016	39	0.047	39	0.064
31 ATLANTIC, WESTERN CENTRAL						
Snappers	7	0.012	7	0.021	7	0.032

TABLE 7.30 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Eel, European	5	0.007	5	0.006	5	0.013
34 ATLANTIC, EASTERN CENTRAL						
Tuna	4	0.016	4	0.129	4	0.146
Sardines and sardine-type fishes	4	0.060	4	0.060	4	0.120
Sole	4	0.009	4	0.023	4	0.032
37 MEDITERRANEAN AND BLACK SEA						
Tuna	5	1.21	9	15.5	5	26.1
Eel, European	4	0.328	4	2.34	4	2.67
Mackerel, Atlantic	5	0.359	5	2.23	5	2.58
Sardines and sardine-type fishes	15	0.217	16	1.75	15	2.02
Mackerel, chub	2	0.164	2	1.75	2	1.91
European sardine	15	0.209	15	1.56	15	1.77
Salmons, trouts, smelts	4	0.256	3	0.631	3	0.870
Mackerel	2	0.241	2	0.570	2	0.811
Salmons	5	0.205	5	0.521	5	0.725
Mullets	3	0.132	3	0.398	3	0.530
Swordfish	3	0.080	3	0.439	3	0.518
Hakes	4	0.100	4	0.358	4	0.458
Gilthead seabream	6	0.111	6	0.329	6	0.440
Sea bass	96	0.078	97	0.353	96	0.432
Rainbow trout	5	0.066	5	0.189	5	0.255
Trouts	13	0.087	12	0.129	11	0.204
Cod	2	0.087	2	0.086	2	0.173
Sole	3	0.040	3	0.051	3	0.091
47 ATLANTIC, SOUTHEAST						
Hakes	2	0.010	2	0.003	2	0.013
48 ATLANTIC, ANTARCTIC						
Halibut, Greenland	2	0.837	2	1.08	2	1.92
51 INDIAN OCEAN, WESTERN						
Swordfish	17	0.061	17	0.215	17	0.275
Tuna, bigeye	6	0.014	6	0.040	6	0.055
Tuna	18	0.015	20	0.038	17	0.049
57 INDIAN OCEAN, EASTERN						
Swordfish	4	0.023	4	0.423	4	0.445
Tuna	16	0.052	16	0.082	16	0.134
61 PACIFIC, NORTHWEST						
Mackerel	7	0.257	7	0.618	7	0.875
Halibut, Atlantic	2	0.167	2	0.321	2	0.489
Pink salmon	3	0.095	3	0.279	3	0.374

TABLE 7.30 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Atlantic salmon	2	0.064	2	0.125	2	0.190
Salmons	10	0.051	10	0.100	10	0.151
Coalfish	4	0.046	4	0.019	4	0.066
Salmons, trouts, smelts	2	0.025	2	0.032	2	0.057
Hakes	6	0.019	6	0.031	6	0.050
Cod	10	0.014	10	0.009	10	0.022
Pacific salmon (generic)	5	0.003	5	0.005	5	0.009
67 PACIFIC, NORTHEAST						
Ocean perch	3	0.029	3	0.041	3	0.069
Plaice, European	5	0.032	5	0.030	5	0.062
Plaice	14	0.026	15	0.031	14	0.058
Salmons	2	0.012	2	0.024	2	0.036
71 PACIFIC, WESTERN CENTRAL						
Tuna	52	0.039	55	0.019	52	0.058
87 PACIFIC, SOUTHEAST						
Mackerel	2	0.152	2	0.395	2	0.547
Salmons	9	0.109	9	0.348	9	0.456
Atlantic salmon	4	0.050	4	0.148	4	0.198
Tuna	3	0.076	3	0.041	3	0.117
Hakes	2	0.013	2	0.004	2	0.017
CANADA, UNSPECIFIED						
Halibut, Greenland	4	0.283	4	0.440	4	0.723
Herrings	3	0.268	3	0.345	3	0.613
FRANCE, UNSPECIFIED						
Halibut, Atlantic	6	0.992	6	1.55	6	2.54
Mackerel, Atlantic	15	0.499	15	1.76	15	2.26
Mackerel	6	0.558	19	2.41	6	2.25
Halibut, Greenland	8	0.648	8	1.25	8	1.90
Herrings	2	0.562	5	0.62	2	1.70
Shads	2	0.583	2	1.00	2	1.58
Sardines and sardine-type fishes	3	0.303	12	1.45	3	1.55
European sardine	6	0.239	6	1.01	6	1.25
Salmons	6	0.246	7	0.512	6	0.770
Sea bass	27	0.079	30	0.412	27	0.452
Atlantic salmon	4	0.087	4	0.221	4	0.308
Hakes	5	0.028	10	0.211	5	0.216
Trouts	27	0.039	31	0.145	27	0.185
Cod	12	0.028	21	0.110	12	0.149
Sole	2	0.034	4	0.084	2	0.107

TABLE 7.30 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN MUSCLE TISSUE OF DIFFERENT SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) FINFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Coalfish	2	0.017	3	0.046	2	0.060
Haddock	12	0.019	12	0.036	12	0.055
Tuna	3	0.016	5	1.19	3	0.031
GREENLAND, UNSPECIFIED						
Halibut, Greenland	20	0.238	20	0.431	20	0.669
Halibut	2	0.162	2	0.317	2	0.479
Halibut, Atlantic	10	0.192	10	0.267	10	0.459
INDIAN OCEAN, UNSPECIFIED						
Swordfish	6	0.044	6	0.373	6	0.417
Tuna	32	0.022	32	0.046	31	0.071
Freshwater bream - Europe	2	0.005	2	0.016	2	0.021
PACIFIC OCEAN, UNSPECIFIED						
Tuna	11	0.017	11	0.055	11	0.072
Cod, Atlantic	2	0.047	2	0.019	2	0.066
Cod	2	0.010	2	0.005	2	0.015
Pacific salmon (generic)	4	0.0003	3	0.0001	3	0.0004
SPAIN, UNSPECIFIED						
European sardine	2	0.292	2	1.23	2	1.53
Sea bass	3	0.061	3	0.359	3	0.420
Salmons	2	0.131	2	0.206	2	0.338
Trouts	3	0.087	3	0.154	3	0.242
Tuna	4	0.018	5	0.027	4	0.049
THE UNITED STATES, UNSPECIFIED						
Salmons, trouts, smelts	2	0.124	2	0.177	2	0.301
Salmons	2	0.120	2	0.163	2	0.283
Atlantic salmon	6	0.086	6	0.131	6	0.217
VIET NAM, UNSPECIFIED						
Tuna and bonito (generic)	2	0.089	2	0.115	2	0.204
Tuna	14	0.077	14	0.068	14	0.145
Mackerel	5	0.024	5	0.016	5	0.040

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.3 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN FINFISH, SUMMARY

Data on dioxins and dl-PCBs from both the literature search and the EFSA database showed that there was a large variation in concentrations of dioxins and dl-PCBs depending on species/species groups. On average, farmed finfish had lower concentrations of dioxins and dl-PCBs than wild finfish, with little difference between farmed freshwater and farmed marine fish. Fish captured from wild stocks in inland waters had higher concentrations of dioxins and dl-PCBs than wild-caught finfish from marine waters.

Within the category of wild-caught finfish from inland waters, two species from the literature data, grass carp (*Ctenopharyngodon idella*) and goldfish (*Carassius aurata*), from Asia, and three species/species groups from the EFSA data, river eels, European eel and barbs from Europe, stood out with particularly high concentrations of dioxins and dl-PCBs in muscle (8.24–49 ng TEQ/kg). For European eel from FAO area 05 Europe there was, however, a large difference between the results from the literature data and the EFSA data. European eel (*Anguilla anguilla*) from the literature data (n = 16) had a very low mean value of dioxins and dl-PCBs of 0.013 ng TEQ/kg, compared with 8.74 ng TEQ/kg for European eel from the EFSA data (n = 60) (**Table 7.23** and **Table 7.28**).

Wild-caught finfish from marine waters made up the largest volume of results in both the literature data and the EFSA data. Within this category, two species groups from the EFSA data, shads from FAO area 27 (Atlantic Northeast) and tuna from the FAO area 37 (Mediterranean and Black Sea) stood out with particularly high concentrations of dioxins and dl-PCBs in muscle (7.49–26.1 ng TEQ/kg) (**Table 7.30**). Also, in the literature data the large tuna species in the genus *Thunnus* was among the genera with highest concentrations in the area Mediterranean and Black Sea, but the concentration in the literature data was nevertheless much lower (2.6 ng TEQ/kg) (**Table 7.24**). In other marine areas, tuna and bigeye tuna from the EFSA data and *Thunnus* from the literature data had much lower levels of dioxins and dl-PCBs. Apart from shads and tuna, no other finfish from marine areas had concentrations of dioxins and dl-PCBs above 6.5 ng TEQ/kg (maximum level in European Union), but several species/species groups had high concentrations close to this level, including wild-caught whitefishes or coregonus, European eel, smelt and river eels from FAO area 27 (**Table 7.30**). Mackerel from the EFSA data and the genus *Scomber* from the literature data had relatively high concentrations of dioxins and dl-PCBs throughout different regions of the world's oceans, but, in general, there was a wide variation with regard to which species/species groups had the highest levels in the different marine areas. Comparison of geographical areas is difficult, since different species are represented in the different areas, and very different amounts of data have been reported from the different areas. It appears from the data (without any statistical analyses), that the differences in concentrations of dioxins and dl-PCBs among species or species groups were more important than differences between geographical areas.

7.5.4 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN SHELLFISH FROM THE LITERATURE REVIEW

In the literature, results for dioxins and dl-PCBs were found for 352 analysed samples of shellfish. Of the analysed shellfish, 212 samples were from farmed shellfish, while the rest were from wild stocks (140 samples). Most of the analysed shellfish originated from marine waters (328 samples), and only 24 shellfish samples originated from inland waters.

7.5.4.1 Farmed shellfish from inland and marine waters

No data was found in the literature for dioxins and dl-PCBs in farmed shellfish from inland waters.

Published data on farmed shellfish from marine waters was limited to 210 samples of Mediterranean mussel (*Mytilus galloprovincialis*) from the coast of Europe (**Table 7.31**). The mean value of dioxins and dioxins and dl-PCBs in this species was higher in FAO area 37, Mediterranean and Black Sea, than in FAO area 27, Atlantic, Northeast, but in both areas the mean values were well below the maximum levels for both dioxins and dioxins and dl-PCBs.

TABLE 7.31 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN TISSUE OF FARMED SHELLFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

FAO AREA/ SPECIES LATIN NAME	N	DIOXINS	DI-PCBs	DIOXINS+ dl-PCBs
27 ATLANTIC, NORTHEAST				
Mytilus galloprovincialis	8	0.135	0.573	0.712
37 MEDITERRANEAN AND BLACK SEA				
Mytilus galloprovincialis	202	0.465	1.78	2.25

Note: N is the number of analytical samples, including both individual and composite samples.

7.5.4.2 Wild-caught shellfish from inland waters

For wild-caught shellfish from inland waters, data from the literature review was limited to only three species. The highest concentration of dioxins and dl-PCBs was found in the wild-caught snail *Bellamya purificata* from FAO area 04, Asia, with a very high concentration of sum dioxins and dl-PCBs of 38.5 ng TEQ/kg wet weight (**Table 7.32**). The result for this species was, however, based on only three samples and should therefore be interpreted with caution. Two other wild-caught species or species groups of shellfish from inland waters had concentrations of dioxins and dl-PCBs of 1.06 ng TEQ/kg wet weight, or lower (**Table 7.32**).

TABLE 7.32 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN TISSUE OF WILD SHELLFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

FAO AREA/SPECIES LATIN NAME	SHELLFISH GROUP	N	DIOXINS	DI-PCBs	Dioxins+ dl-PCBs
04 ASIA INLAND WATERS					
Bellamya purificata	Snail	3			38.5
Ampullaria gigas apix	Snail	4			1.06
05 EUROPE INLAND WATERS					
Eriocheir sinensis	Crab	16	0.375	0.320	0.680

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.4.3 Wild-caught shellfish from marine waters

Wild-caught shellfish from marine waters made up the largest volume of data for dioxins and dl-PCBs in shellfish from the literature review. Results were found for several species and species groups, but the number of samples was low for many of the species/species groups (**Table 7.33**). The concentrations were low in all reported species/species groups from all areas, with mean values of sum dioxins and dl-PCBs of 1.60 ng TEQ/kg, or lower. Wild-caught Mediterranean mussels (*Mytilus galloprovincialis*) were reported for both FAO area 37, Mediterranean and Black Sea, and for FAO area 27, Atlantic, Northeast. The results showed that this species had lower concentrations of dioxins and dl-PCBs in FAO area 37 than in FAO area 27 (**Table 7.33**), contrary to the results for farmed Mediterranean mussel from the same areas (**Table 7.31**). Farmed Mediterranean mussel from FAO area 37 had the highest concentrations overall, with mean values about ten times higher than in wild-caught Mediterranean mussel from FAO area 37 and about three times higher than in both farmed and wild-caught Mediterranean mussel from FAO area 27 (**Table 7.31** and **Table 7.33**).

7.5.5 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN SHELLFISH FROM DATA FROM THE EUROPEAN FOOD SAFETY AUTHORITY

In the data from EFSA, values for dioxins and dl-PCBs in shellfish (as in finfish) were reported using codes for species or species groups, rather than their less ambiguous Latin names (which are used in the literature data). Because of this, some species groups may include a wide range of species that may have very different levels of dioxins and dl-PCBs. Also, some species may be present both with their specific species names and in terms of a larger group of species. For instance, the species named blue mussel could be included also in the species groups "mussels" or "molluscs". The EFSA data includes samples analysed in Europe, but includes both samples of fish of European origin and fish imported to Europe from other countries.

The final dataset on dioxins and dl-PCBs compiled from the EFSA data contained 2 129 analysed samples of shellfish. Of these, 1 952 samples had results for both dioxins and dl-PCBs (all 29 congeners), 3 samples had results only for dioxins (17 congeners)

TABLE 7.33 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN TISSUE OF WILD SHELLFISH FROM DIFFERENT MARINE REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

FAO AREA/SPECIES LATIN NAME	SHELLFISH GROUP	N	DIOXINS	DI-PCBs	Dioxins+ dl-PCBs
27 ATLANTIC, NORTHEAST					
Eusergestes arcticus	Shrimp	4	0.830	0.720	1.60
Mytilus galloprovincialis	Bivalve	12	0.209	0.504	0.708
Pasiphaea spp.	Shrimp	3	0.370	0.280	0.660
Meganyctiphanes norvegica	Krill	3	0.290	0.260	0.540
Ostrea edulis	Bivalve	2	0.220	0.670	
37 MEDITERRANEAN AND BLACK SEA					
Illex coindetii	Squid	3	0.774	0.405	0.921
Mytilus galloprovincialis	Bivalve	33	0.0835	0.240	0.220
«Clam»	Bivalve	2	0.047	0.12	0.167
«Squid»	Squid	2	0.025	0.13	0.155
Chamelea gallina	Bivalve	14	0.036		0.154
«Shrimp»	Shrimp	2	0.051	0.09	0.141
Cuttlefish	Cuttlefish	2	0.025	0.04	0.065
Hexaplex trunculus	Snail	9		2.72	
27 ATLANTIC, NORTHEAST OR 37 MEDITERRANEAN AND BLACK SEA					
Mytilus galloprovincialis	Bivalve	2	0.320	0.120	0.440
Chamelea gallina	Bivalve	2	0.280	0.060	0.340
Argopecten irradians or Aequipecten opercularis	Bivalve	2	0.120	0.070	0.190
Aristeus antennatus	Shrimp	2	0.080	0.010	0.090
Squilla mantis	Shrimp	2	0.080	0.010	0.090
Nephrops norvegicus	Lobster	2	0.070	0.010	0.080
Loligo vulgaris	Squid	2	0.020	0.020	0.040
Octopus vulgaris	Octopus	2	0.040	0.001	0.040
Sepia officinalis	Cuttlefish	2	0.010	0.001	0.010

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

and 174 samples had results only for dl-PCBs (12 congeners). Of the analysed shellfish, 218 samples were from farmed shellfish and 223 samples were from wild stocks. The remaining 1 688 samples were reported without indication as to whether the samples were from shellfish farming or from wild stocks. These unspecified samples were assumed to be from wild stocks and were combined with the wild-caught shellfish, even if they may have been farmed. Most of the analysed shellfish originated from marine waters (1 459 samples), with only 75 samples being reported to be from inland waters. There was also a large portion of the samples (n = 595) for which this information was not given, and these were included together with the results for marine shellfish. Analysed tissue for shellfish was not specified in the dataset, but it is assumed that edible tissue was used, either muscle tissue (such as for crustaceans) or the whole soft part of the animal (as in the case of for bivalves).

7.5.5.1 Farmed shellfish from inland and marine waters

The dataset obtained from the EFSA database included no data on dioxins and dl-PCBs in farmed shellfish from inland waters, except for a single sample of mussels from European inland waters.

For farmed shellfish from marine waters, data was available for several species/species groups, and the results showed that the mean values of dioxins and dl-PCBs were below 0.80 ng TEQ/kg in all species and species groups reported (**Table 7.34**). The highest mean values were found in the species/species groups oysters, mussels and European oyster, with values between 0.601 and 0.792 ng TEQ/kg. All other species/species groups had mean values below 0.25 ng TEQ/kg.

TABLE 7.34 **MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF FARMED SHELLFISH FROM MARINE WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)**

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Oysters	20	0.430	20	0.362	20	0.792
Mussels	22	0.218	22	0.407	22	0.625
Oyster, European	13	0.478	13	0.123	13	0.601
Blue mussel	117	0.189	117	0.053	117	0.242
Lobster, European	2	0.095	2	0.098	2	0.193
Molluscs	2	0.120	2	0.054	2	0.174
Clams	3	0.052	3	0.065	3	0.117
Crabs, sea-spiders	2	0.041	2	0.067	2	0.108
Scallop, great	17	0.080	17	0.006	17	0.087
Water snails, conches and whelks	3	0.072	3	0.006	3	0.077
Scallops, pectens	9	0.068	9	0.005	9	0.073
Shrimps and prawns	6	0.017	6	0.010	6	0.027

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.5.2 Wild-caught shellfish from inland waters

For wild-caught shellfish from inland waters, the data received from the EFSA database showed low concentrations of dioxins and dl-PCBs for all species groups (**Table 7.35**). The concentrations of dioxins and dl-PCBs in freshwater shrimps and prawns and freshwater crayfishes varied between the different FAO areas, with the highest mean values in FAO area 05 (Europe), and much lower mean values in the FAO areas 04 (Asia) and 03 (South America) (**Table 7.36**). The results for the two latter FAO areas were, however, based on very few samples and should be interpreted with caution.

TABLE 7.35 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD (OR UNSPECIFIED) SHELLFISH FROM INLAND WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Freshwater shrimps or prawns	29	0.291	31	0.382	29	0.698
Mussels	2	0.124	2	0.331	2	0.454
Freshwater crayfishes	27	0.228	29	0.191	27	0.420
Oysters	5	0.116	5	0.154	5	0.270
Shrimps and prawns	4	0.096	4	0.022	4	0.117
Metapenaeus shrimps	3	0.006	3	0.004	3	0.010

Notes: N is the number of analytical samples and may include both individual and composite samples. Cases where N = 1 are excluded.

TABLE 7.36 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT INLAND REGIONS (FAO AREAS) (NG TOXIC EQUIVALENT QUOTIENT/KG WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
03 SOUTH-AMERICA INLAND WATERS						
Freshwater shrimps or prawns	2	0.014	2	0.009	2	0.023
04 ASIA INLAND WATERS						
Freshwater crayfishes	2	0.051	2	0.043	2	0.094
Shrimps and prawns	2	0.014	2	0.004	2	0.018
Freshwater shrimps or prawns	2	0.011	3	0.012	2	0.018
Metapenaeus shrimps	3	0.006	3	0.004	3	0.010
05 EUROPE INLAND WATERS						
Freshwater shrimps or prawns	25	0.336	25	0.471	25	0.807
Mussels	2	0.124	2	0.331	2	0.454
Freshwater crayfishes	25	0.242	27	0.202	25	0.447
Oysters	5	0.116	5	0.154	5	0.270

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.5.3 Wild-caught shellfish from marine waters

Wild-caught (or unspecified) shellfish from marine waters made up the largest volume of shellfish results for dioxins and dl-PCBs reported in the EFSA dataset. Results for several species/species groups from a wide range of geographical areas were reported (**Table 7.37** and **Table 7.38**). The highest concentrations of dioxins and dl-PCBs were found in squids from FAO area 27 (Atlantic, Northeast) with a mean value for sum dioxins of 5.15 ng TEQ/kg, and a mean value for sum dioxins and dl-PCBs of 5.20 ng TEQ/kg (**Table 7.38**). These results were, however, based on only six samples and should therefore be interpreted with caution. The mean value of dioxins and dl-PCBs in wild-caught squids from other marine regions (FAO areas 61 and 87, and Spain, unspecified area), showed much lower levels of

dioxins and dl-PCBs in squids (**Table 7.38**). All other wild-caught shellfish species/species groups from all the different marine areas had mean concentrations of dioxins and dl-PCBs of 1.72 ng TEQ/kg or lower (**Table 7.38**).

TABLE 7.37 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM MARINE OR UNSPECIFIED WATERS (ALL REGIONS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Squids	24	1.31	27	0.064	24	1.36
Oysters	356	0.382	444	0.456	356	0.850
Crabs, sea-spiders	242	0.405	253	0.423	241	0.836
Mussels	406	0.191	426	0.354	404	0.548
Water snails, conches and whelks	22	0.124	22	0.221	22	0.346
Cuttlefish, common	7	0.112	7	0.173	7	0.285
Lobsters	14	0.104	14	0.161	14	0.265
Oyster, Pacific cupped	2	0.150	2	0.099	2	0.249
Blue mussel	17	0.136	17	0.064	17	0.200
Lobster, European	3	0.136	3	0.062	3	0.198
Lobster, Norway	63	0.125	65	0.071	63	0.196
Edible crab	17	0.104	17	0.058	17	0.162
Shrimps, common	17	0.079	17	0.071	17	0.149
Shrimps and prawns	49	0.065	65	0.059	49	0.140
Cockles	11	0.062	13	0.074	11	0.140
Scallops, pectens	274	0.064	277	0.042	274	0.105
Scallop, great	6	0.079	6	0.021	6	0.100
Clams	20	0.048	26	0.036	20	0.085
Clams, cockles, arkshells	3	0.037	3	0.024	3	0.061
Cuttlefishes	7	0.036	8	0.021	7	0.058
Octopus, curled	6	0.028	6	0.028	6	0.057
Scallop, queen	64	0.034	78	0.025	64	0.056
Squids, cuttlefishes, octopuses	17	0.021	17	0.028	17	0.049
Octopus, common	2	0.018	2	0.028	2	0.046
Prawn, northern	8	0.035	8	0.006	8	0.041
Spiny and rock lobsters	8	0.011	9	0.008	8	0.020

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

TABLE 7.38 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
21 ATLANTIC, NORTHWEST						
Mussels	7	0.210	7	0.411	7	0.621
Oysters	6	0.209	6	0.249	6	0.457
Lobsters	3	0.111	3	0.117	3	0.229
Crabs, sea-spiders	9	0.066	9	0.041	9	0.107
Edible crab	2	0.062	2	0.034	2	0.096
Scallops, pectens	33	0.031	33	0.018	33	0.050
27 ATLANTIC, NORTHEAST						
Squids	6	5.15	6	0.050	6	5.20
Shrimps and prawns	5	0.454	6	0.548	5	1.11
Crabs, sea-spiders	204	0.452	212	0.477	203	0.936
Oysters	142	0.406	144	0.453	142	0.863
Mussels	146	0.278	148	0.462	145	0.746
Cuttlefish, common	4	0.179	4	0.296	4	0.475
Shrimps, common	4	0.196	4	0.276	4	0.473
Water snails, conches and whelks	20	0.119	20	0.199	20	0.318
Oyster, pacific cupped	2	0.150	2	0.099	2	0.249
Lobsters	6	0.109	6	0.108	6	0.218
Blue mussel	17	0.136	17	0.064	17	0.200
Lobster, Norway	54	0.132	54	0.068	54	0.200
Lobster, European	3	0.136	3	0.062	3	0.198
Edible crab	10	0.100	10	0.056	10	0.156
Scallops, pectens	184	0.071	184	0.046	184	0.117
Scallop, great	6	0.079	6	0.021	6	0.100
Squids, cuttlefishes, octopuses	3	0.033	3	0.062	3	0.095
Cockles	4	0.043	4	0.039	4	0.082
Cuttlefishes	5	0.045	5	0.030	5	0.075
Scallop, queen	32	0.046	38	0.023	32	0.071
Clams	6	0.032	6	0.021	6	0.053
31 ATLANTIC, WESTERN CENTRAL						
Crabs, sea-spiders	2	0.500	2	0.740	2	1.24
Oysters	10	0.380	10	0.499	10	0.879
Mussels	4	0.264	4	0.474	4	0.739
Shrimps and prawns	5	0.019	6	0.010	5	0.030
Spiny and rock lobsters	3	0.009	4	0.005	3	0.015
34 ATLANTIC, EASTERN CENTRAL						
Oysters	2	0.304	2	0.362	2	0.667
Octopus, curled	2	0.019	2	0.026	2	0.044
37 MEDITERRANEAN AND BLACK SEA						
Oysters	28	0.278	29	0.447	28	0.729

TABLE 7.38 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Mussels	49	0.138	49	0.389	48	0.529
Scallops, pectens	3	0.057	3	0.025	3	0.081
41 ATLANTIC, SOUTHWEST						
Oysters	2	0.661	2	1.06	2	1.72
Shrimps and prawns	8	0.008	8	0.003	8	0.011
Scallop, queen	5	0.007	6	0.002	5	0.010
Scallops, pectens	5	0.006	6	0.002	5	0.008
51 INDIAN OCEAN, WESTERN						
Shrimps and prawns	5	0.035	5	0.008	5	0.043
57 Indian Ocean, Eastern						
Shrimps and prawns	3	0.040	3	0.006	3	0.046
Shrimps, common	4	0.021	4	0.004	4	0.025
61 PACIFIC, NORTHWEST						
Scallop, queen	2	0.037	2	0.036	2	0.073
Squids	4	0.013	5	0.014	4	0.030
Scallops, pectens	4	0.013	4	0.014	4	0.026
77 Pacific, Eastern Central						
Scallops, pectens	2	0.010	2	0.006	2	0.015
87 PACIFIC, SOUTHEAST						
Scallop, queen	9	0.017	12	0.028	9	0.053
Mussels	32	0.017	36	0.015	32	0.034
Squids, cuttlefishes, octopuses	3	0.014	3	0.004	3	0.018
Scallops, pectens	19	0.011	19	0.006	19	0.017
Shrimps and prawns	4	0.009	9	0.009	4	0.015
Squids	2	0.007	2	0.005	2	0.012
CANADA, UNSPECIFIED						
Shrimps, common	2	0.020	2	0.012	2	0.032
Scallop, queen	2	0.008	2	0.008	2	0.016
Scallops, pectens	2	0.009	2	0.005	2	0.015
FRANCE, UNSPECIFIED						
Oysters	164	0.386	249	0.461	164	0.870
Mussels	104	0.216	114	0.429	104	0.637
Crabs, sea-spiders	24	0.161	27	0.152	24	0.318
Scallops, pectens	15	0.158	16	0.126	15	0.270
Lobsters	4	0.046	4	0.200	4	0.246
Lobster, Norway	4	0.089	6	0.119	4	0.242
Cockles	6	0.071	8	0.097	6	0.183
Squids, cuttlefishes, octopuses	2	0.055	2	0.101	2	0.156
Clams	8	0.036	12	0.045	8	0.086
Scallop, queen	9	0.034	13	0.050	9	0.052

TABLE 7.38 MEAN CONCENTRATIONS OF DIOXINS, DIOXIN-LIKE POLYCHLORINATED BIPHENYLS (dl-PCBs) AND THE SUM OF DIOXINS AND dl-PCBs IN VARIOUS SPECIES OR SPECIES GROUPS OF WILD-CAUGHT (OR UNSPECIFIED) SHELLFISH FROM DIFFERENT MARINE (OR UNSPECIFIED) REGIONS (FAO AREAS) (ng TOXIC EQUIVALENT QUOTIENT/kg WET WEIGHT) (cont.)

SPECIES/SPECIES GROUP	N	DIOXINS	N	DI-PCBs	N	Dioxins+ dl-PCBs
Shrimps and prawns	2	0.012	2	0.020	2	0.032
Squids			2	0.267		
INDIAN OCEAN, UNSPECIFIED						
Shrimps and prawns	4	0.031	8	0.019	4	0.053
Octopus, curled	2	0.027	2	0.008	2	0.035
Squids, cuttlefishes, octopuses	3	0.015	3	0.012	3	0.027
SPAIN, UNSPECIFIED						
Mussels	60	0.077	64	0.137	60	0.211
Clams	6	0.080	6	0.037	6	0.117
Squids	2	0.024	2	0.012	2	0.037
Squids, cuttlefishes, octopuses	4	0.009	4	0.006	4	0.015
the United States, unspecified						
Scallop, queen	2	0.013	2	0.007	2	0.020
Unspecified						
Crabs, sea-spiders	2	0.069	2	0.008	2	0.078
VIET NAM, UNSPECIFIED						
Edible crab	2	0.106	2	0.057	2	0.163
Prawn, northern	7	0.036	7	0.006	7	0.042
Shrimps and prawns	10	0.026	12	0.007	10	0.033

Notes: N is the number of analytical samples, including both individual and composite samples. Cases where N = 1 are excluded.

7.5.6 DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN SHELLFISH, SUMMARY

The data for dioxins and dl-PCBs were much more limited for shellfish than for finfish, with only 352 analysed samples of shellfish from the literature review and 2 129 analysed samples of shellfish from the EFSA data. The overall results for these data showed that, in general, the concentrations of dioxins and dl-PCBs were lower in shellfish than in finfish. Farmed shellfish had, on average, lower concentrations than wild shellfish, and the highest concentrations of dioxins and dl-PCBs in shellfish were found among shellfish from wild stocks. Most of the shellfish data were from marine waters, with only a very limited number of shellfish samples from inland waters (24 samples from the literature data and 75 samples from the EFSA data, all wild shellfish).

For wild-caught shellfish from marine waters, the highest concentrations of dioxins and dl-PCBs were found in the species group "squids" from FAO area 27 (Atlantic, Northeast), with a mean value of sum dioxins exceeding 6.5 ng TEQ/kg (maximum level in the European Union). These results were based on only six samples and

should therefore be interpreted with caution. The mean value of wild-caught squids from other marine regions, showed much lower levels. No other shellfish species/species groups had concentrations of dioxins or dioxins and dl-PCBs higher than 6.5 ng TEQ/kg. With very few exceptions, most species/species groups (wild or farmed) from marine areas had concentrations of dioxins and dl-PCBs well below 1.0 ng TEQ/kg wet weight.

For wild-caught shellfish from inland waters, the highest mean concentration of dioxins and dl-PCBs were found in the snail *Bellamya purificata* from China, with a concentration of sum dioxins and dl-PCBs of 38.5 ng TEQ/kg wet weight. The results for this species were based on only three samples and should therefore be regarded with caution. All other wild-caught species/species groups of shellfish from inland waters had concentrations of dioxins and dl-PCBs of 1.06 ng TEQ/kg wet weight or lower, and no data were available for farmed shellfish from inland waters.

Comparison of geographical areas is difficult, since different species are represented in the different areas and because very different amounts of data were reported from the different areas. Most of the shellfish samples analysed for dioxins and dl-PCBs were from European waters, mainly from FAO areas 27 (Atlantic, Northeast) and 37 (Mediterranean and Black Sea) or from the unspecified marine areas of France and Spain (likely to be either FAO area 27 or FAO area 37). Mean concentrations of dioxins and dl-PCBs in bivalves from wild stocks, including *Mytilus galloprovincialis*, "oysters", "mussels" and "scallops, pectens" were generally higher in FAO area 27 than in FAO area 37. In contrast, for farmed *Mytilus galloprovincialis*, the mean concentration of dioxins and dl-PCBs was considerably higher in area 37 than in area 27. A limited number of shellfish results were available from several other marine areas of the world, with some species groups represented in several different marine areas. The species groups "shrimps and prawns" and "scallops, pectens" were among the species groups with very low concentrations of dioxins and dl-PCBs – below 0.10 ng TEQ/kg in all the marine areas where they were represented, except in area 27, where the concentrations were somewhat higher. In general, it appears from the data (without any statistical analyses), that the differences in concentrations of dioxins and dl-PCBs among species or species groups were more important than differences between geographical areas.

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References for all included articles for the "Occurrence data for MeHg, dioxins and dl-PCBs" are given in Appendix 7, **Table A7.3**.

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APPENDIX 1
TERMS OF REFERENCE PROVIDED BY FAO/WHO

DEFINITION OF OUTCOME AND OUTPUTS

OUTCOME

Scientific evidence provided about risks and benefits of fish consumption for an update of the Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption.

Outputs

1. Background document including a literature review.
2. Draft update of the Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption.

DESCRIPTION OF SERVICES

The Service Provider will:

1. Develop an outline for the background document (including the literature review) to be discussed with FAO.
2. Carry out a systematic literature review that will include:
    c. Evidence of health benefits from fish consumption other than from long-chain n-3 polyunsaturated fatty acids (LCn3PUFAs).
    d. New data (published in the last 10 years) on toxic effects of dioxins (defined here to include polychlorinated dibenzo-p-dioxins [PCDDs], polychlorinated dibenzofurans [PCDFs] and dioxin-like polychlorinated biphenyls [dl-PCBs]) for all population groups.
    e. New data (published in the last 10 years) on toxic effects of methylmercury (MeHg) for all population groups.

f. The role of selenium with regard to the health effects of MeHg.

g. Occurrence data for MeHg and dioxins in fisheries and aquaculture products published in the last 10 years.

Develop a background document including the above-mentioned literature review and other relevant information that could add value to the background document.

APPENDIX 2
QUALITY ASSESSMENT TOOLS (RISK OF BIAS)

TABLE A2.1 **QUESTIONS INCLUDED IN AMSTAR 2 – A CRITICAL APPRAISAL TOOL FOR SYSTEMATIC REVIEWS**

1. Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: ☐ Population ☐ Intrvention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☐ Yes ☐ No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☐ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		☐ Yes ☐ No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference lists / bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☐ Partial Yes ☐ No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.		☐ Yes ☐ No
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.		☐ Yes ☐ No
7. Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: ☐ provided a list of all potentially relevant studies that were read ☐ in full-text form but excluded from the review	For Yes, must also have: ☐ Justified the exclusion from the review of each potentially relevant	☐ Yes ☐ Partial Yes ☐ No

TABLE A2.1 **QUESTIONS INCLUDED IN AMSTAR 2 – A CRITICAL APPRAISAL TOOL FOR SYSTEMATIC REVIEWS (cont.)**

8. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☐ described populations ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described intervention in detail (including doses where relevant) ☐ described comparator in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☐ No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from ☐ unconcealed allocation, and ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: ☐ allocation sequence that was not truly random, and ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes ☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies		☐ Yes ☐ No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity		☐ Yes ☐ No ☐ No meta-analysis conducted
For NRSI For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		☐ Yes ☐ No ☐ No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.		☐ Yes ☐ No ☐ No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?		
For Yes: ☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results		☐ Yes ☐ No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		
For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review		☐ Yes ☐ No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?		
For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias		☐ Yes ☐ No ☐ No meta-analysis conducted

Source: Shea B.J. Reeves B.C. Wells G. Thuku M. Hamel C. Moran J. Moher D. *et al.* 2017. *AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both.* BMJ.
https://doi.org/10.1136/bmj.j4008

TABLE A2.2 QUESTIONS INCLUDED IN THE RISK-OF-BIAS TOOL FOR THE QUALITY ASSESSMENT OF RANDOMIZED CONTROLLED TRIALS AND TRIALS IN THE REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"

Quality assessment of RCTs and trials	Yes	No	Can't tell	NA	Requires yes for level			If "no" on this question, the study is graded C and further excluded
Questions					A	B	C	
1. General questions and study design								
1a) Research question/hypothesis clearly formulated?					✖	✖		✖
1b) Was the study design suited to test the research question?					✖	✖		✖
1c) Was the duration of the study suited to test the research hypothesis?					✖			
2. Participation and compliance								
2a) Population (target group) well described?					✖	✖		✖
2b) Sample (possible participants) recruited in an acceptable way?					✖			
2c) Criteria for inclusion/exclusion clearly formulated and acceptable?					✖			
2d) Actual participants comparable with the relevant (target) population?					✖			
2e) Method of randomization allocation stated and appropriate?					✖			
2f) Was there an account for the comparability of intervention and control groups with regard to relevant/possible factors that might affect outcome?					✖			
2g) Compliance reported in an acceptable way, and compliance acceptable?					✖			
2h) Drop-out rate within an acceptable range? 6mo<30%, 12mo<40%, 24mo<50%					✖			
2i) The drop-outs did not differ between the groups?					✖			
3. Dietary interventions and assessment								
3a) Intervention diets clearly defined and characterized (fish intake)?					✖	✖		✖
3b) Method used for dietary assessment valid/adequately validated?					✖			
3c) Intervention diets consist of normal foods/relevance to research question?					✖			
3d) Measurement errors in dietary reporting considered?					✖			
3e) Energy adjustment adequately done?					✖			
4. Anthropometry								
4a) Assessment details clearly reported, and assessment adequately performed?					✖			
5. Outcome, results, and analyses								
5a) Acceptable and clear definition of the outcome/endpoint?					✖	✖		✖
5b) Results analysed blind?					✖			
5c) Attempts in the analysis phase made to adjust for imbalances between treatment arms with regard to important determinants for the outcome (e.g. through multivariate modelling)?					✖			
5d) Possible use of medication/supplements taken into account?					✖			
6. Statistical power								
6a) Sample size and power calculation reported/considered (relevant for main outcome variable)?					✖			
Summary of the study quality (A, B or C):								
Reasons for grade C and other comments:								

TABLE A2.3 **QUESTIONS INCLUDED IN THE RISK-OF-BIAS TOOL FOR THE QUALITY ASSESSMENT OF PROSPECTIVE COHORT STUDIES IN THE REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**

Quality assessment of prospective cohort studies	Yes	No	Can't tell	NA	Requires yes for level			If "no" on this question, the study is graded C and further excluded
Questions					A	B	C	
1 General questions and study design								
1a) Research question clearly formulated?					✖	✖		✖
1b) Endpoint/outcome clearly formulated?					✖	✖		✖
1c) Was the study design suited to test the research hypothesis?					✖	✖		✖
2 Sampling (ascertainment of cases and non-cases)								
2a) Source population/study base well defined?					✖	✖		✖
2b) Response rate reported and acceptable?					✖	✖		✖
2c) Time period of baseline examinations clearly identified?					✖			
2d) Endpoint clearly ascertained and assessed in a valid way?					✖	✖		✖
2e) Follow-up period clearly identified?					✖			
3 Dietary exposure								
3a) Fish or seafood intake according to inclusion criteria (individual intake and at least frequency)?					✖	✖		✖
3b) Was the dietary assessment method validated?					✖			
3c) Measurement errors in dietary reporting considered or mentioned?					✖			
3d) Energy adjustment adequately done?					✖			
3e) Repeated assessment of diet during follow up, and data considered?					✖			
4 Anthropometry								
4a) Assessment details clearly reported, and assessment adequately performed?					✖			
5 Confounding								
5a) Were important confounders identified/ascertained and considered by authors?					✖	✖		✖
6 Statistical power								
6a) Was the study power considered and power calculations and sample size reported?					✖			
6b) In view of multiple tests, were by chance findings considered?					✖			✖
6c) Sufficient size of study population and no. of outcomes/cases?					✖			
7 Statistical analysis								
7a) Appropriately handled?					✖			
7b) Relevant confounders adequately handled (e.g., restriction, stratified analyses, multivariate modelling, interaction tested)?					✖	✖		✖
7c) Ascertainment/detection bias considered (e.g. cases detected due to screening)?					✖			
7d) Cases detected early during the follow-up period removed?					✖			
Summary of the study quality (A, B or C):								
Reasons for grade C and other comments:								

TABLE A2.4 **QUESTIONS INCLUDED IN THE OHAT RISK OF BIAS RATING TOOL FOR HUMAN AND ANIMAL STUDIES OF THE OFFICE OF HEALTH ASSESSMENT AND TRANSLATION**

Q	Bias domain	Questions	Applies to study designs
Q1	Selection bias	Was administered dose or exposure level adequately randomized?	EA, HCT
Q2	Selection bias	Was allocation to study groups adequately concealed?	EA, HCT
Q3	Selection bias	Did selection of study participants result in appropriate comparison groups?	Co, CaCo, CrSe
Q4 (Key)*	Confounding	Did the study design or analysis account for important confounding and modifying variables?	Co, CaCo, CrSe, CaS
Q5	Performance bias	Were experimental conditions identical across study groups?	EA
Q6	Performance bias	Were the research personnel and human subjects blinded to the study group during the study?	EA, HCT
Q7	Attrition/exclusion bias	Were outcome data complete without attrition or exclusion from analysis?	EA, HCT, Co, CaCo CrSe
Q8 (Key)*	Detection bias	Can we be confident in the exposure characterization?	EA, HCT, Co, CaCo CrSe, CaS
Q9 (Key)*	Detection bias	Can we be confident in the outcome assessment?	EA, HCT, Co, CaCo CrSe, CaS
Q10	Selective reporting bias	Were all measured outcomes reported?	EA, HCT, Co, CaCo CrSe, CaS
Q11	Other sources of bias	Were there no other potential threats to internal validity (e.g. statistical methods were appropriate, and researchers adhered to the study protocol)?	EA, HCT, Co, CaCo CrSe, CaS

Notes: *Questions are considered key questions when assessing the risk of bias for human observational studies (Co, CaCo, CrSe).
Abbreviations: EA: experimental animal; HCT: human controlled trials; Co: cohort; CaCo: case-control; CrSe: cross-sectional; CaS: case series
Source: OHAT (Office of Health Assessment and Translation). 2015. OHAT Risk of Bias Tool for human and Animal Studies. Division of the National Toxicology Program. National Institute of Environmental Health Sciences.

APPENDIX 3
EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION

LITERATURE SEARCH STRATEGY

TABLE A3.1 LITERATURE SEARCH STRATEGY FOR THE SYSTEMATIC REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"

Databases: Web of Science, PubMed, Cochrane						
Date of literature searches: Week 47, 2021						
#	Search group	Literature search string				
#1	Fish	(Fish* or finfish* or crayfish* or crawfish* or cuttlefish* or inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clams or cockle* or urchin* or echinoderm* or echinoid* or "sea cucumber*" or holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* or whelk* or gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)				
#2	Study design	("systematic review*" or "systematic report*" or "cochrane review*" or "umbrella review*" or meta-analysis or "meta analysis" or "meta analyses" or RCT* or "randomized controlled" or prospective cohort or prospective observational or cohort or longitudinal or controlled trial*)				
#3	Dietary consumption	(eat* or ate or intake* or consumption or consume* or consuming or ingestion or serving* or meal* or diet* or dine or dinner* or lunch* or breakfast* or snack*)				
		Search string	Hits Web of Science	Hits PubMed	Hits Cochrane	Total hits
#4		#1 #2 #3	11 719	13 583	46	25 348
#	Search group	Literature search string				
#5	Overweight and obesity	(obesity or obesities or obese or adiposity or fatness or overweight or "over weight" or (excess* adj (fat or weight)) or "BMI" or (body adj (height or size or weight or mass)) or (abdominal adj (diameter index or height)) or "height weight ratio*" or "waist circumference*" or "waist height ratio*" or "waist to height ratio*" or (weight adj (change* or gain* or loss)))				
#6	Cardiovascular diseases and outcomes	((Cardiovascular or heart or cardiac or myocardial or myo cardial or cerebrovascular or vascular or coronary or cerebral or peripheral or endothelial) adj (disease* or disorder* or failure or event* or health or effect* or accident* or calcification* or "risk factor*" or riskfactor* or syndrom* or revascularization* or revascularisation* or arter* or function* or dysfunction* or attack* or arrest or apoplex* or insufficienc* or injur* or insult* or scleros* or stenos* or restenos*)) or cardioprotect* or "cardio protect*" or "high cardiovascular risk*" or CVD or infarct* or reinfarction* or aneurysm* or angina or artherosclero* or "arthero sclero*" or arteriosclero* or "arterio sclero*" or ischemi* or ischaemi* or nonischemi* nonischaemi* or "non ischemi*" or "non ischaemi*" or thrombos* or thrombolism* or tachycardia* or tachyarrhythmia* or arrhythmia* or ((ventricular or arterial) adj (fibrillation* or compliance* or stiffness*)) or "sudden cardiac death*" or stroke* or TIA or (brain adj (hemorrhage* or haemorrhage* or accident* or attack* or infarct* or insult*))				

TABLE A3.1 **LITERATURE SEARCH STRATEGY FOR THE SYSTEMATIC REVIEW "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)**

Databases: Web of Science, PubMed, Cochrane						
Date of literature searches: Week 47, 2021						
#7	Type 2 diabetes	(diabetes or sugar sickness or hypoglycemia or hypo glycemia or hyperglycemia or hyper glycemia or insulin resistance)				
#8	Birth and growth outcomes	(growth or ((premature or "pre term" or preterm) adj birth*) or SGA or ((birth or gestational or neonatal or neo natal or newborn or "new born" or foetal or fetal or foetus or fetus or baby or babies or infan*) adj (weight or size*)) or ((pregnancy or birth or obstetric) adj outcome*))				
#9	Allergy	(("allerg*" or "hypersensitivit*" or "hyper sensitivit*" or "sensiti#ation*" or "atopic?" or "atopy" or "atopies"))				
#10	Neurodevelopment and cognitive diseases	(((Child* or infant* or fetal or foetal or prenatal or "pre natal" or postnatal or "post natal" or human or "antepartum period*" or "ante partum period*") adj3 development*) or inhibition or (brain adj2 (damage* or injur* or development* or disorder*)) or psychomotor* or "psycho motor*" or motor or sensorimotor or "sensori motor" or sensorymotor or "sensory motor" or cognition or "cognitive function*" or "Mental health" or "Disorder* of higher cerebral function*" or (psychological adj ("well being" or wellbeing)) or ((neurocognit* or "neuro cognit*" or neurological or "nervous system" or nervoussystem or cognitive or development* or mental) adj2 (dysfunction* or function* or decline* or deterioration* or Defici* or illness* or retardation* or disturbance* or impairment* or disorder* or impact* or disabilit* or deviation* or development*)) or neurodevelopment* or "neuro development*" or autis* or Asperger* or kanner* or ASD or "attention deficit" or hyperactiv* or ADDH or ADHD or AD/HD or ADD or "minimal brain dysfunction" or impulsiveness or dyslexia or dyslexic* or dyscalculia or dyscalculic* or attention or learning or reading or mathematic* or math* or (aptitude adj1 test*) or ((Education or Educational or academic or school) adj1 (Status or attainment* or achievement* or performance* or underachievement* or "under achievement*" or score* or success* or failure*)) or "executive function*" or "information processing" or "school readiness" or "school ready" or Emotion* or socioemotional or "social emotional" or socioemotional or "socio emotional" or (social adj (development* or behaviour* or adjustment*)) or (intellectual adj2 (development* or deficien* or disorder* or retardation* or disabilit* or disturbance* or impairment*)) or Communication or language* or literacy or literacies or IQ or intelligence or "Speech disorder*" or mutism* or aphasia or stutter* or dysphasia or alexia or anxiet* or depression* or depressive or "mood disorder*" or schizophrenia or schizophrenic or aggression or behaviour* or affect or anger or bipolar or Temperament* or personalit* or amnesia or dementia or Alzheimer* or Parkinson* or huntington* or (memory adj3 (disorder* or impairment* or disturbance* or deficianc* or disabilit* or "short term" or shortterm or "long term" or longterm or "verbal recognition*")))				
#11	Dental health	((("dental" or "tooth" or "teeth" or "enamel") and ("enamel" or "discolo?ration?" or "malformation?" or "opacit*")) or "hypo?minerali#ation" or ("developmental" and ("dental" or "teeth" or "tooth" or "enamel") and "defect?"))				
#12	Immunology	(("immunolog*" or "infection resistance" or immunity or autoimmunity or "auto immunity" or immunodeficienc* or "immuno deficienc*" or (immun* adj (system or status or defense* or defence* or deficienc*)) or "vaccination response*" or ((upper or lower) adj "respiratory tract infection*") or "respiratory Sound*" or wheez* or asthma* or psoriasis or eczema* or dermatiti* or rheumatoid arthritis or (((Sjogren* or sicca) adj syndrome*) or syndrome*) or Antinuclear antibod* or "Multiple scleros*" or "Systemic lupus erythematosus" or ((Scleroderma or scleros*) adj (localized or systemic))))				
#13	Cancer	(cyst* or neoplasm* or neurofibroma* or tumor* or tumour* or cancer* or malign*)				
#14	Mortality	(mortalit* or "death rate*" or deathrate* or death*)				
#15	Bone health	((Osteoporos* or Osteopenia or Rickets or Osteomalacia or "vitamin D deficienc*" or (bone adj2 (diseas* or density or (low adj fractur*) or fragil* or broken or demineralization* or demineralisation* decalcification*)) or "Accidental Fall*" or ((Slip* or trip*) adj2 fall*)))				
#	Search group	Search string	Hits Web of Science	Hits PubMed	Hits Cochrane	Total hits
#16	Overweight and obesity	#4 #5	3 498	1 584	13	5 095
#17	Cardiovascular diseases and outcomes	#4 #6	2 425	1 282	10	3 717
#18	Diabetes	#4 #7	848	1 370	5	2 223
#19	Birth and growth outcomes	#4 #8	4 236	1 731	6	5 973
#20	Allergy	#4 #9	345	530	3	878
#21	Neurodevelopment and cognitive diseases	#4 #10	4 033	4 533	46	8 612
#22	Dental health	#4 #11	5	13	1	19
#23	Immunology	#4 #12	2 037	2 220	1	4 258
#24	Cancer	#4 #13	1 554	2 273	4	3 831
#25	Mortality	#4 #14	1 825	1 893	21	3 739
#26	Bone health	#4 #15	304	387	2	693
Number of total hits in all databases				39 092		

RECORDS EXCLUDED DURING FULL-TEXT SCREENING

ALLERGY AND IMMUNOLOGY

TABLE A3.2 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY", BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 8)	Reason for exclusion
Shoormasti, R. S. Sabetkish, N. Kazemnejad, A. Vahabi, N. Fazlollahi, M. R. *&* Pourpak, Z. 2019. Are the most common food allergens in an Iranian atopic population compatible with worldwide reports? A systemic review and meta-analysis with molecular classification of frequent allergens. *Allergologia et Immunopathologia*, 47(6):604-618.	Excluded based on inclusion and exclusion criteria. Not measured health outcome.
Best, K. P. Gold, M. Kennedy, D. Martin, J. *&* Makrides, M. 2016. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. *The American Journal of Clinical Nutrition*, 103(1):128-143.	Excluded as the review has already been assessed in VKM 2022.
Malmir, H. Larijani, B. *&* Esmaillzadeh, A. 2022. Fish consumption during pregnancy and risk of allergic diseases in the offspring: A systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition*, 62(27):7449-7459.	Excluded as the review has already been assessed in VKM 2022.
Miles, E. A. *&* Calder, P. C. 2012. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. *British Journal of Nutrition*, 107(S2):S171-S184.	Excluded based on inclusion and exclusion criteria: focus on n-3 PUFAs and not fish consumption.
Papamichael, M. M. Shrestha, S. K. Itsiopoulos, C. *&* Erbas, B. 2018. The role of fish intake on asthma in children: A meta-analysis of observational studies. *Pediatric Allergy and Immunology*, 29(4):350-360.	Excluded as the review has already been assessed in VKM 2022.
Rezaeizadeh, H. Mohammadpour, Z. Bitarafan, S. Harirchian, M. H. Ghadimi, M. *&* Homayon, I. A. 2022. Dietary fish intake and the risk of multiple sclerosis: a systematic review and meta-analysis of observational studies. *Nutritional Neuroscience*, 25(4):681-689.	Excluded as the review has already been assessed in VKM 2022.
Yang, H. Xun, P. *&* He, K. 2013. Fish and fish oil intake in relation to risk of asthma: a systematic review and meta-analysis. *PloS One*, 8(11):e80048.	Excluded as the review has already been assessed in VKM 2022.
Zhang, G. Q. Liu, B. Li, J. Luo, C. Q. Zhang, Q. Chen, J. L. Li, Z. Y. *et al.* 2017. Fish intake during pregnancy or infancy and allergic outcomes in children: A systematic review and meta-analysis. *Pediatric Allergy and Immunology*, 28(2):152-161.	Excluded as the review has already been assessed in VKM 2022.

TABLE A3.3 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY"**

Study (*n* = 120)	Reason for exclusion
Abdollahpour, I., Sormani, M.P., Nedjat, S., Mansournia, M.A. & van der Mei, I. 2021. The role of nutritional factors during adolescence in multiple sclerosis onset: a population-based incident case-control study. *Nutritional Neuroscience*, 24(7):500-507.	Excluded based on inclusion and exclusion criteria: population-based incident case–control study
Andersen, V., Olsen, A., Carbonnel, F., Tjonneland, A. & Vogel, U. 2012. Diet and risk of inflammatory bowel disease. *Digestive and Liver Disease*, 44(3): 185-194.	Excluded based on inclusion and exclusion criteria: retrospective case–control
Andrusaityte, S., Grazuleviciene, R. & Petraviciene, I. 2017. Effect of diet and maternal education on allergies among preschool children: A case-control study. *Environ Res*, 159: 374-380.	Excluded based on inclusion and exclusion criteria: nested case-control study
Atkins, F.M., Steinberg, S.S. & Metcalfe, D.D. 1985. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. *J Allergy Clin Immunol*, 75(3): 348-55	Excluded based on inclusion and exclusion criteria: people with immediate adverse reaction to food
Barman, M., Rabe, H., Hesselmar, B., Johansen, S., Sandberg, A.S. & Wold, A.E. 2020. Cord Blood Levels of EPA, a Marker of Fish Intake, Correlate with Infants' T- and B-Lymphocyte Phenotypes and Risk for Allergic Disease. *Nutrients*, 12(10).	Excluded based on inclusion and exclusion criteria: inflammatory markers and not specified health outcome
Barman, M., Jonsson, K., Sandin, A., Wold, A.E. & Sandberg, A.S. 2014. Serum fatty acid profile does not reflect seafood intake in adolescents with atopic eczema. *Acta Paediatr*, 103(9): 968-76.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Benvenga, S., Vigo, M.T., Metro, D., Granese, R., Vita, R. & Le Donne, M. 2016. Type of fish consumed and thyroid autoimmunity in pregnancy and postpartum. *Endocrine*, 52(1): 120-9.	Excluded based on inclusion and exclusion criteria: autoimmunity markers and not measured specified health outcome
Beyer, K. & Niggemann, B. 2017. Immunoglobulin E-mediated food allergies in childhood. *Monatsschrift Kinderheilkunde*, 165(2): 108-116.	Excluded based on inclusion and exclusion criteria: non-English language
Chandra, R.K., Puri, S. & Hamed, A. 1989. Influence of maternal diet during lactation and use of formula feeds on development of atopic eczema in high risk infants. *BMJ*, 299(6693): 228-30.	Excluded based on inclusion and exclusion criteria: retracted paper
Chandra, R.K. 2002. Breast feeding, hydrolysate formulas and delayed introduction of selected foods in the prevention of food hypersensitivity and allergic disease. *Nutrition Research*, 22(1-2): 125-135.	Excluded based on inclusion and exclusion criteria: narrative review
Chiang, W.C., Kidon, M.I., Liew, W.K., Goh, A., Tang, J.P. & Chay, O.M. 2007. The changing face of food hypersensitivity in an Asian community. *Clin Exp Allergy*, 37(7): 1055-61.	Excluded based on inclusion and exclusion criteria: patient population
Collier, P.M., Ursell, A., Zaremba, K., Payne, C.M., Staughton, R.C. & Sanders, T. 1993. Effect of regular consumption of oily fish compared with white fish on chronic plaque psoriasis. *Eur J Clin Nutr*, 47(4): 251-4.	Excluded based on inclusion and exclusion criteria: patient population
Connett, G.J., Gerez, I., Cabrera-Morales, E.A., Yuenyongviwat, A., Ngamphaiboon, J., Chatchatee, P., Sangsupawanich, P. *et al.* 2012. A population-based study of fish allergy in the Philippines, Singapore and Thailand. *Int Arch Allergy Immunol*, 159(4): 384-90.	Excluded based on inclusion and exclusion criteria: cross-sectional study
de Mello, V.D., Dahlman, I., Lankinen, M., Kurl, S., Pitkänen, L., Laaksonen, D.E., Schwab, U.S. & Erkkilä, A.T. 2019. The effect of different sources of fish and camelina sativa oil on immune cell and adipose tissue mRNA expression in subjects with abnormal fasting glucose metabolism: a randomized controlled trial. *Nutr Diabetes*, 9(1): 1	Excluded based on inclusion and exclusion criteria: patient population
Devereux, G. 2008. Maternal diet during pregnancy: an emerging risk factor for childhood asthma. *Expert Rev Clin Immunol*, 4(6): 663-8.	Excluded based on inclusion and exclusion criteria: narrative review
D'Hooghe M, B., Haentjens, P., Nagels, G. & De Keyser, J. 2012. Alcohol, coffee, fish, smoking and disease progression in multiple sclerosis. *Eur J Neurol*, 19(4): 616-24.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Douros, K., Tsabouri, S., Feketea, G., Grammeniatis, V., Koliofoti, E.G., Papadopoulos, M., Sardeli, O., Triga, M. & Priftis, K.N. 2019. Retrospective study identified fish and milk as the main culprits in cases of food protein-induced enterocolitis syndrome. *Acta Paediatr*, 108(10): 1901-1904	Excluded based on inclusion and exclusion criteria: retrospective study
Eigenmann, P.A., Sicherer, S.H., Borkowski, T.A., Cohen, B.A. & Sampson, H.A. 1998. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics*, 101(3): E8.	Excluded based on inclusion and exclusion criteria: patient population
Ellul-Micallef, R. 1983. Effect of oral sodium cromoglycate and ketotifen in fish-induced bronchial asthma. *Thorax*, 38(7): 527-30.	Excluded based on inclusion and exclusion criteria: patient population
Ferraro, V., Zanconato, S. & Carraro, S. 2019. Timing of Food Introduction and the Risk of Food Allergy. *Nutrients*, 11(5)	Excluded based on inclusion and exclusion criteria: narrative review
García-Rodríguez, C.E., Olza, J., Aguilera, C.M., Mesa, M.D., Miles, E.A., Noakes, P.S., Vlachava, M. *et al.* 2012. Plasma inflammatory and vascular homeostasis biomarkers increase during human pregnancy but are not affected by oily fish intake. *J Nutr*, 142(7): 1191-6.	Excluded based on inclusion and exclusion criteria: inflammatory markers and not measured health outcome
Hageman, J.H., Hooyenga, P., Diersen-Schade, D.A., Scalabrin, D.M., Wichers, H.J. & Birch, E.E. 2012. The impact of dietary long-chain polyunsaturated fatty acids on respiratory illness in infants and children. *Curr Allergy Asthma Rep*, 12(6): 564-73.	Excluded based on inclusion and exclusion criteria: narrative review
Hansen, T.K. & Bindslev-Jensen, C. 1992. Codfish allergy in adults. Identification and diagnosis. *Allergy*, 47(6): 610-7	Excluded based on inclusion and exclusion criteria: patient population
Hanson, C., Sayles, H., Rutten, E., Wouters, E.F.M., MacNee, W., Calverley, P., Meza, J.L. & Rennard, S. 2014. The Association Between Dietary Intake and Phenotypical Characteristics of COPD in the ECLIPSE Cohort. *Chronic Obstr Pulm Dis*, 1(1): 115-124.	Excluded based on inclusion and exclusion criteria: not included health outcome
Hattevig, G., Kjellman, B., Sigurs, N., Grodzinsky, E., Hed, J. & Björkstén, B. 1990. The effect of maternal avoidance of eggs, cow's milk, and fish during lactation on the development of IgE, IgG, and IgA antibodies in infants. *J Allergy Clin Immunol*, 85(1 Pt 1): 108-15..	Excluded based on inclusion and exclusion criteria: wrong health outcome (only IgE antibodies)

TABLE A3.3 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY" (cont.)**

Study (*n* = 120)	Reason for exclusion
Helbling, A., Haydel, R., Jr., McCants, M.L., Musmand, J.J., El-Dahr, J. & Lehrer, S.B. 1999. Fish allergy: is cross-reactivity among fish species relevant? Double-blind placebo-controlled food challenge studies of fish allergic adults. *Ann Allergy Asthma Immunol*, 83(6 Pt 1): 517-23	Excluded based on inclusion and exclusion criteria: patients with fish allergy
Hong, S.J., Lee, M.S., Lee, S.Y., Ahn, K.M., Oh, J.W., Kim, K.E., Lee, J.S. & Lee, H.B. 2006. High body mass index and dietary pattern are associated with childhood asthma. *Pediatr Pulmonol*, 41(12): 1118-24.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Hooper, R., Heinrich, J., Omenaas, E., Sausenthaler, S., Garcia-Larsen, V., Bakolis, I. & Burney, P. 2010. Dietary patterns and risk of asthma: results from three countries in European Community Respiratory Health Survey-H. *British Journal of Nutrition*, 103(9): 1354-1365.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Hua, M.C., Yao, T.C., Chen, C.C., Tsai, M.H., Liao, S.L., Lai, S.H., Chiu, C.Y., Su, K.W., Yeh, K.W. & Huang, J.L. 2017. Introduction of various allergenic foods during infancy reduces risk of IgE sensitization at 12 months of age: a birth cohort study. *Pediatr Res*, 82(5): 733-740.	Excluded based on inclusion and exclusion criteria: wrong health outcome (only IgE sensitization)
Infante, S., Marco-Martín, G., Sánchez-Domínguez, M., Rodríguez-Fernández, A., Fuentes-Aparicio, V., Alvarez-Perea, A., Cabrera-Freitag, P., Morales-Cabeza, C., Zubeldia, J.M. & Zapatero, L. 2018. Food protein-induced enterocolitis syndrome by fish: Not necessarily a restricted diet. *Allergy*, 73(3): 728-732..	Excluded based on inclusion and exclusion criteria: not included health outcome (food protein-induced enterocolitis syndrome)
Infante, S., Pérez-Pallisé, E., Skrabski, F., Cabrera-Freitag, P., Morales-Cabeza, C., Fuentes-Aparicio, V., Alvarez-Perea, A. & Zubeldia, J.M. 2021. Poor prognosis of food protein-induced enterocolitis syndrome to fish. *Pediatr Allergy Immunol, 32(3): 560-565*	Excluded based on inclusion and exclusion criteria: not included health outcome (food protein-induced enterocolitis syndrome)
Jelinek, G.A., Hadgkiss, E.J., Weiland, T.J., Pereira, N.G., Marck, C.H. & van der Meer, D.M. 2013. Association of fish consumption and Ω 3 supplementation with quality of life, disability and disease activity in an international cohort of people with multiple sclerosis. *Int J Neurosci*, 123(11): 792-800.	Excluded based on inclusion and exclusion criteria: omega-3 supplementation only
Jonsson, K., Barman, M., Brekke, H.K., Hesselmar, B., Johansen, S., Sandberg, A.S. & Wold, A.E. 2017. Late introduction of fish and eggs is associated with increased risk of allergy development - results from the FARMFLORA birth cohort. *Food & Nutrition Research*, 61.	Excluded based on inclusion and exclusion criteria: retrospective study
Jonsson, K., Barman, M., Moberg, S., Sjöberg, A., Brekke, H.K., Hesselmar, B., Sandberg, A.S. & Wold, A.E. 2016. Serum fatty acids in infants, reflecting family fish consumption, were inversely associated with allergy development but not related to farm residence. *Acta Paediatr*, 105(12): 1462-1471.	Excluded based on inclusion and exclusion criteria: not measured fish consumption (only fatty acids)
Jonsson, K., Green, M., Barman, M., Sjöberg, A., Brekke, H.K., Wold, A.E. & Sandberg, A.S. 2016. Diet in 1-year-old farm and control children and allergy development: results from the FARMFLORA birth cohort. *Food Nutr Re*s, 60: 32721.	Excluded based on inclusion and exclusion criteria: retrospective study
Klingberg, S., Brekke, H.K. & Ludvigsson, J. 2019. Introduction of fish and other foods during infancy and risk of asthma in the All Babies In Southeast Sweden cohort study. *European Journal of Pediatrics*, 178(3): 395-402..	Excluded based on inclusion and exclusion criteria: covered by birth and growth
Knope, K., Sloan-Gardner, T.S. & Stafford, R.J. 2014. Histamine fish poisoning in Australia, 2001 to 2013. *Commun Dis Intell Q Rep*, 38(4): E285-93..	Excluded based on inclusion and exclusion criteria: patient population
Kusunoki, T., Takeuchi, J., Morimoto, T., Sakuma, M., Yasumi, T., Nishikomori, R., Higashi, A. & Heike, T. 2017. Fruit intake reduces the onset of respiratory allergic symptoms in schoolchildren. *Pediatr Allergy Immunol*, 28(8): 793-800.	Excluded based on inclusion and exclusion criteria: questionnaire
Lavon, O., Lurie, Y. & Bentur, Y. 2008. Scombroid fish poisoning in Israel, 2005-2007. *Isr Med Assoc J*, 10(11): 789-92.	Excluded based on inclusion and exclusion criteria: fish poisoning
Lee, H.L., Tang, M.M., Bakhtiar, M.F., Mohamad Yadzir, Z.H. & Johar, A. 2021. Sensitization to Local Seafood Allergens in Adult Patients with Atopic Dermatitis in Malaysia. *Int Arch Allergy Immunol*, 182(2): 153-157	Excluded based on inclusion and exclusion criteria: patients with atopic dermatitis
Lindqvist, H.M., Gjertsson, I., Eneljung, T. & Winkvist, A. 2018. Influence of Blue Mussel (Mytilus edulis) Intake on Disease Activity in Female Patients with Rheumatoid Arthritis: The MIRA Randomized Cross-Over Dietary Intervention. *Nutrients*, 10(4).	Excluded based on inclusion and exclusion criteria: patients with rheumatoid arthritis
Losol, P., Rezwan, F.I., Patil, V.K., Venter, C., Ewart, S., Zhang, H., Arshad, S.H., Karmaus, W. & Holloway, J.W. 2019. Effect of gestational oily fish intake on the risk of allergy in children may be influenced by FADS1/2, ELOVL5 expression and DNA methylation. *Genes Nutr*, 14: 20	Excluded based on inclusion and exclusion criteria: children
Ludman, S., Harmon, M., Whiting, D. & du Toit, G. 2014. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. *Ann Allergy Asthma Immunol*, 113(3): 290-4.	Excluded based on inclusion and exclusion criteria: food protein-induced enterocolitis syndrome
Machowicz, A., Hall, I., de Pablo, P., Rauz, S., Richards, A., Higham, J., Poveda-Gallego, A. *et al.* 2020. Mediterranean diet and risk of Sjogren's syndrome. *Clinical and Experimental Rheumatology*, 38(4): S216-S221	Excluded based on inclusion and exclusion criteria: patients with Sjögren's syndrome
Merchant, A.T., Curhan, G.C., Rimm, E.B., Willett, W.C. & Fawzi, W.W. 2005. Intake of n-6 and n-3 fatty acids and fish and risk of community-acquired pneumonia in US men. *Am J Clin Nutr*, 82(3): 668-74.	Excluded based on inclusion and exclusion criteria: pneumonia is not allergy, mostly caused by microorganisms
Miles, E.A. & Calder, P.C. 2017. Can Early Omega-3 Fatty Acid Exposure Reduce Risk of Childhood Allergic Disease? *Nutrients*, 9(7)	Excluded based on inclusion and exclusion criteria: only omega-3
Milewska-Wróbel, D. & Lis-βwiβty, A. 2020. Does maternal diet during pregnancy influence clinical and laboratory characteristics of infantile-onset atopic dermatitis? *Eur Ann Allergy Clin Immunol*, 52(6): 277-279.	Excluded based on inclusion and exclusion criteria: exposure during maternal diet during pregnancy
Minamino, H., Katsushima, M., Torii, M., Hashimoto, M., Fujita, Y., Ikeda, K., Yamamoto, W. *et al.* 2021. Habitual fish intake negatively correlates with prevalence of frailty among patients with rheumatoid arthritis. *Scientific Reports*, 11(1).	Excluded based on inclusion and exclusion criteria: cross-sectional study
Miyake, Y., Sasaki, S., Tanaka, K., Ohya, Y., Matsunaga, I., Yoshida, T., Hirota, Y. & Oda, H. 2008. Relationship between dietary fat and fish intake and the prevalence of atopic eczema in pregnant Japanese females: baseline data from the Osaka Maternal and Child Health Study. *Asia Pac J Clin Nutr*, 17(4): 612-9.	Excluded based on inclusion and exclusion criteria: cross-sectional study

TABLE A3.3 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY" (cont.)**

Study (n = 120)	Reason for exclusion
Mori, T.A. & Beilin, L.J. 2004. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*, 6(6): 461-7.	Excluded based on inclusion and exclusion criteria: only omega-3
Muche-Borowski, C., Kopp, M., Reese, I., Sitter, H., Werfel, T. & Schäfer, T. 2009. Allergy prevention. *Dtsch Arztebl Int*, 106(39): 625-31.	Excluded based on inclusion and exclusion criteria: review article
Murakami, I., Murakami, K., Hashimoto, M., Tanaka, M., Ito, H., Fujii, T., Torii, M. *et al.* 2020. Intake frequency of vegetables or seafoods negatively correlates with disease activity of rheumatoid arthritis. *Plos One*, 15(2).	Excluded based on inclusion and exclusion criteria: patient population
Nagel, G., Weinmayr, G., Kleiner, A., Garcia-Marcos, L., Strachan, D.P. & Grp, I.P.T.S. 2010. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. *Thorax*, 65(6): 516-522.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Norback, D., Zhao, Z.H., Wang, Z.H., Wieslander, G., Mi, Y.H. & Zhang, Z. 2007. Asthma, eczema, and reports on pollen and cat allergy among pupils in Shanxi province, China. *International Archives of Occupational and Environmental Health*, 80(3): 207-216.	Excluded based on inclusion and exclusion criteria: not related to fish consumption
Papadopol, A. 2018. A retrospective cohort analysis investigating the effects of salmon consumption during pregnancy on signs of allergy in children at 30 months of age. *Clinical and Experimental Allergy*, 48(11):1565-1565.	Excluded based on inclusion and exclusion criteria: covered by birth and growth
Papadopoulou, A., Lagousi, T., Hatzopoulou, E., Korovessi, P., Kostaridou, S. & Mermiri, D.Z. 2021. Atypical food protein-induced enterocolitis syndrome in children: Is IgE sensitisation an issue longitudinally? *Allergol Immunopathol (Madr)*, 49(3): 73-82.	Excluded based on inclusion and exclusion criteria: not related to fish consumption
Resano, A., Crespo, E., Fernández Benítez, M., Sanz, M.L. & Oehling, A. 1998. Atopic dermatitis and food allergy. *J Investig Allergol Clin Immunol*, 8(5): 271-6.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Rodriguez-Rodriguez, E., Perea, J.M., Jimenez, A.I., Rodriguez-Rodriguez, P., Lopez-Sobaler, A.M. & Ortega, R.M. 2010. Fat intake and asthma in Spanish schoolchildren. *European Journal of Clinical Nutrition*, 64(10): 1065-1071	Excluded based on inclusion and exclusion criteria: cross-sectional study
Sampson, H.A. 2001. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*, 107(5): 891-6.	Excluded based on inclusion and exclusion criteria: modelling
Shams, K., Grindlay, D.J.C. & Williams, H.C. 2011. What's new in atopic eczema? An analysis of systematic reviews published in 2009-2010. *Clinical and Experimental Dermatology*, 36(6): 573-578.	Excluded based on inclusion and exclusion criteria: review of systematic review studies
Sinitkul, R., Manuyakorn, W., Kamchaisatian, W., Vilaiyuk, S., Benjaponpitak, S., Lertudompholwanit, C. & Treepongkaruna, S. 2018. De novo food allergy in pediatric liver transplantation recipients. *Asian Pac J Allergy Immunol*, 36(3): 166-174.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Sopo, S.M., Giorgio, V., Dello Iacono, I., Novembre, E., Mori, F. & Onesimo, R. 2012. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy*, 42(8): 1257-65.	Excluded based on inclusion and exclusion criteria: retrospective study
Sparks, J.A., Iversen, M.D., Kroouze, R.M., Mahmoud, T.G., Triedman, N.A., Kalia, S.S., Atkinson, M.L. *et al.* 2014. Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study: Rationale and design for a randomized controlled trial evaluating rheumatoid arthritis risk education to first-degree relatives. *Contemporary Clinical Trials*, 39(1): 145-157.	Excluded based on inclusion and exclusion criteria: protocol
Stratakis, N., Conti, D.V., Borras, E., Sabido, E., Roumeliotaki, T., Papadopoulou, E., Agier, L. *et al.* 2020. Association of Fish Consumption and Mercury Exposure During Pregnancy With Metabolic Health and Inflammatory Biomarkers in Children. *Jama Network Open*, 3(3)	Excluded based on inclusion and exclusion criteria: mercury and inflammatory markers; exclusion criteria
Syrjälä, E., Nevalainen, J., Peltonen, J., Takkinen, H.M., Hakola, L., Åkerlund, M., Veijola, R. *et al.* 2019. A Joint Modeling Approach for Childhood Meat, Fish and Egg Consumption and the Risk of Advanced Islet Autoimmunity. *Sci Rep*, 9(1): 7760.	Excluded based on inclusion and exclusion criteria: modelling
Saadeh, D., Salameh, P., Caillaud, D., Charpin, D., De Blay, F., Kopferschmitt, C., ... & Raherison, C. 2015. Prevalence and association of asthma and allergic sensitization with dietary factors in schoolchildren: data from the french six cities study. *BMC Public Health*, 15, 1-11.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Tamay, Z., Akcay, A., Ergin, A. & Guler, N. 2013. Effects of dietary habits and risk factors on allergic rhinitis prevalence among Turkish adolescents. *Int J Pediatr Otorhinolaryngol*, 77(9): 1416-23.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Tani, S., Matsuo, R., Atsumi, W., Kawauchi, K., Ashida, T., Yagi, T., Imatake, K. *et al.* 2021. Higher Frequency of Fish Intake May Be Associated with a Lower Neutrophil/Lymphocyte Ratio: Anti-Atherosclerotic Effects of Fish Consumption. *Annals of Nutrition and Metabolism*, 77(3): 146-153	Excluded based on inclusion and exclusion criteria: cross-sectional study
Tedeschi, S.K., Bathon, J.M., Giles, J.T., Lin, T.C., Yoshida, K. & Solomon, D.H. 2018. Relationship Between Fish Consumption and Disease Activity in Rheumatoid Arthritis. *Arthritis Care & Research*, 70(3): 327-332	Excluded based on inclusion and exclusion criteria: cross-sectional analysis
Thong, B.Y., Cheng, Y.K., Leong, K.P., Tang, C.Y. & Chng, H.H. 2007. Immediate food hypersensitivity among adults attending a clinical immunology/allergy centre in *Singapore. Singapore Med J*, 48(3): 236-40.	Excluded based on inclusion and exclusion criteria: retrospective review
Turner, P., Ng, I., Kemp, A. & Campbell, D. 2011. Seafood allergy in children: a descriptive study. *Ann Allergy Asthma Immunol*, 106(6): 494-501.	Excluded based on inclusion and exclusion criteria: retrospective review
Untersmayr, E., Vestergaard, H., Malling, H.J., Jensen, L.B., Platzer, M.H., Boltz-Nitulescu, G., Scheiner, O., Skov, P.S., Jensen-Jarolim, E. & Poulsen, L.K. 2007. Incomplete digestion of codfish represents a risk factor for anaphylaxis in patients with allergy. *J Allergy Clin Immunol*, 119(3): 711-7.	Excluded based on inclusion and exclusion criteria: absorption kinetics of fish protein was tested in patients with fish allergy
Urwin, H.J., Miles, E.A., Noakes, P.S., Kremmyda, L.S., Vlachava, M., Diaper, N.D., Godfrey, K.M., Calder, P.C., Vulevic, J. & Yaqoob, P. 2014. Effect of salmon consumption during pregnancy on maternal and infant faecal microbiota, secretory IgA and calprotectin. *Br J Nutr*, 111(5): 773-84.	Excluded based on inclusion and exclusion criteria: cross-sectional study

TABLE A3.3 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY" (cont.)**

Study (n = 120)	Reason for exclusion
Wang, J.J., Rochtchina, E., Smith, W., Klein, R., Klein, B.E., Joshi, T., Sivakumaran, T.A., Iyengar, S. & Mitchell, P. 2009. Combined effects of complement factor H genotypes, fish consumption, and inflammatory markers on long-term risk for age-related macular degeneration in a cohort. *Am J Epidemiol*, 169(5): 633-41.	Excluded based on inclusion and exclusion criteria: age-related macular degeneration
Xepapadaki, P., Kitsioulis, N.A., Manousakis, E., Manolaraki, I., Douladiris, N. & Papadopoulos, N.G. 2019. Remission Patterns of Food Protein-Induced Enterocolitis Syndrome in a Greek Pediatric Population. *Int Arch Allergy Immunol*, 180(2): 113-119.	Excluded based on inclusion and exclusion criteria: retrospective study
Yadana, S., Talegawkar, S.A., Mathad, J.S., Alexander, M., Rajagopalan, K., Kumar, P., Naik, S. *et al.* 2020. Association of Vegetable and Animal Flesh Intake with Inflammation in Pregnant Women from India. *Nutrients*, 12(12).	Excluded based on inclusion and exclusion criteria: dietary patterns study and markers of immunity
Ye, S.Q., Mo, X.M., Liu, J.F., Yan, F.G. & Chen, D.C. 2019. Factors Influencing Atopic Dermatitis Incidence in Offspring. *Iranian Journal of Allergy Asthma and Immunology*, 18(4): 347-357.	Excluded based on inclusion and exclusion criteria: review paper
Zhan, T., Ali, A., Choi, J.G., Lee, M., Leung, J., Dellon, E.S., Garber, J.J. & Hur, C. 2018. Model to Determine the Optimal Dietary Elimination Strategy for Treatment of Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol*, 16(11): 1730-1737.e2.	Excluded based on inclusion and exclusion criteria: modelling study
Calvani, M., Alessandri, C., Sopo, S.M., Panetta, V., Pingitore, G., Tripodi, S., Zappalà, D. & Zicari, A.M. 2006. Consumption of fish, butter and margarine during pregnancy and development of allergic sensitizations in the offspring: role of maternal atopy. *Pediatr Allergy Immunol*, 17(2): 94-102.	Excluded for further assessment as the primary study had already been assessed in one of the included systematic reviews
Alm, B., Goksor, E., Thengilsdottir, H., Pettersson, R., Mollborg, P., Norvenius, G., Erdes, L., Aberg, N. & Wennergren, G. 2011. Early protective and risk factors for allergic rhinitis at age 41/2 yr. *Pediatric Allergy and Immunology*, 22(4): 398-404	Excluded for further assessment as the primary study had already been assessed in a systematic review that was included in VKM 2022
Benito-Garcia, E., Feskanich, D., Hu, F.B., Mandl, L.A. & Karlson, E.W. 2007. Protein, iron, and meat consumption and risk for rheumatoid arthritis: a prospective cohort study. *Arthritis Research & Therapy*, 9(1).	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Di Giuseppe, D., Wallin, A., Bottai, M., Askling, J. & Wolk, A. 2014. Long-term intake of dietary long-chain n-3 polyunsaturated fatty acids and risk of rheumatoid arthritis: a prospective cohort study of women. *Annals of the Rheumatic Diseases*, 73(11): 1949-1953.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Dotterud, C.K., Storrø, O., Simpson, M.R., Johnsen, R. & Øien, T. 2013. The impact of pre- and postnatal exposures on allergy related diseases in childhood: a controlled multicentre intervention study in primary health care. *BMC Public Health*, 13: 123.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hamazaki, K., Tsuchida, A., Takamori, A., Tanaka, T., Ito, M., Inadera, H., Kawamoto, T. *et al.* 2019. Dietary intake of fish and omega-3 polyunsaturated fatty acids and physician-diagnosed allergy in Japanese population: The Japan Environment and Children's Study. *Nutrition*, 61: 194-201.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Jedrychowski, W., Flak, E., Mroz, E., Pac, A., Jacek, R., Sochacka-Tatara, E., Spengler, J., Rauh, V. & Perera, F. 2008. Modulating effects of maternal fish consumption on the occurrence of respiratory symptoms in early infancy attributed to prenatal exposure to fine particles. *Annals of Nutrition and Metabolism*, 52(1): 8-16.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Jedrychowski, W., Perera, F., Maugeri, U., Mrozek-Budzyn, D., Miller, R.L., Flak, E., Mroz, E., Jacek, R. & Spengler, J.D. 2011. Effects of Prenatal and Perinatal Exposure to Fine Air Pollutants and Maternal Fish Consumption on the Occurrence of Infantile Eczema. *International Archives of Allergy and Immunology*, 155(3): 275-281	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Kampman, M.T., Wilsgaard, T. & Mellgren, S.I. 2007. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *J Neurol*, 254(4): 471-7.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Khan, F., Orson, F., Ogawa, Y., Parker, C. & Davis, C.M. 2011. Adult seafood allergy in the Texas Medical Center: A 13-year experience. *Allergy Rhinol (Providence)*, 2(2): e71-7.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kiefte-de Jong, J.C., de Vries, J.H., Franco, O.H., Jaddoe, V.W., Hofman, A., Raat, H., de Jongste, J.C. & Moll, H.A. 2012. Fish consumption in infancy and asthma-like symptoms at preschool age. *Pediatrics*, 130(6): 1060-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kull, I., Bergström, A., Lilja, G., Pershagen, G. & Wickman, M. 2006. Fish consumption during the first year of life and development of allergic diseases during childhood. *Allergy*, 61(8): 1009-15.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Leermakers, E.T., Sonnenschein-van der Voort, A.M., Heppe, D.H., de Jongste, J.C., Moll, H.A., Franco, O.H., Hofman, A., Jaddoe, V.W. & Duijts, L. 2013. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: the Generation R Study. *Eur J Clin Nutr*, 67(4): 353-9.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that was included in VKM 2022
Li, J., Xun, P., Zamora, D., Sood, A., Liu, K., Daviglus, M., Iribarren, C., Jacobs, D., Jr., Shikany, J.M. & He, K. 2013. Intakes of long-chain omega-3 (n-3) PUFAs and fish in relation to incidence of asthma among American young adults: the CARDIA study. *Am J Clin Nutr*, 97(1): 173-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Loo, E.X.L., Ong, L., Goh, A., Chia, A.R., Teoh, O.H., Colega, M.T., Chan, Y.H. *et al.* 2017. Effect of Maternal Dietary Patterns during Pregnancy on Self-Reported Allergic Diseases in the First 3 Years of Life: Results from the GUSTO Study. *Int Arch Allergy Immunol*, 173(2): 105-113.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Lumia, M., Luukkainen, P., Tapanainen, H., Kaila, M., Erkkola, M., Uusitalo, L., Niinistö, S. *et al.* 2011. Dietary fatty acid composition during pregnancy and the risk of asthma in the offspring. *Pediatr Allergy Immunol*, 22(8): 827-35	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Lumia, M., Takkinen, H.M., Luukkainen, P., Kaila, M., Lehtinen-Jacks, S., Nwaru, B.I., Tuokkola, J. *et al.* 2015. Food consumption and risk of childhood asthma. *Pediatr Allergy Immunol*, 26(8): 789-96.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Lundgren, S.N., Madan, J.C., Emond, J.A., Morrison, H.G., Christensen, B.C., Karagas, M.R. & Hoen, A.G. 2018. Maternal diet during pregnancy is related with the infant stool microbiome in a delivery mode-dependent manner. *Microbiome*, 6	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Magnusson, J., Kull, I., Westman, M., Håkansson, N., Wolk, A., Melén, E., Wickman, M. & Bergström, A. 2015. Fish and polyunsaturated fat intake and development of allergic and nonallergic rhinitis. *J Allergy Clin Immunol*, 136(5): 1247-53.e1-2.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TABLE A3.3 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "ALLERGY AND IMMUNOLOGY" (cont.)**

Study (n = 120)	Reason for exclusion
Magnusson, J., Kull, I., Rosenlund, H., Håkansson, N., Wolk, A., Melén, E., Wickman, M. & Bergström, A. 2013. Fish consumption in infancy and development of allergic disease up to age 12 y. *Am J Clin Nutr*, 97(6): 1324-30.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Maslova, E., Strøm, M., Oken, E., Campos, H., Lange, C., Gold, D. & Olsen, S.F. 2013. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis - longitudinal evidence from the Danish National Birth Cohort. *Br J Nutr*, 110(7): 1313-25.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Miyake, Y., Tanaka, K., Okubo, H., Sasaki, S. & Arakawa, M. 2012. Dietary meat and fat intake and prevalence of rhinoconjunctivitis in pregnant Japanese women: baseline data from the Kyushu Okinawa Maternal and Child Health Study. *Nutr J*, 11: 19.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Miyake, Y., Sasaki, S., Tanaka, K., Ohya, Y., Miyamoto, S., Matsunaga, I., Yoshida, T., Hirota, Y. & Oda, H. 2007. Fish and fat intake and prevalence of allergic rhinitis in Japanese females: the Osaka Maternal and Child Health Study. *J Am Coll Nutr*, 26(3): 279-87.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Miyake, Y., Tanaka, K., Okubo, H., Sasaki, S. & Arakawa, M. 2013. Maternal fat intake during pregnancy and wheeze and eczema in Japanese infants: the Kyushu Okinawa Maternal and Child Health Study. *Annals of Epidemiology*, 23(11): 674-680.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Nafstad, P., Nystad, W., Magnus, P. & Jaakkola, J.J.K. 2003. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. *Journal of Asthma*, 40(4): 343-348	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Noakes, P.S., Vlachava, M., Kremmyda, L.S., Diaper, N.D., Miles, E.A., Erlewyn-Lajeunesse, M., Williams, A.P., Godfrey, K.M. & Calder, P.C. 2012. Increased intake of oily fish in pregnancy: effects on neonatal immune responses and on clinical outcomes in infants at 6 mo. *Am J Clin Nutr*, 95(2): 395-404.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Nwaru, B.I., Takkinen, H.M., Niemelä, O., Kaila, M., Erkkola, M., Ahonen, S., Tuomi, H. *et al.* 2013. Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. *Allergy*, 68(4): 507-16.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Oien, T., Storrø, O. & Johnsen, R. 2010. Do early intake of fish and fish oil protect against eczema and doctor-diagnosed asthma at 2 years of age? A cohort study. *J Epidemiol Community Health*, 64(2): 124-9.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Ozawa, N., Shimojo, N., Suzuki, Y., Ochiai, S., Nakano, T., Morita, Y., Inoue, Y., Arima, T., Suzuki, S. & Kohno, Y. 2014. Maternal intake of Natto, a Japan's traditional fermented soybean food, during pregnancy and the risk of eczema in Japanese babies. *Allergol Int*, 63(2): 261-6.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Pedersen, M., Stripp, C., Klarlund, M., Olsen, S.F., Tjonneland, A.M. & Frisch, M. 2005. Diet and risk of rheumatoid arthritis in a prospective cohort. *Journal of Rheumatology*, 32(7): 1249-1252	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Pele, F., Bajeux, E., Gendron, H., Monfort, C., Rouget, F., Multigner, L., Viel, J.F. & Cordier, S. 2013. Maternal fish and shellfish consumption and wheeze, eczema and food allergy at age two: a prospective cohort study in Brittany, France. *Environmental Health*, 12..	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Romieu, I., Torrent, M., Garcia-Esteban, R., Ferrer, C., Ribas-Fito, N., Anto, J.M. & Sunyer, J. 2007. Maternal fish intake during pregnancy and atopy and asthma in infancy. *Clinical and Experimental Allergy*, 37(4): 518-525.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Saito, K., Yokoyama, T., Miyake, Y., Sasaki, S., Tanaka, K., Ohya, Y. & Hirota, Y. 2010. Maternal meat and fat consumption during pregnancy and suspected atopic eczema in Japanese infants aged 3-4 months: The Osaka Maternal and Child Health Study. *Pediatric Allergy and Immunology*, 21(1): 38-46.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Sausenthaler, S., Koletzko, S., Schaaf, B., Lehmann, I., Borte, M., Herbarth, O., von Berg, A., Wichmann, H.E. & Heinrich, J. 2007. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr*, 85(2): 530-7	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Sparks, J.A., O'Reilly, E.J., Barbhaiya, M., Tedeschi, S.K., Malspeis, S., Lu, B., Willett, W.C., Costenbader, K.H. & Karlson, E.W. 2019. Association of fish intake and smoking with risk of rheumatoid arthritis and age of onset: a prospective cohort study. *BMC Musculoskeletal Disorders*, 20:1-13.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Stratakis, N., Roumeliotaki, T., Oken, E., Ballester, F., Barros, H., Basterrechea, M., Cordier, S. *et al.* 2017. Fish and seafood consumption during pregnancy and the risk of asthma and allergic rhinitis in childhood: a pooled analysis of 18 European and US birth cohorts. *Int J Epidemiol*, 46(5): 1465-1477.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Talaei, M., Sdona, E., Calder, P.C., Jones, L.R., Emmett, P.M., Granell, R., Bergstrom, A., Melen, E. & Shaheen, S.O. 2021. Intake of n-3 polyunsaturated fatty acids in childhood, FADS genotype and incident asthma. *European Respiratory Journal*, 58(3)	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Willers, S.M., Wijga, A.H., Brunekreef, B., Scholtens, S., Postma, D.S., Kerkhof, M., de Jongste, J.C. & Smit, H.A. 2011. Childhood diet and asthma and atopy at 8 years of age: the PIAMA birth cohort study. *Eur Respir J*, 37(5): 1060-7.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Willers, S.M., Devereux, G., Craig, L.C., McNeill, G., Wijga, A.H., Abou El-Magd, W., Turner, S.W., Helms, P.J. & Seaton, A. 2007. Maternal food consumption during pregnancy and asthma, respiratory and atopic symptoms in 5-year-old children. *Thorax*, 62(9): 773-9.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Willers, S.M., Wijga, A.H., Brunekreef, B., Kerkhof, M., Gerritsen, J., Hoekstra, M.O., de Jongste, J.C. & Smit, H.A. 2008. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Respir Crit Care Med*, 178(2): 124-31.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Zeiger, R.S., Heller, S., Mellon, M.H., Forsythe, A.B., O'Connor, R.D., Hamburger, R.N. & Schatz, M. 1989. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol*, 84(1): 72-89.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews

BIRTH AND GROWTH OUTCOMES

TABLE A3.4 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "BIRTH AND GROWTH OUTCOMES"

Study (n = 1)	Reason for exclusion
Hibbeln, J. R. Spiller, P. Brenna, J. T. Golding, J. Holub, B. J. Harris, W. S. ... & Carlson, S. E. (2019). Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews. Prostaglandins, Leukotrienes and Essential Fatty Acids, 151, 14-36.	Excluded based on inclusion and exclusion criteria: Wrong outcome (review included in neurocognitive outcomes)

TABLE A3.5 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "BIRTH AND GROWTH"

Study (*n* = 31)	Reason for exclusion
Andersen, R. Biltoft-Jensen, A. Christensen, T. Andersen, E.W., Ege, M. Thorsen, A.V., Tetens, I. *et al*. 2014. Dietary effects of introducing school meals based on the New Nordic Diet–a randomised controlled trial in Danish children. The OPUS School Meal Study. *British Journal of Nutrition*, 111(11):1967-1976.	Excluded based on inclusion and exclusion criteria: Nordic diet meal study, data on nutrient intake and fish but no relevant outcome
Bryant, J. Hanson, M. Peebles, C. Davies, L. Inskip, H. Robinson, S. Godfrey, K.M. *et al*. 2015. Higher oily fish consumption in late pregnancy is associated with reduced aortic stiffness in the child at age 9 years. *Circulation research*, 116(7):1202-1205.	Excluded based on inclusion and exclusion criteria: oily fish consumption and aortic stiffness; wrong outcome
Buck, G.M. Tee, G.P. Fitzgerald, E. F. Vena, J. E. Weiner, J.M. Swanson, M. *&* Msall, M.E. 2003. Maternal fish consumption and infant birth size and gestation: New York State Angler Cohort Study. *Environmental Health*, 2(1):1-9.	Excluded based on inclusion and exclusion criteria: retrospective fish consumption linked to cross-sectional infant data
Butler, L.J. Janulewicz, P.A. Carwile, J.L. White, R.F. Winter, M.R. *&* Aschengrau, A. 2017. Childhood and adolescent fish consumption and adult neuropsychological performance: An analysis from the Cape Cod Health Study. *Neurotoxicology and teratology*, 61:47-57.	Excluded based on inclusion and exclusion criteria: retrospective cohort
Daniels, J.L. Longnecker, M.P. Rowland, A.S. Golding, J. *&* ALSPAC Study Team – University of Bristol Institute of Child Health. 2004. Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology*, 394-402.	Excluded based on inclusion and exclusion criteria: mercury and wrong outcome (cognitive development)
Emmett, P. M. Jones, L. R. *&* Golding, J. 2015. Pregnancy diet and associated outcomes in the Avon Longitudinal Study of Parents and Children. *Nutrition reviews*, 73(suppl_3):154-174.	Excluded based on inclusion and exclusion criteria: supplement article, narrative review
Fereidooni, B. *&* Jenabi, E. 2014. The use of omega 3 on pregnancy outcomes: a single-center study. *J Pak Med Assoc*, 64(12):1363-5.	Excluded based on inclusion and exclusion criteria: n-3 use and effects on pregnancy outcome
Larsen, S.C. Ängquist, L. Laurin, C. Morgen, C.S. Jakobsen, M.U. Paternoster, L. Nohr, E.A. *et al*. 2016. Association between maternal fish consumption and gestational weight gain: influence of molecular genetic predisposition to obesity. *PloS One*, 11(3):e0150105.	Excluded based on inclusion and exclusion criteria: no data on children (maternal fish intake and weight gain in pregnancy)
Maslova, E. Hansen, S. Strøm, M. Halldorsson, T.I. Grunnet, L.G. Vaag, A.A. *&* Olsen, S.F. 2018. Fish Intake in Pregnancy and Offspring Metabolic Parameters at Age 9–16 – Does Gestational Diabetes Modify the Risk? *Nutrients*, 10(10):1534.	Excluded based on inclusion and exclusion criteria: case-control study
Rylander, L. Strömberg, U. *&* Hagmar, L. 1995. Decreased birthweight among infants born to women with a high dietary intake of fish contaminated with persistent organochlorine compounds. *Scandinavian journal of work, environment & health*, 368-375.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Rylander, L. Strömberg, U. *&* Hagmar, L. 2000. Lowered birth weight among infants born to women with a high intake of fish contaminated with persistent organochlorine compounds. *Chemosphere*, 40(9-11):1255-1262.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Amezcua-Prieto, C. Martínez-Galiano, J. M. Salcedo-Bellido, I. Olmedo-Requena, R. Bueno-Cavanillas, A. *&* Delgado-Rodríguez, M. 2018. Maternal seafood intake and the risk of small for gestational age newborns: a case–control study in Spanish women. *BMJ Open*, 8(8):e020424.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Brantsæter, A.L. Birgisdottir, B.E. Meltzer, H.M. Kvalem, H.E. Alexander, J. Magnus, P. *&* Haugen, M. 2012. Maternal seafood consumption and infant birth weight, length and head circumference in the Norwegian Mother and Child Cohort Study. British *Journal of Nutrition*, 107(3):436-444.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Brantsæter, A.L. Englund-Ögge, L. Haugen, M. Birgisdottir, B.E. Knutsen, H.K. Sengpiel, V. Meltzer, H.M. *et al*. 2017. Maternal intake of seafood and supplementary long chain n-3 poly-unsaturated fatty acids and preterm delivery. *BMC pregnancy and childbirth*, 17(1):1-15.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Drouillet, P. Kaminski, M. De Lauzon-Guillain, B. Forhan, A. Ducimetière, P. Schweitzer, M. Charles, M.A. 2009. Association between maternal seafood consumption before pregnancy and fetal growth: evidence for an association in overweight women. The EDEN mother-child cohort. *Paediatric and perinatal epidemiology*, 23(1):76-86.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Guldner, L. Monfort, C. Rouget, F. Garlantezec, R. *&* Cordier, S. 2007. Maternal fish and shellfish intake and pregnancy outcomes: a prospective cohort study in Brittany, France. *Environmental Health*, 6, 1-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Halldorsson, T.I. Meltzer, H.M. Thorsdottir, I. Knudsen, V. *&* Olsen, S.F. 2007. Is high consumption of fatty fish during pregnancy a risk factor for fetal growth retardation? A study of 44,824 Danish pregnant women. *American journal of epidemiology,* 166(6):687-696.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Heppe, D.H. Steegers, E.A. Timmermans, S. den Breeijen, H. Tiemeier, H. Hofman, A. *&* Jaddoe, V. W. 2011. Maternal fish consumption, fetal growth and the risks of neonatal complications: the Generation R Study. *British journal of nutrition*, 105(6):938-949.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Guldner, L. Monfort, C. Rouget, F. Garlantezec, R. *&* Cordier, S. 2007. Maternal fish and shellfish intake and pregnancy outcomes: a prospective cohort study in Brittany, France. *Environmental Health*, 6, 1-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TABLE A3.5 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "BIRTH AND GROWTH" (cont.)

Klebanoff, M.A. Harper, M. Lai, Y. Thorp Jr, J. Sorokin, Y. Varner, M.W. Anderson, G.D. 2011. Fish consumption, erythrocyte fatty acids, and preterm birth. *Obstetrics and gynecology*, 117(5):1071.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Leventakou, V. Roumeliotaki, T. Martinez, D. Barros, H. Brantsaeter, A.L. Casas, M. Chatzi, L. *et al.* 2014. Fish intake during pregnancy, fetal growth, and gestational length in 19 European birth cohort studies. *The American journal of clinical nutrition*, 99(3):506-516.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mendez, M.A. Plana, E. Guxens, M. Morillo, C.M.F. Albareda, R.M. Garcia-Esteban, R. Sunyer, J. *et al.* 2010 Seafood consumption in pregnancy and infant size at birth: results from a prospective Spanish cohort. *Journal of Epidemiology & Community Health*, 64(3):216-222.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mohanty, A.F. Thompson, M.L. Burbacher, T.M. Siscovick, D.S. Williams, M.A. *&* Enquobahrie, D.A. 2015. Periconceptional seafood intake and fetal growth. *Paediatric and perinatal epidemiology*, 29(5):376-387.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Muthayya, S. Dwarkanath, P. Thomas, T. Ramprakash, S. Mehra, R. Mhaskar, A. Kurpad, A. *et al.* 2009. The effect of fish and ω-3 LCPUFA intake on low birth weight in Indian pregnant women. *European journal of clinical nutrition*, 63(3):340-346.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Nykjaer, C. Higgs, C. Greenwood, D.C. Simpson, N.A. Cade, J.E. *&* Alwan, N.A. 2019. Maternal fatty fish intake prior to and during pregnancy and risks of adverse birth outcomes: findings from a British Cohort. *Nutrients*, 11(3):643.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Olsen, S. F. 2002. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *Bmj*, 324(7335):447.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Ramon, R. Ballester, F. Aguinagalde, X. Amurrio, A. Vioque, J. Lacasana, M. Iniguez, C. *et al.* 2009. Fish consumption during pregnancy, prenatal mercury exposure, and anthropometric measures at birth in a prospective mother-infant cohort study in Spain. *The American journal of clinical nutrition*, 90(4):1047-1055.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Rogers, I. Emmett, P. Ness, A. *&* Golding, J. 2004. Maternal fish intake in late pregnancy and the frequency of low birth weight and intrauterine growth retardation in a cohort of British infants. *Journal of Epidemiology & Community Health*, 58(6):486-492.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Smid, M.C. Stuebe, A.M. Manuck, T.A. *&* Sen, S. 2019. Maternal obesity, fish intake, and recurrent spontaneous preterm birth. *The Journal of Maternal-Fetal & Neonatal Medicine*, 32(15):2486-2492.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Stratakis, N. Roumeliotaki, T. Oken, E. Barros, H. Basterrechea, M. Charles, M.A. Chatzi, L. *et al.* 2016. Fish intake in pregnancy and child growth: a pooled analysis of 15 European and US birth cohorts. *JAMA pediatrics*, 170(4):381-390.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
van Den Berg, S.W. Wijga, A.H. van Rossem, L. Gehring, U. Koppelman, G.H. Smit, H.A. *&* Boer, J.M. 2016. Maternal fish consumption during pregnancy and BMI in children from birth up to age 14 years: the PIAMA cohort study. *European journal of nutrition*, 55, 799-808.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

BONE HEALTH

TABLE A3.6 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "BONE HEALTH"

Study (n = 7)	Reason for exclusion
Abdelhamid, A. Hooper, L. Sivakaran, R. Hayhoe, R. P. *&* Welch, A. 2019. The relationship between omega-3, omega-6 and total polyunsaturated fat and musculoskeletal health and functional status in adults: a systematic review and meta-analysis of RCTs. *Calcified tissue international*, 105(4):353-372.	Excluded based on inclusion and exclusion criteria: Studies included in the review investigated dietary supplements (two studies included nuts), none with fish. All studies used dietary supplements.
Salari, P. Rezaie, A. Larijani, B. *&* Abdollahi, M. 2008. A systematic review of the impact of n-3 fatty acids in bone health and osteoporosis. *Medical science monitor: International medical journal of experimental and clinical research*, 14(3):RA37-44.	Excluded based on inclusion and exclusion criteria: Studies included in the review only investigated intake of fats, no mention of fish.
Sadeghi, O. Djafarian, K. Ghorabi, S. Khodadost, M. Nasiri, M. *&* Shab-Bidar, S. 2019. Dietary intake of fish, n-3 polyunsaturated fatty acids and risk of hip fracture: A systematic review and meta-analysis on observational studies. *Critical reviews in food science and nutrition*, 59(8):1320-1333.	Excluded, as the review had already been assessed in VKM 2022.
Perna, S. Avanzato, I. Nichetti, M. D'Antona, G. Negro, M. *&* Rondanelli, M. 2017. Association between dietary patterns of meat and fish consumption with bone mineral density or fracture risk: a systematic literature. *Nutrients*, 9(9):1029.	Excluded, as the review had already been assessed in VKM 2022.
Albertazzi, P. *&* Coupland, K. 2002. Polyunsaturated fatty acids. Is there a role in postmenopausal osteoporosis prevention?. *Maturitas*, 42(1):13-22.	Excluded based on inclusion and exclusion criteria: not a systematic review
Molfino, A. Gioia, G. Fanelli, F.R. *&* Muscaritoli, M. 2014. The role for dietary omega-3 fatty acids supplementation in older adults. *Nutrients*, 6(10):4058-4072.	Excluded based on inclusion and exclusion criteria: not a systematic review
Pampaloni, B. Quattrini, S. *&* Brandi, M.L. 2018. The Mediterranean diet for bone health in osteoporosis. Children and adolescents. *Clinical Cases in Mineral & Bone Metabolism*, 15(1).	Excluded based on inclusion and exclusion criteria: not a systematic review

TABLE A3.7 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "BONE HEALTH"**

Study (n = 26)	Reason for exclusion
Alveblom, A. K. *et al.* Incidence of hospitalized osteoporotic fractures in cohorts with high dietary intake of persistent organochlorine compounds. *Int Arch Occup Environ Health*, 76(3):246-248.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Langsetmo, L. *et al.* Dietary patterns in men and women are simultaneously determinants of altered glucose metabolism and bone metabolism. *Nutr Res*, 36(4):328-336.	Excluded based on inclusion and exclusion criteria: dietary patterns as exposure, not fish alone
Macdonald, H. M. *et al.* Vitamin D status in postmenopausal women living at higher latitudes in the UK in relation to bone health, overweight, sunlight exposure and dietary vitamin D. *Bone*, 42(5):996-1003.	Excluded based on inclusion and exclusion criteria: only vitamin d status, not fish as exposure alone
Mangano, K. M. *et al.* Dietary protein is associated with musculoskeletal health independently of dietary pattern: the Framingham Third Generation Study. *Am J Clin Nutr*, 105(3):714-722.	Excluded based on inclusion and exclusion criteria: protein intake, not fish as exposure alone
Melaku, Y. A. *et al.* Association between dietary patterns and low bone mineral density among adults aged 50 years and above: findings from the North West Adelaide Health Study (NWAHS). *Br J Nutr*, 116(8):1437-1446.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Meyer, H. E. *et al.* Dietary factors and the incidence of hip fracture in middle-aged Norwegians - A prospective study. *American Journal of Epidemiology*, 145(2):117-123.	Excluded based on inclusion and exclusion criteria: protein intake, not fish as exposure alone
Paunescu, A. C. *et al.* 2013. Polyunsaturated fatty acids and calcaneal ultrasound parameters among Inuit women from Nuuk (Greenland): a longitudinal study. *Int J Circumpolar Health*, 72:20988.	Excluded based on inclusion and exclusion criteria: n-3 and n-6, not fish as exposure alone
Rogers, T. S. *et al.* Dietary patterns and longitudinal change in hip bone mineral density among older men. *Osteoporos Int*, 29(5):1135-1145.	Excluded based on inclusion and exclusion criteria: dietary patterns as exposure, not fish alone
Rosendahl-Riise, H. *et al.* Total and lean fish intake is positively associated with bone mineral density in older women in the community-based Hordaland Health Study. *Eur J Nutr*, 58(4):1403-1413.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Shaw, S. C. *et al.* Diet Quality and Bone Measurements Using HRpQCT and pQCT in Older Community-Dwelling Adults from the Hertfordshire Cohort Study. *Calcif Tissue Int*,103(5):494-500.	Excluded based on inclusion and exclusion criteria: diet quality as exposure, not fish alone
Umaretiya, P. J. *et al.* Bone mineral density in Nigerian children after discontinuation of calcium supplementation. *Bone*, 55(1):64-68.	Excluded based on inclusion and exclusion criteria: Calcium supplements, not fish
van den Hooven, E. H. *et al.* Identification of a dietary pattern prospectively associated with bone mass in Australian young adults. *Am J Clin Nutr*, 102(5):1035-1043.	Excluded based on inclusion and exclusion criteria: dietary patterns as exposure, not fish alone
Vatanparast, H. *et al.* Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. *Am J Clin Nutr*, 82(3):700-706.	Excluded based on inclusion and exclusion criteria: fish was not exposure variable
Wallin, E. *et al.* Exposure to CB-153 and p,p'-DDE and bone mineral density and bone metabolism markers in middle-aged and elderly men and women. *Osteoporos Int*, 16(12):2085-2094.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Wallin, E. *et al.* Exposure to persistent organochlorine compounds through fish consumption and the incidence of osteoporotic fractures. *Scand J Work Environ Health*, 30(1):30-35.	Excluded based on inclusion and exclusion criteria: retrospective cohort study
Whiting, S. J. *et al.* Factors that affect bone mineral accrual in the adolescent growth spurt. *J Nutr,* 134(3):696s-700s.	Excluded based on inclusion and exclusion criteria: no fish as exposure
Wu, F. *et al.* Associations of dietary patterns with bone mass, muscle strength and balance in a cohort of Australian middle-aged women. *Br J Nutr,* 118(8):598-606.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Appleby, *P. et al.* Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford. *Eur J Clin Nutr*, 61(12):1400-1406.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Chan, R. *et al.* Effects of food groups and dietary nutrients on bone loss in elderly Chinese population. *J Nutr Health* Aging, 15(4):287-294.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Farina, E. K. *et al.* Dietary intakes of arachidonic acid and alpha-linolenic acid are associated with reduced risk of hip fracture in older adults. *J Nutr,* 141(6):1146-1153.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Farina, E. K. *et al.* Protective effects of fish intake and interactive effects of long-chain polyunsaturated fatty acid intakes on hip bone mineral density in older adults: the Framingham Osteoporosis Study. *Am J Clin Nutr*, 93(5):1142-1151.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Virtanen, J. K. *et al.* Dietary intake of polyunsaturated fatty acids and risk of hip fracture in men and women. *Osteoporos Int*, 23(11):2615-2624.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Virtanen, J. K. *et al.* Fish consumption, bone mineral density, and risk of hip fracture among older adults: the cardiovascular health study. *J Bone Miner Res*, 25(9):1972-1979.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Erkkilä, A. T. *et al.* Associations of Baltic Sea and Mediterranean dietary patterns with bone mineral density in elderly women. *Public Health Nutr*, 20(15):2735-2743.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that was included in VKM 2022
Feskanich, D. *et al.* Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr*, 77(2):504-511.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that was included in VKM 2022
Longo, A.B. & Ward, W.E. PUFAs, Bone Mineral Density, and Fragility Fracture: Findings from Human Studies. *Adv Nutr*, 7(2): 299-312.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that was included in VKM 2022

CANCER

TABLE A3.8 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CANCER", BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 17)	Reason for exclusion
Wilson, K.M. & Mucci, L.A. 2019. Diet and Lifestyle in Prostate Cancer. *Adv Exp Med Biol*, 1210:1-27.	Excluded based on inclusion and exclusion criteria: book chapter, wrong publication type
Yoo, J.Y. Cho, H.J. Moon, S. Choi, J. Lee, S. Ahn, C. Yoo, K.Y. Kim, I. Ko, K.P. Lee, J.E. & Park, S.K. 2020. Pickled Vegetable and Salted Fish Intake and the Risk of Gastric Cancer: Two Prospective Cohort Studies and a Meta-Analysis. *Cancers (Basel)*, 12.	Excluded based on inclusion and exclusion criteria: narrative review with meta-analysis
Hu, S. Yu, J. Wang, Y. Li, Y. Chen, H. Shi, Y. & Ma, X. 2019. Fish consumption could reduce the risk of oral cancer in Europeans: A meta-analysis. *Arch Oral Biol*, 107:104494.	Excluded based on inclusion and exclusion criteria: 2 cohort studies before 2018, and the rest was 13 case-control studies
Jiang, W. Wang, M. Jiang, H.Z. Chen, G.C. and Hua, Y.F. 2019. Meta-analysis of fish consumption and risk of pancreatic cancer in 13 prospective studies with 1.8 million participants. *PLoS One*, 14:e0222139.	Excluded based on inclusion and exclusion criteria: only one study included after 2018, and this is also included in the search of primary studies
Yang, L. Shi, W.Y. Xu, X.H. Wang, X.F. Zhou, L. & Wu, D.P. 2020. Fish consumption and risk of non-Hodgkin lymphoma: A meta-analysis of observational studies. *Hematology*, 25:194-202.	Excluded based on inclusion and exclusion criteria: all studies included are older than 2018
Zhang, Z.H. & Xin, J.Z. 2019. Dietary fresh fish and processed fish intake and the risk of glioma: A meta-analysis of observational studies. *Cellular and Molecular Biology*, 65:48-53.	Excluded based on inclusion and exclusion criteria: all studies included are older than 2018
Chapelle, N. Martel, M. Toes-Zoutendijk, E. Barkun, A.N. & Bardou, M. 2020. Recent advances in clinical practice: colorectal cancer chemoprevention in the average-risk population. *Gut*, 69:2244-2255.	Excluded based on inclusion and exclusion criteria: all relevant studies included are older than 2018
Fakhri, G. Al Assaad, M. & Tfayli, A. 2020. Association of various dietary habits and risk of lung cancer: an updated comprehensive literature review. *Tumori*, 106:445-456.	Excluded based on inclusion and exclusion criteria: all studies regarding fish intake and cancer are older than 2018
Ghaffari, H.R. Yunesian, M. Nabizadeh, R. Nasseri, S. Sadjadi, A. Pourfarzi, F. Poustchi, H. & Eshraghian, A. 2019. Environmental etiology of gastric cancer in Iran: a systematic review focusing on drinking water, soil, food, radiation, and geographical conditions. *Environ Sci Pollut Res Int*, 26:10487-10495.	Excluded based on inclusion and exclusion criteria: all studies regarding fish intake and cancer are older than 2018
Lei, H.C. To, C.H. & Lei, U.P. 2020. Association between fish intake and glioma risk: a systematic review and meta-analysis. *Journal of International Medical Research*, 48.	Excluded based on inclusion and exclusion criteria: all studies included are older than 2018
Li, N. Wu, X.T. Zhuang, W. Xia, L. Chen, Y. Wu, C.C. Rao, Z.Y. Du, L. Zhao, R. Yi, M.S. *et al.* 2020. Fish consumption and multiple health outcomes: Umbrella review. *Trends in Food Science & Technology*, 99:273-283.	Excluded based on inclusion and exclusion criteria: only one study after 2018, and this is also included in the review Jayedi, 2020
Lv, D. Wang, R. Chen, M. Li, Y. & Cao, C. 2021. Fish Intake, Dietary Polyunsaturated Fatty Acids, and Lung Cancer: Systematic Review and Dose-Response Meta-Analysis of 1.7 Million Men and Women. *Nutr Cancer*, 74(6): 1976-1985	Excluded based on inclusion and exclusion criteria: main focus on n-3 PUFAs, and fish-intake studies are older than 2018
Okekpa, S.I. RB, S.M.N.M. Mangantig, E. Azmi, N.S.A. Zahari, S.N.S. Kaur, G. & Musa, Y. 2019. Nasopharyngeal Carcinoma (NPC) Risk Factors: A Systematic Review and Meta-Analysis of the Association with Lifestyle, Diets, Socioeconomic and Sociodemographic in Asian Region. *Asian Pac J Cancer Prev*, 20:3505-3514.	Excluded based on inclusion and exclusion criteria: all studies included are older than 2018 and only case-control studies
Poorolajal, J. Moradi, L. Mohammadi, Y. Cheraghi, Z. & Gohari-Ensaf, F. 2020. Risk factors for stomach cancer: a systematic review and meta-analysis. *Epidemiol Health*, 42:e2020004.	Excluded based on inclusion and exclusion criteria: all studies regarding fish intake and cancer are older than 2018
Sergentanis, T.N. Ntanasis-Stathopoulos, I. Tzanninis, I.G. Gavriatopoulou, M. Sergentanis, I.N. Dimopoulos, M.A. & Psaltopoulou, T. 2019. Meat, fish, dairy products and risk of hematological malignancies in adults - a systematic review and meta-analysis of prospective studies. *Leuk Lymphoma*, 60:1978-1990.	Excluded based on inclusion and exclusion criteria: all studies included are older than 2018
Ubago-Guisado, E. Rodríguez-Barranco, M. Ching-López, A. Petrova, D. Molina-Montes, E. Amiano, P. Barricarte-Gurrea, A. Chirlaque, M.D. Agudo, A. & Sánchez, M.J. 2021. Evidence Update on the Relationship between Diet and the Most Common Cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: A Systematic Review. *Nutrients*, 13 (10): 3582.	Excluded based on inclusion and exclusion criteria: only one study included after 2018, and this is also included in our search of primary studies (Aglago, 2020)
Cao, C. & Xu, N. 2019. Fish Intake, Dietary Polyunsaturated Fatty Acids, and Lung Cancer: Systematic Review and Dose-Response Meta-Analysis of 1.7 Million Men and Women. *American Journal of Respiratory and Critical Care Medicine*, 199:A7277.	Excluded based on inclusion and exclusion criteria: conference abstract
Lee, K.H. Seong, H.J. Kim, G. Jeong, G.H. Kim, J.Y. Park, H. Jung, E. Kronbichler, A. Eisenhut, M. Stubbs, B. *et al.* 2020. Consumption of Fish and β-3 Fatty Acids and Cancer Risk: An Umbrella Review of Meta-Analyses of Observational Studies. *Adv Nutr*, 11: 1134-1149.	Excluded based on inclusion and exclusion criteria: all relevant studies included are older than 2018

TABLE A3.9 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CANCER"**

Study (n = 10)	Reason for exclusion
Dydjow-Bendek, D. & Zagożdżon, P. 2020. Total Dietary Fats, Fatty Acids, and Omega-3/Omega-6 Ratio as Risk Factors of Breast Cancer in the Polish Population - a Case-Control Study. *In Vivo*, 34:423-431.	Excluded based on inclusion and exclusion criteria: case-control study
Golozar, A. Etemadi, A. Kamangar, F. Fazeltabar Malekshah, A. Islami, F. Nasrollahzadeh, D. Abedi-Ardekani, B. Khoshnia, M. Pourshams, A. Semnani, S. *et al.* 2018. Food preparation methods, drinking water source, and esophageal squamous cell carcinoma in the high-risk area of Golestan, Northeast Iran. *Eur J Cancer Prev*, 25, 123-129.	Excluded based on inclusion and exclusion criteria: case-control study
Gonzalez, C.A. 2022. The European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr*, 9, 124-126.	Excluded based on inclusion and exclusion criteria: wrong study design/article type
Liu, Z. Luo, Y. Ren, J. Yang, L. Li, J. Wei, Z. He, Y. Wang, J. Li, R. He, L. *et al.* 2022. Association between fish oil supplementation and cancer risk according to fatty fish consumption: A large prospective population-based cohort study using UK Biobank. *Int J Cancer*,150 (4): 562-571	Excluded based on inclusion and exclusion criteria: main aim to investigate fish oil supplementation and cancer risk
Oh, C.C. Jin, A.Z. Yuan, J.M. & Koh, W.P. 2020. Fish intake and risk of nonmelanoma skin cancer in a Chinese population: the Singapore Chinese Health Study. *Clin Exp Dermatol*, 45:461-463.	Excluded based on inclusion and exclusion criteria: not a research article, only a correspondence in the journal
McClain, K.M. Bradshaw, P.T. Khankari, N.K. Gammon, M.D. & Olshan, A.F. 2019. Fish/shellfish intake and the risk of head and neck cancer. *Eur J Cancer Prev*, 28:102-108.	Excluded based on inclusion and exclusion criteria: case-control study
Rada-Fern, ez de Jauregui, D. Evans, C.E.L. Jones, P. Greenwood, D.C. Hancock, N. & Cade, J.E. 2018. Common dietary patterns and risk of cancers of the colon and rectum: Analysis from the United Kingdom Women's Cohort Study (UKWCS). *Int J Cancer*, 143:773-781.	Excluded based on inclusion and exclusion criteria: dietary patterns
Wang, Y. Jacobs, E.J. Shah, R.A. Stevens, V.L. Gansler, T. & McCullough, M.L. 2020. Red and Processed Meat, Poultry, Fish, and Egg Intakes and Cause-Specific and All-Cause Mortality among Men with Nonmetastatic Prostate Cancer in a U.S. Cohort. *Cancer Epidemiol Biomarkers Prev*, 29:1029-1038.	Excluded based on inclusion and exclusion criteria: outcome is mortality/survival
Marcondes, L.H. Franco, O.H. Ruiter, R. Ikram, M.A. Mulder, M. Stricker, B.H. & Kiefte-de Jong, J.C. 2019. Animal foods and postmenopausal breast cancer risk: a prospective cohort study. *Br J Nutr*, 122:583-591.	Excluded for further assessment, as the primary study had already been assessed in the included systematic review Kazemi *et al.*, 2021.
McCullough, M.L. Jacobs, E.J. Shah, R. Campbell, P.T. Wang, Y. Hartman, T.J. & Gapstur, S.M. 2018. Meat consumption and pancreatic cancer risk among men and women in the Cancer Prevention Study-II Nutrition Cohort. *Cancer Causes Control*, 29:125-133.	Excluded for further assessment, as the primary study had already been assessed in the included systematic review Gao *et al.*, 2022.

CARDIOVASCULAR DISEASES AND OUTCOMES

TABLE A3.10 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES", BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 13)	Reason for exclusion
Alhassan, A. *et al.* 2017, Consumption of fish and vascular risk factors: A systematic review and meta-analysis of intervention studies. *Atherosclerosis*, 266:87-94.	Excluded based on inclusion and exclusion criteria: only measured biomarkers as outcome
Bechthold, A. *et al.* 2019. Food groups and risk of coronary heart disease, stroke and heart failure: A systematic review and dose-response meta-analysis of prospective studies. *Critical Reviews in Food Science and Nutrition*, 59(7):1071-1090.	Excluded, as the review has already been assessed in VKM 2022.
Chen, C. *et al.* 2021. Fish consumption, long-chain omega-3 fatty acids intake and risk of stroke: An updated systematic review and meta-analysis. *Asia Pacific Journal of Clinical Nutrition*, 30(1):140-152.	Excluded, as the review has already been assessed in VKM 2022.
Djousse, L. *et al.* 2012, Fish consumption, omega-3 fatty acids and risk of heart failure: A meta-analysis. *Clinical Nutrition*, 31(6):846-853.	Excluded based on inclusion and exclusion criteria: not a systematic review, only meta-analysis.
Jayedi, A. & Shab-Bidar, S. 2020. Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies. *Advances in Nutrition*, 11(5):1123-1133.	Excluded, as the review has already been assessed in VKM 2022.
Jayedi, A. *et al.* 2018. Fish consumption and risk of all-cause and cardiovascular mortality: a dose-response meta-analysis of prospective observational studies. *Public Health Nutrition*, 21(7):1297-1306.	Excluded, as the review has already been assessed in VKM 2022.
Jayedi, A. *et al.* 2021. Fish consumption and the risk of cardiovascular disease and mortality in patients with type 2 diabetes: a dose-response meta-analysis of prospective cohort studies. *Critical Reviews in Food Science and Nutrition*, 61(10):1640-1650.	Excluded, as the review had already been assessed in VKM 2022.
Jayedi, A. M.S. Zargar & S. Shab-Bidar, 2019. Fish consumption and risk of myocardial infarction: a systematic review and dose-response meta analysis suggests a regional difference. *Nutrition Research*, 62:1-12.	Excluded, as the review had already been assessed in VKM 2022.
Krittanawong, C. *et al.* 2021. Fish Consumption and Cardiovascular Health: A Systematic Review. American Journal of Medicine. 134(6): p. 713-720.	Excluded, as the review had already been assessed in VKM 2022.
Kwok, C.S. *et al.* 2019. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *European Journal of Preventive Cardiology*, 26(13):1415-1429.	Excluded, as the review had already been assessed in VKM 2022.
Mattiuzzi, C. *et al.* 2016. Fish Intake and Venous Thromboembolism: A Systematic Literature Review. *Clinical and Applied Thrombosis-Hemostasis*, 22(4):309-313.	Excluded, as the review had already been assessed in VKM 2022.
Ness, A.R. *et al.* 1999. The long-term effect of advice to eat more fish on blood pressure in men with coronary disease: results from the Diet and Reinfarction Trial. *Journal of Human Hypertension*, 13(11):729-733.	Excluded based on inclusion and exclusion criteria: not a systematic review.
Wang, C.C. *et al.* 2006, n-3 fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *American Journal of Clinical Nutrition*, 84(1):5-17.	Excluded based on inclusion and exclusion criteria: not measured fish consumption, only n-3 biomarkers

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES"**

Study (*n* = 139)	Reason for exclusion
Amoah, J. *et al.* 2021. Effects of a school-based intervention to reduce cardiovascular disease risk factors among secondary school students: A cluster- randomized, controlled trial. *PLoS One*, 16(11):e0259581.	Excluded based on inclusion and exclusion criteria: fish consumption not included
Archer, S.L. *et al.* 1998. Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the coronary artery risk development in young adults (CARDIA) study. *Arterioscler Thromb Vasc Biol*, 18(7): 1119-23.	Excluded based on inclusion and exclusion criteria: intermediate CVD biomarkers
Borgi, L. *et al.* 2015. Long-term intake of animal flesh and risk of developing hypertension in three prospective cohort studies. *J Hypertens*, 33(11): 2231-8.	Excluded based on inclusion and exclusion criteria: not CVD
Bravata, D.M. *et al.* 2007. Dietary fish or seafood consumption is not related to cerebrovascular disease risk in twin veterans. *Neuroepidemiology*, 28(3):186-190.	Excluded based on inclusion and exclusion criteria: information of fish consumption not given properly
Burke, V. *et al.* 2007. A lifestyle program for treated hypertensives improved health-related behaviors and cardiovascular risk factors, a randomized controlled trial. *J Clin Epidemiol*, 60(2):133-41.	Excluded based on inclusion and exclusion criteria
Burr, M.L. 2007. Secondary prevention of CHD in UK men: the Diet and Reinfarction Trial and its sequel. *Proc Nutr Soc*, 66(1):9-15.	Excluded based on inclusion and exclusion criteria: not relevant
Chrysohoou, C. *et al.* 2007. Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region - The ATTICA study. *American Journal of Clinical Nutrition*, 85(5):1385-1391.	Excluded based on inclusion and exclusion criteria: the design was cross-sectional (exclusion criteria)
Damsgaard, C.T. *et al.* 2016. Effects of oily fish intake on cardiovascular risk markers, cognitive function, and behavior in school-aged children: study protocol for a randomized controlled trial. *Trials*, 17(1):510.	Excluded based on inclusion and exclusion criteria: study protocol
De Lorgeril, M. & Salen, P. 2002. Fish and N-3 fatty acids for the prevention and treatment of coronary heart disease: Nutrition is not pharmacology. *American Journal of Medicine*, 112(4):316-319.	Excluded based on inclusion and exclusion criteria: narrative review/opinion
Engell, R.E. *et al.* 2013. Seafood omega-3 intake and risk of coronary heart disease death: an updated meta-analysis with implications for attributable burden. *Lancet*, 381:45-45.	Excluded based on inclusion and exclusion criteria: not relevant
Eshak, E.S. *et al.* 2014. Modification of the excess risk of coronary heart disease due to smoking by seafood/fish intake. *Am J Epidemiol*, 179(10):1173-81.	Excluded based on inclusion and exclusion criteria: exposure focused on smoking
Gerhard, G.T. *et al.* 1991. Comparison of three species of dietary fish: effects on serum concentrations of low-density-lipoprotein cholesterol and apolipoprotein in normotriglyceridemic subjects. *Am J Clin Nutr*, 54(2):334-9.	Excluded based on inclusion and exclusion criteria: only markers, not CVD
Guasch-Ferre, M. *et al.* 2019. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. *Circulation*, 139(15):1828-1845.	Excluded based on inclusion and exclusion criteria: systematic review
Gunnarsdottir, I. *et al.* 2008. Inclusion of fish or fish oil in weight-loss diets for young adults: effects on blood lipids. *Int J Obes* (Lond), 32(7):1105-12.	Excluded based on inclusion and exclusion criteria: wrong outcome
Hallgren, C.G. *et al.* 2001. Markers of high fish intake are associated with decreased risk of a first myocardial infarction. *Br J Nutr*, 86(3):397-404.	Excluded based on inclusion and exclusion criteria: case-control study
Hallund, J. *et al.* 2010. The effect of farmed trout on cardiovascular risk markers in healthy men. *Br J Nutr*, 104(10):1528-36.	Excluded based on inclusion and exclusion criteria: wrong outcome
He, K. *et al.* 2004. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*, 109(22):2705-11.	Excluded based on inclusion and exclusion criteria
He, K. *et al.* 2004. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*, 109(22):2705-11.	Excluded based on inclusion and exclusion criteria
He, K. *et al.* 2009. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*,103(9):1238-43.	Excluded based on inclusion and exclusion criteria: not CVD, only biomarkers
He, K. *et al.* 2004. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke*, 35(7):1538-42.	Excluded based on inclusion and exclusion criteria
Hou, L.N. *et al.* 2012. Fish intake and risk of heart failure: A meta-analysis of five prospective cohort studies. *Exp Ther Med*, 4(3):481-486.	Excluded based on inclusion and exclusion criteria
Hu, F.B. *et al.* 1999. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. American Journal of Clinical Nutrition, 70(6):1001-1008.	Excluded based on inclusion and exclusion criteria
Johansson, A. & Acosta, S. 2020. Diet and Lifestyle as Risk Factors for Carotid Artery Disease: A Prospective Cohort Study. *Cerebrovascular Diseases*, 2020. 49(5):563-569.	Excluded based on inclusion and exclusion criteria: not relevant
Johnsen, S.H. *et al.* 2018. Fish consumption, fish oil supplements and risk of atherosclerosis in the Tromso study. *Nutr J*, 17(1):56.	Excluded based on inclusion and exclusion criteria: wrong study design
Kim, S.A. *et al.* 2019. Oily Fish Consumption and the Risk of Dyslipidemia in Korean Adults: A Prospective Cohort Study Based on the Health Examinees Gem (HEXA-G) Study. *Nutrients*, 11(10).	Excluded based on inclusion and exclusion criteria: not CVD, only biomarkers
Konig, A. *et al.* 2005. A quantitative analysis of fish consumption and coronary heart disease mortality. *Am J Prev Med*, 29(4):335-46.	Excluded based on inclusion and exclusion criteria: narrative review (exclusion criteria)
Kris-Etherton, P.M. Harris, W.S. & Appel, L.J. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol*, 23(2):e20-30.	Excluded based on inclusion and exclusion criteria: narrative review (exclusion criteria)
Lamlili, E.N.M. *et al.* 2016. Fish Consumption Impact on Coronary Heart Disease Mortality in Morocco: A Mathematical Model with Optimal Control. *Engineering Letters*, 24(3):246-251.	Excluded based on inclusion and exclusion criteria: not relevant

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (cont.)**

Lapidus, L. *et al.* 1986. Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Am J Clin Nutr*, 44(4):444-8.	Excluded based on inclusion and exclusion criteria
Lee, H.A. & Park, H. 2018. Diet-Related Risk Factors for Incident Hypertension During an 11-Year Follow-Up: The Korean Genome Epidemiology Study. *Nutrients*, 10(8):1077.	Excluded based on inclusion and exclusion criteria: not CVD
Lentjes, M.A.H. *et al.* 2016. Total (food and supplement) n-3 PUFA intake is associated with lower Coronary Heart Disease mortality, independently of fish intake. *Proceedings of the Nutrition Society*, 75(Oce1):E42-E42.	Excluded based on inclusion and exclusion criteria: just an abstract (summary from a winter meeting)
Li, Y.H. *et al.* 2013. Fish consumption and incidence of heart failure: a meta-analysis of prospective cohort studies. *Chin Med J* (Engl), 126(5):942-8.	Excluded based on inclusion and exclusion criteria: review article
Lilja, E. *et al.* 2019. The association between dietary intake, lifestyle and incident symptomatic peripheral arterial disease among individuals with diabetes mellitus: insights from the Malmo Diet and Cancer study. Therapeutic *Advances in Endocrinology and Metabolism*, 10:1-8	Excluded based on inclusion and exclusion criteria: not general population, patients with diabetes
Lindqvist, H. *et al.* 2007. Herring (Clupea harengus) supplemented diet influences risk factors for CVD in overweight subjects. *Eur J Clin Nutr*, 61(9):1106-13.	Excluded based on inclusion and exclusion criteria
Mark, K. *et al.* 1998. Eating fish may reduce infarct size and the occurrence of Q wave infarcts. *European Journal of Clinical Nutrition*, 52(1):40-44.	Excluded based on inclusion and exclusion criteria: not CVD
Masson, S. *et al.* 2013. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. *Am Heart J*, 165(2):208-15 e4.	Excluded based on inclusion and exclusion criteria: not general population
Matsumoto, C. *et al.* 2019. Fish and omega-3 fatty acid consumption and risk of hypertension. *J Hypertens*, 37(6):1223-1229.	Excluded based on inclusion and exclusion criteria: not CVD
Meng, L.X. *et al.* 2011. Association of Fish Consumption Factors with Stroke Mortality in The Multiethnic Cohort Study. *Stroke*, 42(3):E276-E276.	Excluded based on inclusion and exclusion criteria: just an abstract.
Mori, T.A. *et al.* 1994. Effects of Varying Dietary-Fat, Fish, and Fish Oils on Blood-Lipids in a Randomized Controlled Trial in Men at Risk of Heart-Disease. *American Journal of Clinical Nutrition*, 59(5):1060-1068.	Excluded based on inclusion and exclusion criteria: only biomarkers
Ness, A.R. *et al.* 2005. Diet in childhood and adult cardiovascular and all-cause mortality: the Boyd Orr cohort. *Heart*, 91(7):894-898.	Excluded based on inclusion and exclusion criteria: not CVD
Panagiotakos, D.B. & Kastorini, C.M. 2011. Fish consumption and risk of stroke. *Womens Health (Lond)*, 7(3):279-81.	Excluded based on inclusion and exclusion criteria: commentary article
Petsini, F. Fragopoulou, E. & Antonopoulou, S. 2019. Fish consumption and cardiovascular disease related biomarkers: A review of clinical trials. *Crit Rev Food Sci Nutr*, 59(13):2061-2071.	Excluded based on inclusion and exclusion criteria: narrative review (exclusion criteria)
Raisi-Estabragh, Z. *et al.* 2021. Associations of Meat and Fish Consumption With Conventional and Radiomics Cardiovascular Magnetic Resonance Phenotypes in the UK Biobank. *Front Cardiovasc Med*, 8:667849.	Excluded based on inclusion and exclusion criteria: biomarker
Ramel, A. *et al.* 2010. Moderate consumption of fatty fish reduces diastolic blood pressure in overweight and obese European young adults during energy restriction. *Nutrition*, 26(2):168-74.	Excluded based on inclusion and exclusion criteria
Rundblad, A. *et al.* 2018. Effects of krill oil and lean and fatty fish on cardiovascular risk markers: a randomised controlled trial. *J Nutr Sci*, 7:e3.	Excluded based on inclusion and exclusion criteria: not CVD
Salisbury, A.C. *et al.* 2011. Predictors of omega-3 index in patients with acute myocardial infarction. *Mayo Clin Proc*, 86(7):626-32.	Excluded based on inclusion and exclusion criteria: omega-3 and not fish intake
Steur, M. *et al.* 2021. Dietary Fatty Acids, Macronutrient Substitutions, Food Sources and Incidence of Coronary Heart Disease: Findings From the EPIC-CVD Case-Cohort Study Across Nine European Countries. *J Am Heart Assoc*, 10(23):e019814.	Excluded based on inclusion and exclusion criteria: case-cohort study (exclusion criteria)
Sun, Y. *et al.* 2016. Plasma alpha-Linolenic and Long-Chain omega-3 Fatty Acids Are Associated with a Lower Risk of Acute Myocardial Infarction in Singapore Chinese Adults. *J Nutr*, 146(2):275-82.	Excluded based on inclusion and exclusion criteria: no food frequency questionnaire data
Vuholm, S. *et al.* 2019. Effects of oily fish intake on cardiometabolic markers in healthy 8- to 9-y-old children: the FiSK Junior randomized trial. *Am J Clin Nutr,* 110(6):1296-1305.	Excluded based on inclusion and exclusion criteria: biomarkers
Whelton, S.P. *et al.* 2004. Meta-analysis of observational studies on fish intake and coronary heart disease. *Am J Cardiol*, 93(9):1119-23.	Excluded based on inclusion and exclusion criteria: review
Yinko, S.S.L.L. *et al.* 2014. Fish Consumption and Acute Coronary Syndrome: A Meta-Analysis. *American Journal of Medicine*,127(9): p. 848-+.	Excluded based on inclusion and exclusion criteria: review
Zhang, J. *et al.* 2010. Inclusion of Atlantic salmon in the Chinese diet reduces cardiovascular disease risk markers in dyslipidemic adult men. *Nutr Res*, 30(7): 447-54.	Excluded based on inclusion and exclusion criteria: wrong outcome
Zhang, Y. *et al.* 2020. Associations of Fish and Omega-3 Fatty Acids Consumption With the Risk of Venous Thromboembolism. A Meta-Analysis of Prospective Cohort Studies. *Front Nutr,* 7: 614784.	Excluded based on inclusion and exclusion criteria: review
Zhu, N.B. *et al.* 2019. Adherence to a healthy lifestyle and all-cause and cause-specific mortality in Chinese adults: a 10-year prospective study of 0.5 million people. International Journal of Behavioral *Nutrition and Physical Activity,* 16: 1-13	Excluded based on inclusion and exclusion criteria: not CVD
Aadland, *et al.* 2016. Lean Seafood Intake Reduces Postprandial C-peptide and Lactate Concentrations in Healthy Adults in a Randomized Controlled Trial with a Crossover Design. *Journal of Nutrition*, 146(5):1027-1034.	Excluded based on inclusion and exclusion criteria: not CVD
Aadland, *et al.* 2015. Lean-seafood intake reduces cardiovascular lipid risk factors in healthy subjects: results from a randomized controlled trial with a crossover design. *American Journal of Clinical Nutrition*,102(3):582-592.	Excluded based on inclusion and exclusion criteria: not CVD

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (cont.)**

Albert, C.M. *et al.* 1998. Fish consumption and risk of sudden cardiac death. *JAMA*, 279(1):23-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Amiano, P. *et al.* 2016. No association between fish consumption and risk of stroke in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain): a 13.8-year follow-up study. *Public Health Nutr*, 19(4):674-81.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Ascherio, A. *et al.* 1995. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med*, 332(15):977-82.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Atkinson, C. *et al.* 2011. Associations between types of dietary fat and fish intake and risk of stroke in the Caerphilly Prospective Study (CaPS). *Public Health*,125(6):345-8.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Belin, R.J. *et al.* 2011. Fish intake and the risk of incident heart failure: the Women's Health Initiative. *Circ Heart Fail*, 4(4):404-13.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Bernstein, A.M. *et al.* 2012. Dietary protein sources and the risk of stroke in men and women. *Stroke*,43(3):637-44.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Bernstein, A.M. *et al.* 2010. Major dietary protein sources and risk of coronary heart disease in women. *Circulation*,122(9):876-83.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Berry, J.D. *et al.* 2010. Dietary fish intake and incident atrial fibrillation (from the Women's Health Initiative). *Am J Cardiol*,105(6):844-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Bierregaard, L.J. *et al.* 2010. Fish intake and acute coronary syndrome. *European Heart Journal*, 31(1):29-34.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Bonaccio, M. *et al.* 2017. Fish intake is associated with lower cardiovascular risk in a Mediterranean population: Prospective results from the Moli-sani study. *Nutrition Metabolism and Cardiovascular Diseases*, 27(10):865-873.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Bouzan, C. *et al.* 2005. A quantitative analysis of fish consumption and stroke risk. *Am J Prev Med*, 2005. 29(4): p. 347-52.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Brouwer, I.A. *et al.* 2006. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. *American Heart Journal*,151(4):857-862.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Burr, M.L. & Fehily, A.M. 1991. Fatty fish and heart disease: a randomized controlled trial. *World Rev Nutr Diet*,66:306-12.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Burr, M.L. *et al.* 1989. Diet and reinfarction trial (DART): design, recruitment, and compliance. *Eur Heart J*, 10(6):558-67.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Burr, M.L. *et al.* 1989. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*, 2(8666):757-61.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Burr, M.L. 1993. Fish and ischaemic heart disease. *World Rev Nutr Diet*, 72:49-60.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Daviglus, M.L. *et al.* 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med*, 336(15):1046-53.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
de Goede, J. *et al.* 2012. Gender-specific associations of marine n-3 fatty acids and fish consumption with 10-year incidence of stroke. *PLoS One*, 7(4):e33866.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
de Goede, J. *et al.* 2010. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and nonfatal coronary heart disease in a large population of Dutch adults with low fish intake. *J Nutr*, 140(5):1023-8.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Dijkstra, S.C. *et al.* 2009. Intake of very long chain n-3 fatty acids from fish and the incidence of heart failure: the Rotterdam Study. *Eur J Heart Fail*, 11(10):922-8.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Erkkila, A.T. *et al.* 2004. Fish intake is associated with a reduced progression of coronary artery atherosclerosis in postmenopausal women with coronary artery disease. *American Journal of Clinical Nutrition*, 80(3):626-632.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Gammelmark, A. *et al.* 2016. Association of fish consumption and dietary intake of marine n-3 PUFA with myocardial infarction in a prospective Danish cohort study. *Br J Nutr*, 116(1):167-77.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Gillum, R.F. 1996. Fish consumption and stroke incidence. *Stroke*, 27(7):1254.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Gillum, R.F. M. Mussolino, & Madans, J.H. 2000. The relation between fish consumption, death from all causes, and incidence of coronary heart disease. the NHANES I Epidemiologic Follow-up Study. *J Clin Epidemiol*, 53(3):237-44.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Gillum, R.F. Mussolino, M.E. & Madans, J.H. 1996.The relationship between fish consumption and stroke incidence - The NHANES I epidemiologic follow-up study. *Archives of Internal Medicine*, 156(5):537-542.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (cont.)**

Gronroos, N.N. *et al.* 2012. Fish, fish-derived n-3 fatty acids, and risk of incident atrial fibrillation in the Atherosclerosis Risk in Communities (ARIC) study. *PLoS One*, 7(5):e36686.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hansen-Krone, I.J. *et al.* 2014. High fish plus fish oil intake is associated with slightly reduced risk of venous thromboembolism: the Tromso Study. *J Nutr*, 144(6):861-7.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Haring, B. *et al.* 2014. Dietary protein intake and coronary heart disease in a large community based cohort: results from the Atherosclerosis Risk in Communities (ARIC) study [corrected]. *PLoS One*, 9(10):e109552.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
He, K. *et al.* 2002. Fish consumption and risk of stroke in men. *JAMA*, 288(24):3130-6.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hengeveld, L.M. *et al.* 2018. Fish consumption and risk of stroke, coronary heart disease, and cardiovascular mortality in a Dutch population with low fish intake. *Eur J Clin Nutr*, 72(7):942-950.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Holmberg, S. Thelin, A. & Stiernstrom, E.L. 2009. Food choices and coronary heart disease: a population based cohort study of rural Swedish men with 12 years of follow-up. In*t J Environ Res Public Health*, 6(10):2626-38.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hu, F.B. *et al.* 2003. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*, 107(14):1852-7.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hu, F.B. *et al.* 2002. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *Jama*, 287(14):1815-21.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Iso, H. *et al.* 2006. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*, 113(2):195-202.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Iso, H. *et al.* 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA*, 285(3):304-12.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Jarvinen, R. *et al.* 2006. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *Br J Nutr*, 95(4):824-9.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Jiang, L. *et al.* 2021. Intake of Fish and Marine n-3 Polyunsaturated Fatty Acids and Risk of Cardiovascular Disease Mortality: A Meta-Analysis of Prospective Cohort Studies. *Nutrients*, 13(7).	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Key, T.J. *et al.* 2019. Consumption of Meat, Fish, Dairy Products, and Eggs and Risk of Ischemic Heart Disease A Prospective Study of 7198 Incident Cases Among 409 885 Participants in the Pan-European EPIC Cohort. *Circulation*, 139(25):2835-2845.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kuhn, T. *et al.* 2013. Fish consumption and the risk of myocardial infarction and stroke in the German arm of the European Prospective Investigation into Cancer and Nutrition (EPIC-Germany). *British Journal of Nutrition*, 110(6):1118-1125.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Larsson, S.C. & Wolk, A. 2017. Fish, long-chain omega-3 polyunsaturated fatty acid intake and incidence of atrial fibrillation: A pooled analysis of two prospective studies. *Clin Nutr*, 36(2):537-541.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Larsson, S.C. & Orsini, N. 2011. Fish consumption and the risk of stroke: a dose-response meta-analysis. *Stroke*, 42(12):3621-3.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Levitan, E.B. Wolk, A. & Mittleman, M.A. 2010. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. *European Journal of Clinical Nutrition*, 64(6):587-594.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Levitan, E.B. Wolk, A. & Mittleman, M.A. 2009. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: a population-based prospective study of middle-aged and elderly men. *Eur Heart J*, 30(12):1495-500.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Li, F.R. *et al.* 2017. Dietary Fish and Long-Chain n-3 Polyunsaturated Fatty Acids Intake and Risk of Atrial Fibrillation: A Meta-Analysis. *Nutrients*, 9(9).	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Manson, J.E. *et al.* 2020. Vitamin D, Marine n-3 Fatty Acids, and Primary Prevention of Cardiovascular Disease Current Evidence. *Circ Res*, 126(1):112-128.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Micha, R. *et al.* 2017. Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States. *Jama-Journal of the American Medical Association*, 317(9):912-924.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mohan, D. *et al.* 2021. Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries. *Jama Internal Medicine*, 181(5): 631-649.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Montonen, J. *et al.* 2009. Fish consumption and the incidence of cerebrovascular disease. *Br J Nutr*, 102(5):750-6.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Morris, M.C. *et al.* 1995. Fish consumption and cardiovascular disease in the physicians' health study: a prospective study. *Am J Epidemiol*, 142(2):166-75.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mozaffarian, D. *et al.* 2003. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation*, 107(10):1372-7.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mozaffarian, D. *et al.* 2005. Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. *Arch Intern Med*, 165(2): 200-6.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (cont.)**

Mozaffarian, D. *et al.* 2004. Fish intake and risk of incident atrial fibrillation. *Circulation*, 110(4):368-373.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Mozaffarian, D. *et al.* 2011. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. *N Engl J Med*, 364(12):1116-25.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Myint, P.K. *et al.* 2006. Habitual fish consumption and risk of incident stroke: the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study. *Public Health Nutrition*, 2006. 9(7):882-888.	Excluded for further assessment, as the primary study had already been assessed in the included systematic review Chowdhury et al 2012.
Nahab, F. *et al.* 2016. Dietary fried fish intake increases risk of CVD: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Public Health Nutr*, 19(18):3327-3336.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Orencia, A.J. *et al.* 1996. Fish consumption and stroke in men. 30-year findings of the Chicago Western Electric Study. *Stroke*, 27(2):204-9.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Osler, M. Andreasen, A.H. & Hoidrup, S. 2003. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *Journal of Clinical Epidemiology*, 56(3):274-279.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Qin, Z.Z. *et al.* 2018. Effects of fatty and lean fish intake on stroke risk: a meta-analysis of prospective cohort studies. *Lipids Health Dis*, 17(1):264.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Rhee, J.J. et al 2017. Fish Consumption, Omega-3 Fatty Acids, and Risk of Cardiovascular Disease. *Am J Prev Med*, 52(1):10-19.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Rodriguez, B.L. *et al.* 1995. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers - The Honolulu Heart Program. *Circulation*, 94(5):952-956.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Salonen, J.T. Nyyssonen, K. & Salonen, R. 1995. Fish intake and the risk of coronary disease. *N Engl J Med*, 333(14):937; author reply 938.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Severinsen, M.T. *et al.* 2014. Fish intake and venous thromboembolism: a Danish follow-up study. *Thromb Res*, 133(3):352-6.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Shen, J. *et al.* 2011. Dietary factors and incident atrial fibrillation: the Framingham Heart Study. *Am J Clin Nutr*, 93(2):261-6.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Steffen, L.M. *et al.* 2007. Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology. *Circulation*, 115(2):188-95.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Strom, M. *et al.* 2011. Fish consumption measured during pregnancy and risk of cardiovascular diseases later in life: an observational prospective study. *PLoS One*, 6(11):e27330.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Strom, M. *et al.* 2012. Fish, n-3 fatty acids, and cardiovascular diseases in women of reproductive age: a prospective study in a large national cohort. *Hypertension*, 59(1):36-43.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Virtanen, J.K. *et al.* 2008. Fish consumption and risk of major chronic disease in men. *Am J Clin Nutr*, 88(6):1618-25.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Wallin, A. *et al.* 2018. Fish consumption in relation to myocardial infarction, stroke and mortality among women and men with type 2 diabetes: A prospective cohort study. *Clinical Nutrition*, 37(2):590-596.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Ward, R.E. *et al.* 2020. Omega-3 supplement use, fish intake, and risk of non-fatal coronary artery disease and ischemic stroke in the Million Veteran Program. *Clin Nutr*, 39(2):574-579.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Wennberg, M. *et al.* 2011. Fish consumption and myocardial infarction: a second prospective biomarker study from northern *Sweden. Am J Clin Nutr*, 93(1):27-36.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Wennberg, M. *et al.* 2007. Fish intake, mercury, long-chain n-3 polyunsaturated fatty acids and risk of stroke in northern Sweden. *Br J Nutr*, 98(5):1038-45.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Wennberg, M. *et al.* 2012. Myocardial infarction in relation to mercury and fatty acids from fish: a risk-benefit analysis based on pooled Finnish and Swedish data in men. *Am J Clin Nutr*, 96(4):706-13.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Wilk, J.B. *et al.* 2012. Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians' Health Study. *Am J Clin Nutr*, 96(4):882-8.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Wurtz, A.M. *et al.* 2016. Substitution of meat and fish with vegetables or potatoes and risk of myocardial infarction. *Br J Nutr*, 116(9):1602-1610.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Wurtz, A.M. *et al.* 2016. Substitutions of red meat, poultry and fish and risk of myocardial infarction. *Br J Nutr*, 115(9):1571-8.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022

TABLE A3.11 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (cont.)**

Xun, P. *et al.* 2012. Fish consumption and risk of stroke and its subtypes: accumulative evidence from a meta-analysis of prospective cohort studies. *Eur J Clin Nutr*, 66(11):1199-207.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Yamagishi, K. *et al.* 2008. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. *J Am Coll Cardiol*, 52(12):988-96.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Yuan, J.M. *et al.* 2001. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol*, 154(9):809-16.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Zhang, B. *et al.* 2020. Fish Consumption and Coronary Heart Disease: A Meta-Analysis. *Nutrients*, 12(8).	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Zhang, H. *et al.* 2021. Familial factors, diet, and risk of cardiovascular disease: a cohort analysis of the UK Biobank. *Am J Clin Nutr*, 114(5):1837-1846.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Zhao, W. *et al.* 2019. Fish Consumption and Stroke Risk: A Meta-Analysis of Prospective Cohort Studies. *J Stroke Cerebrovasc Dis*, 28(3):604-611.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Zheng, J. *et al.* 2012. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutr*, 2012. 15(4):725-37.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Zhong, V.W. *et al.* 2020. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. *JAMA Intern Med*, 180(4):503-512.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TYPE 2 DIABETES

TABLE A3.12 **SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TYPE 2 DIABETES" DURING FULL-TEXT SCREENING BASED ON INCLUSION AND EXCLUSION CRITERIA**

Study (n = 10)	Reason for exclusion
Dàrcy *et al.* 2020 The Role of Diet in the Prevention of Diabetes among Women with Prior Gestational Diabetes: A Systematic Review of Intervention and Observational Studies. *Journal of the Academy of Nutrition and Dietetics*, 120(1), 69-85.	Excluded based on inclusion and exclusion criteria: dietary pattern
Franz *et al.* 2017. Academy of Nutrition and Dietetics Nutrition Practice Guideline for Type 1 and Type 2 Diabetes in Adults: Systematic Review of Evidence for Medical Nutrition Therapy Effectiveness and Recommendations for Integration into the Nutrition Care Process. *Journal of the Academy of Nutrition and Dietetics*, 117(10), 1659-1679.	Excluded based on inclusion and exclusion criteria: Not relevant – the study investigates the effects of different medical nutrition therapies.
Karimi *et al.* 2020. A systematic review and meta-analysis of the association between fish consumption and risk of metabolic syndrome. *Nutrition, Metabolism and Cardiovascular Diseases*, 30(5), 717-729.	Excluded based on inclusion and exclusion criteria: does not meet health outcome criteria
Kim *et al.* 2015. Fish consumption, long-chain omega-3 polyunsaturated fatty acid intake and risk of metabolic syndrome: a meta-analysis. *Nutrients*, 7(4), 2085-2100.	Excluded based on inclusion and exclusion criteria: does not meet health outcome criteria
Schwab *et al.* 2014. Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. *Food & Nutrition research*, 58(1), 25145.	Excluded based on inclusion and exclusion criteria: does not meet intervention/exposure criteria
Tørris *et al.* 2014. Fish consumption and its possible preventive role on the development and prevalence of metabolic syndrome - a systematic review. *Diabetology & Metabolic Syndrome*, 6, 1-11.	Excluded based on inclusion and exclusion criteria: does not meet health outcome criteria
Schwingshackl *et al.* 2017. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *European Journal of Epidemiology*, 32, 363-375.	Excluded, as the review has already been assessed in VKM 2022.
Namazi *et al.* 2019. The association between types of seafood intake and the risk of type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. *Health Promotion Perspectives*, 9(3), 164.	Excluded, as the review has already been assessed in VKM 2022.
Pastorino *et al.* 2021. Heterogeneity of Associations between Total and Types of Fish Intake and the Incidence of Type 2 Diabetes: Federated Meta-Analysis of 28 Prospective Studies Including 956,122 Participants. *Nutrients*, 13(4), 1223.	Excluded, as the review has already been assessed in VKM 2022.
Yang *et al.* 2020. Meat and fish intake and type 2 diabetes: Dose-response meta-analysis of prospective cohort studies. *Diabetes & Metabolism*, 46(5), 345-352.	Excluded, as the review has already been assessed in VKM 2022.

TABLE A3.13 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TYPE 2 DIABETES"**

Study (n = 40)	Reason for exclusion
Amoah, J. *et al.* 2021. Effects of a school-based intervention to reduce cardiovascular disease risk factors among secondary school students: A cluster- randomized, controlled trial. *PloS One*, 16(11):e0259581.	Excluded based on inclusion and exclusion criteria: not general population
Abete, I. Parra, D. Crujeiras, A.B. Goyenechea, E. & Martinez, J.A. 2008. Specific insulin sensitivity and leptin responses to a nutritional treatment of obesity via a combination of energy restriction and fatty fish intake. *Journal of human nutrition and dietetics*, 21(6):591-600.	Excluded based on inclusion and exclusion criteria: type 2 diabetes is not an endpoint
Adamsson, V. Reumark, A. Fredriksson, I.B. Hammarström, E. Vessby, B. Johansson, G. & Risérus, U. 2011. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). *Journal of internal medicine*, 269(2):150-159.	Excluded based on inclusion and exclusion criteria: excluded as fish is studied as a part of a Nordic diet
Baik, I. Abbott, R.D. Curb, J.D. & Shin, C. 2010. Intake of fish and n-3 fatty acids and future risk of metabolic syndrome. *Journal of the American Dietetic Association*, 110(7):1018-1026.	Excluded based on inclusion and exclusion criteria: type 2 diabetes is not an endpoint
Brouwer-Brolsma, E.M. van Woudenbergh, G.J. Elferink, S.O. Singh-Povel, C.M. Hofman, A. Dehghan, A. Feskens, E. J. M. *et al.* 2016. Intake of different types of dairy and its prospective association with risk of type 2 diabetes: the Rotterdam Study. *Nutrition, Metabolism and Cardiovascular Diseases*, 26(11):987-995.	Excluded based on inclusion and exclusion criteria: no fish consumption measured
Díaz-Rizzolo, D. A. Serra, A. Colungo, C. Sala-Vila, A. Sisó-Almirall, A. & Gomis, R. 2021. Type 2 diabetes preventive effects with a 12-months sardine-enriched diet in elderly population with prediabetes: An interventional, randomized and controlled trial. *Clinical Nutrition*, 40(5):2587-2598.	Excluded based on inclusion and exclusion criteria: the population studied is prediabetic
Feskens, E. J. Virtanen, S. M. Räsänen, L. Tuomilehto, J. Stengård, J. Pekkanen, J. Kromhout, D. *et al.* 1995. Dietary factors determining diabetes and impaired glucose tolerance: a 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes care*, 18(8):1104-1112.	Excluded based on inclusion and exclusion criteria: not analysed in a prospective manner
Feskens, E.J. Bowles, C.H. & Kromhout, D. 1991. Inverse association between fish intake and risk of glucose intolerance in normoglycemic elderly men and women. *Diabetes care*, 14(11):935-941.	Excluded based on inclusion and exclusion criteria: not analysed in a prospective manner
Helland, A. Bratlie, M. Hagen, I.V. Mjøs, S.A. Sørnes, S. Halstensen, A.I. Gudbrandsen, O.A. *et al.* 2017. High intake of fatty fish, but not of lean fish, improved postprandial glucose regulation and increased the n-3 PUFA content in the leucocyte membrane in healthy overweight adults: a randomised trial. *British Journal of Nutrition*, 117(10):1368-1378.	Excluded based on inclusion and exclusion criteria: type 2 diabetes is not an endpoint
Hustad, K.S. Ottestad, I. Hjorth, M. Dalen, K.T. Sæther, T. Sheikh, N.A. Holven, K.B. *et al.* 2021. No effect of salmon fish protein on 2-h glucose in adults with increased risk of type 2 diabetes: a randomised controlled trial. *British Journal of Nutrition*, 126(9):1304-1313.	Excluded based on inclusion and exclusion criteria: RCT with salmon fish protein supplement
Ibsen, D.B. Steur, M. Imamura, F. Overvad, K. Schulze, M.B. Bendinelli, B. Wareham, N.J. *et al.* 2020. Replacement of red and processed meat with other food sources of protein and the risk of type 2 diabetes in European populations: the EPIC-InterAct Study. *Diabetes Care*, 43(11):2660-2667.	Excluded based on inclusion and exclusion criteria: wrong study design, case-cohort study
Ibsen, D. Jakobsen, M. Halkjær, J. Parner, E. & Overvad, K. 2020. Replacing Red Meat with Alternative Food Sources of Protein on Risk of Type 2 Diabetes-Modeling Dietary Changes in a Causal Framework. *Current Developments in Nutrition*, 4(Supplement_2):1418-1418.	Excluded based on inclusion and exclusion criteria: wrong study design
Ibsen, D.B. Warberg, C.K. Würtz, A.M.L. Overvad, K. & Dahm, C.C. 2019. Substitution of red meat with poultry or fish and risk of type 2 diabetes: a Danish cohort study. *European journal of nutrition*, 58, 2705-2712.	Excluded based on inclusion and exclusion criteria: wrong study design
Ikeda, K. Sato, T. Nakayama, T. Tanaka, D. Nagashima, K. Mano, F. Nagahama Study Group *et al.* 2018. Dietary habits associated with reduced insulin resistance: The Nagahama study. *Diabetes Research and Clinical Practice*, 141, 26-34.	Excluded based on inclusion and exclusion criteria: wrong study design, cross-sectional analyses
Kim, Y. S. Xun, P. Iribarren, C. Van Horn, L. Steffen, L. Daviglus, M.L. He, K. *et al.* 2016. Intake of fish and long-chain omega-3 polyunsaturated fatty acids and incidence of metabolic syndrome among American young adults: a 25-year follow-up study. *European journal of nutrition*, 55, 1707-1716.	Excluded based on inclusion and exclusion criteria: T2D is not an endpoint
Lankinen, M. Schwab, U. Kolehmainen, M. Paananen, J. Poutanen, K. Mykkänen, H. Orešič, M. *et al.* 2011. Whole grain products, fish and bilberries alter glucose and lipid metabolism in a randomized, controlled trial: the Sysdimet study. *PloS One*, 6(8):e22646.	Excluded based on inclusion and exclusion criteria: RCT, high-risk persons
Mori, T.A. Bao, D.Q. Burke, V. Puddey, I.B. Watts, G.F. & Beilin, L.J. *et al.* 1999. Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *The American journal of clinical nutrition*, 70(5):817-825.	Excluded based on inclusion and exclusion criteria: wrong publication type, type 2 diabetes not an endpoint
Nanri, A. 2013. Nutritional epidemiology of type 2 diabetes and depressive symptoms. *Journal of Epidemiology*, 23(4):243-250.	Excluded based on inclusion and exclusion criteria: wrong study design, review paper
Navas-Carretero, S. Pérez-Granados, A.M. Schoppen, S. & Vaquero, M.P. 2009. An oily fish diet increases insulin sensitivity compared to a red meat diet in young iron-deficient women. *British journal of nutrition*, 102(4):546-553.	Excluded based on inclusion and exclusion criteria: RCT, type 2 diabetes is not an endpoint
Ouellet, V. Marois, J. Weisnagel, S.J. & Jacques, H. 2007. Dietary cod protein improves insulin sensitivity in insulin-resistant men and women: a randomized controlled trial. *Diabetes Care*, 30(11):2816-2821.	Excluded based on inclusion and exclusion criteria: RCT, type 2 diabetes is not an endpoint
Ramel, A. Martinez, A. Kiely, M. Morais, G. Bandarra, N.M. & Thorsdottir, I. 2008. Beneficial effects of long-chain n-3 fatty acids included in an energy-restricted diet on insulin resistance in overweight and obese European young adults. *Diabetologia*, 51, 1261-1268.	Excluded based on inclusion and exclusion criteria: RCT, obese individuals, type 2 diabetes is not an endpoint
Ruidavets, J.B. Bongard, V. Dallongeville, J. Arveiler, D. Ducimetière, P. Perret, B. Ferrières, J. *et al.* 2007. High consumptions of grain, fish, dairy products and combinations of these are associated with a low prevalence of metabolic syndrome. *Journal of Epidemiology & Community Health*, 61(9):810-817.	Excluded based on inclusion and exclusion criteria: T2D is not an endpoint
Torjesen, P.A. Birkeland, K.I. Anderssen, S.A. Hjermann, I. Holme, I. & Urdal, P. 1997. Lifestyle changes may reverse development of the insulin resistance syndrome. The Oslo Diet and Exercise Study: a randomized trial. *Diabetes care*, 20(1):26-31.	Excluded based on inclusion and exclusion criteria: RCT, type 2 diabetes is not an endpoint

TABLE A3.13 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TYPE 2 DIABETES" (cont.)**

Würtz, A.M.L. Jakobsen, M.U. Bertoia, M.L. Hou, T. Schmidt, E.B. Willett, W.C. Rimm, E.B. *et al.* 2021. Replacing the consumption of red meat with other major dietary protein sources and risk of type 2 diabetes mellitus: a prospective cohort study. The *American Journal of Clinical Nutrition*, 113(3):612-621.	Excluded based on inclusion and exclusion criteria: wrong study design
Aadland, E.K. Graff, I.E. Lavigne, C. Eng, Ø. Paquette, M. Holthe, A. Liaset, B. *et al.* 2016. Lean seafood intake reduces postprandial C-peptide and lactate concentrations in healthy adults in a randomized controlled trial with a crossover design. *The Journal of nutrition*, 146(5):1027-1034.	Excluded based on inclusion and exclusion criteria: RCT, type 2 diabetes is not an endpoint
Chen, G.C. Arthur, R. Qin, L.Q. Chen, L.H. Mei, Z. Zheng, Y. Qi, Q. 2021. Association of oily and nonoily fish consumption and fish oil supplements with incident type 2 diabetes: a large population-based prospective study. *Diabetes Care*, 44(3):672-680.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Djousse, L. Gaziano, J.M. Buring, J.E. & Lee, I.M. 2011. Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. *The American journal of clinical nutrition*, 93(1):143-150.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Du, H. Guo, Y. Bennett, D.A. Bragg, F. Bian, Z. Chadni, M. China Kadoorie Biobank collaborative group. *et al.* 2020. Red meat, poultry and fish consumption and risk of diabetes: a 9 year prospective cohort study of the China Kadoorie Biobank. *Diabetologia*, *63*, 767-779.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Kaushik, M. Mozaffarian, D. Spiegelman, D. Manson, J.E. Willett, W.C. & Hu, F.B. 2009. Long-chain omega-3 fatty acids, fish intake, and the risk of type 2 diabetes mellitus. *The American journal of clinical nutrition*, 90(3):613-620.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Löfvenborg, J.E. Carlsson, S. Andersson, T. Hampe, C.S. Koulman, A. Chirlaque Lopez, M.D., Wareham, N. J. *et al.* 2021. Interaction between GAD65 antibodies and dietary fish intake or plasma phospholipid n-3 polyunsaturated fatty acids on incident adult-onset diabetes: the EPIC-InterAct study. *Diabetes care*, *44*(2):416-424.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Nanri, A. Mizoue, T. Noda, M. Takahashi, Y. Matsushita, Y. Poudel-Tandukar, K. Japan Public Health Center–based Prospective Study Group. *et al.* 2011. Fish intake and type 2 diabetes in Japanese men and women: the Japan Public Health Center–based Prospective Study–. *The American journal of clinical nutrition*, *94*(3):884-891.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Patel, P.S. Sharp, S.J. Luben, R.N. Khaw, K.T. Bingham, S.A. Wareham, N.J. & Forouhi, N.G. 2009. Association between type of dietary fish and seafood intake and the risk of incident type 2 diabetes: the European prospective investigation of cancer (EPIC)-Norfolk cohort study. *Diabetes care*, *32*(10):1857-1863.	Excluded for further assessment as the primary study had already been assessed in a systematic review that is included in VKM 2022
Patel *et al.* 2012. The prospective association between total and type of fish intake and type 2 diabetes in 8 European countries: EPIC-InterAct Study. *The American journal of clinical nutrition*, 95.6: 1445-1453.	Excluded for further assessment as the primary study had already been assessed in a systematic review that is included in VKM 2022
Rylander, C. Sandanger, T.M. Engeset, D. & Lund, E. 2014. Consumption of lean fish reduces the risk of type 2 diabetes mellitus: a prospective population based cohort study of Norwegian women. *PloS One*, 9(2):e89845.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Talaei, M. Wang, Y.L. Yuan, J.M. Pan, A. *&* Koh, W.P. 2017. Meat, dietary heme iron, and risk of type 2 diabetes mellitus: the Singapore Chinese Health *Study. American journal of epidemiology*, *186*(7):824-833.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Van Woudenbergh, G.J. van Ballegooijen, A.J. Kuijsten, A. Sijbrands, E.J. van Rooij, F.J. Geleijnse, J.M. Feskens, E.J. *et al.* 2009. Eating fish and risk of type 2 diabetes: a population-based, prospective follow-up study. *Diabetes care*, *32*(11):2021-2026.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Villegas, R. Xiang, Y.B. Elasy, T. Li, H.L. Yang, G. Cai, H. Shu, X.O. *et al.* 2011. Fish, shellfish, and long-chain n– 3 fatty acid consumption and risk of incident type 2 diabetes in middle-aged Chinese men and women. *The American journal of clinical nutrition*, *94*(2):543-551.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Virtanen, J.K. Mursu, J. Voutilainen, S. Uusitupa, M. & Tuomainen, T.P. 2014. Serum omega-3 polyunsaturated fatty acids and risk of incident type 2 diabetes in men: the Kuopio Ischemic Heart Disease Risk Factor study. *Diabetes care*, *37*(1):189-196.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Wallin, A. Di Giuseppe, D. Orsini, N. Åkesson, A. Forouhi, N.G. & Wolk, A. 2017. Fish consumption and frying of fish in relation to type 2 diabetes incidence: a prospective cohort study of Swedish men. *European journal of nutrition*, *56*, 843-852.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Zhang, Y. Zhuang, P. Mao, L. Chen, X. Wang, J. Cheng, L. Jiao, J. *et al.* 2019. Current level of fish and omega-3 fatty acid intakes and risk of Type 2 diabetes in China. *The Journal of nutritional biochemistry*, *74*, 108249.	Excluded for further assessment as the primary study had already been assessed in VKM 2022
Øyen, J. Brantsæter, A.L. Nøstbakken, O. . Birkeland, K.I. Haugen, M. Madsen, L. & Egeland, G.M. 2021. Intakes of fish and long-chain n-3 polyunsaturated fatty acid supplements during pregnancy and subsequent risk of type 2 diabetes in a large prospective cohort study of Norwegian women. *Diabetes Care*, *44*(10):2337-2345.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS

TABLE A3.14 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 20)	Reason for exclusion
Appleton, K.M. Hayward, R.C. Gunnell, D. Peters, T.J. Rogers, P.J. Kessler, D. *&* Ness, A.R. 2006. Effects of n–3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. *The American journal of clinical nutrition*, 84(6):1308-1316.	Excluded based on inclusion and exclusion criteria: focus on n-3 fatty acids.
Appleton, K.M. Rogers, P.J. *&* Ness, A.R. 2010. Updated systematic review and meta-analysis of the effects of n–3 long-chain polyunsaturated fatty acids on depressed mood. *The American journal of clinical nutrition*, 91(3):757-770.	Excluded based on inclusion and exclusion criteria: focus on n-3 fatty acids.
Bakre, A.T. Chen, R. Khutan, R. Wei, L. Smith, T. Qin, G. Ni, J. *et al.* 2018. Association between fish consumption and risk of dementia: a new study from China and a systematic literature review and meta-analysis. *Public health nutrition*, 21(10):1921-1932.	Excluded, as the review has already been assessed in VKM 2022.
Fernandes, A.C. Medeiros, C.O. Bernardo, G.L. Ebone, M.V. Di Pietro, P.F. Assis, M.A.A.D. *&* Vasconcelos, F. 2012. Benefits and risks of fish consumption for the human health. *Revista de Nutrição*, 25, 283-295.	Excluded based on inclusion and exclusion criteria: review
Fotuhi, M. Mohassel, P. *&* Yaffe, K. 2009. Fish consumption, long-chain omega-3 fatty acids and risk of cognitive decline or Alzheimer disease: a complex association. *Nature Reviews Neurology*, 5(3):140-152.	Excluded based on inclusion and exclusion criteria: focus on use of n-3 in relation to cognitive impairment and dementia
Grosso, G. Micek, A. Marventano, S. Castellano, S. Mistretta, A. Pajak, A. *&* Galvano, F. 2016. Dietary n-3 PUFA, fish consumption and depression: a systematic review and meta-analysis of observational studies. *Journal of Affective Disorders*, 205, 269-281.	Excluded, as the review has already been assessed in VKM 2022.
Hibbeln, J. R. Spiller, P. Brenna, J. T. Golding, J. Holub, B. J. Harris, W. S., Carlson, S. E. *et al.* 2019. Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 151, 14-36.	Excluded, as the review has already been assessed in VKM 2022.
Ishihara, L. *&* Brayne, C. 2005. A systematic review of nutritional risk factors of Parkinson's disease. *Nutrition research reviews*, 18(2):259-282.	Excluded based on inclusion and exclusion criteria: focus on nutritional factors and not fish intake alone.
Kosti, R. I. Kasdagli, M. I. Kyrozis, A. Orsini, N. Lagiou, P. Taiganidou, F. *&* Naska, A. 2022. Fish intake, n-3 fatty acid body status, and risk of cognitive decline: a systematic review and a dose–response meta-analysis of observational and experimental studies. *Nutrition Reviews*, 80(6):1445-1458.	Excluded, as the review has already been assessed in VKM 2022.
Lee, Y. Back, J.H. Kim, J. Kim, S.H. Na, D.L. Cheong, H.K. Kim, Y.G. *et al.* 2010. Systematic review of health behavioral risks and cognitive health in older adults. *International psychogeriatrics*, 22(2):174-187.	Excluded based on inclusion and exclusion criteria: health behaviour as outcome, and only 3 studies of the 37 included reported on fish intake.
Li, F. Liu, X. *&* Zhang, D. 2016. Fish consumption and risk of depression: a meta-analysis. J Epidemiol *Community Health*, 70(3):299-304.	Excluded, as the review has already been assessed in VKM 2022.
Matison, A.P. Mather, K.A. Flood, V.M. *&* Reppermund, S. 2021. Associations between nutrition and the incidence of depression in middle-aged and older adults: A systematic review and meta-analysis of prospective observational population-based studies. *Ageing Research Reviews*, 70, 101403.	Excluded, as the review has already been assessed in VKM 2022.
Molendijk, M. Molero, P. Sánchez-Pedreño, F.O. Van der Does, W. *&* Martínez-González, M.A. 2018. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *Journal of affective disorders*, 226, 346-354.	Excluded, as the review has already been assessed in VKM 2022.
Solfrizzi, V. Custodero, C. Lozupone, M. Imbimbo, B. P. Valiani, V. Agosti, P., Panza, F. *et al.* 2017. Relationships of dietary patterns, foods, and micro-and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *Journal of Alzheimer's Disease*, 59(3):815-849.	Excluded, as the review has already been assessed in VKM 2022.
Sparling, T.M. Henschke, N. Nesbitt, R.C. *&* Gabrysch, S. 2017. The role of diet and nutritional supplementation in perinatal depression: a systematic review. *Maternal & child nutrition*, 13(1).	Excluded based on inclusion and exclusion criteria: focus on nutritional supplementation and diet overall.
Wu, S. Ding, Y. Wu, F. Li, R. Hou, J. *&* Mao, P. 2015. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. *Neuroscience & Biobehavioral Reviews*, 48, 1-9.	Excluded based on inclusion and exclusion criteria: focus on n-3 fatty acids.
Zhao, X.H.*&* Zhang, Z.H. 2020. Risk factors for postpartum depression: An evidence-based systematic review of systematic reviews and meta-analyses. *Asian journal of psychiatry*, 53, 102353.	Excluded based on inclusion and exclusion criteria: review of risk factors and not on fish intake.
Yang, Y. Kim, Y. *&* Je, Y. 2018. Fish consumption and risk of depression: Epidemiological evidence from prospective studies. *Asia-Pacific Psychiatry*, 10(4):e12335.	Excluded, as the review has already been assessed in VKM 2022.
Zeng, L.F. Cao, Y. Liang, W.X. Bao, W.H. Pan, J.K. Wang, Q., Wang, N.S. *et al.* 2017. An exploration of the role of a fish-oriented diet in cognitive decline: a systematic review of the literature. *Oncotarget*, 8(24):39877.	Excluded, as the review has already been assessed in VKM 2022.
Zhang, Y. Chen, J. Qiu, J. Li, Y. Wang, J. *&* Jiao, J. 2015. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies–3. *The American Journal of Clinical Nutrition*, 103(2):330-340.	Excluded, as the review has already been assessed in VKM 2022.

TABLE A3.15 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" BASED ON INCLUSION AND EXCLUSION CRITERIA**

Study (n = 80)	Reason for exclusion
Batty, G.D. Deary, I.J. Schoon, I. & Gale, C.R. 2007. Childhood mental ability in relation to food intake and physical activity in adulthood: The 1970 British cohort study. *Pediatrics*, 119(1), e38-e45.	Excluded based on inclusion and exclusion criteria: cross sectional study.
Belfort, M.B. Rifas-Shiman, S.L. Kleinman, K.P. Guthrie, L.B. Bellinger, D.C. Taveras, E.M. Gillman, M.W. & Oken, E. 2013. Infant Feeding and Childhood Cognition at Ages 3 and 7 Years Effects of Breastfeeding Duration and Exclusivity. *JAMA Pediatrics*, 167(9), 836-844.	Excluded based on inclusion and exclusion criteria: no data on fish (breastfeeding related to cognition at 3 and 7 years)
Dangour, A. D. Allen, E. Elbourne, D. Fletcher, A. Richards. M. & Uauy, R. 2009. Fish consumption and cognitive function among older people in the UK: baseline data from the Opal Study. *The Journal of Nutrition, Health and Aging*, 13(3), 198-202.	Excluded based on inclusion and exclusion criteria: cross sectional data
Eskelinen, M.H. Ng, T.U., Helkala, E.L. Tuomilehto, J., Nissinen, A. Soininen, H. & Kivipelto, M. 2008. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences*: 741-747.	Excluded based on inclusion and exclusion criteria: no data on fish
Gatto, N.M. Garcia-Cano, J. Irani, C. Jaceldo-Siegl, K. Liu, T. Chen, Z. Paul, J. Fraser, G. Wang, C. & Lee, G.J. 2021. Vegetarian Dietary Patterns and Cognitive Function among Older Adults: The Adventist Health Study-2. *Journal of Nutrition in Gerontology and Geriatrics*, 40(4), 197-214.	Excluded based on inclusion and exclusion criteria: dietary pattern study
Gonzalez, S. Huerta, J.M. Fernandez, Patterson, A.M. & Lasheras, C. 2010. The relationship between dietary lipids and cognitive performance in an elderly population. *International Journal of Food Sciences and Nutrition*, 61(2), 217-225.	Excluded based on inclusion and exclusion criteria: dietary lipids and no fish and cross sectional study
Handeland, K. , Skotheim, S. Baste, V. Graff, I.E. Froyl, L., Lie, O. Kjellevold, M. Markhus, M. Stormark, K.M. Oyen, J. & Dahl, L. 2018.The effects of fatty fish intake on adolescents' nutritional status and associations with attention performance: results from the FINS-TEENS randomized controlled trial. *Nutrition Journal*, 17, 1-12.	Excluded based on inclusion and exclusion criteria: nutrient status in relation to attention
Hansen, A.L. Ambroziak, G. Thornton, D. Dahl, L. & Grung, B. 2018. Age and IQ Explained Working Memory Performance in a RCT with Fatty Fish in a Group of Forensic Inpatients. *The Journal of Nutrition, Health and Aging*, 22(4), 513-518.	Excluded based on inclusion and exclusion criteria: specific population group
Hansen, A.L. Olson, G. Dahl, L. Thornton, D. Grung, B. Graff, I.E. Frøyl, L. & Thayer, J.F. 2014. Reduced anxiety in forensic inpatients after a long-term intervention with Atlantic salmon. *Nutrients*, 6(12), 5405-5418.	Excluded based on inclusion and exclusion criteria: specific population group
Kwok, T.C.Y. Lam, L.C.W. Sea, M.M.M. Goggins, W. & Woo, J. 2012. A randomized controlled trial of dietetic interventions to prevent cognitive decline in old age hostel residents. *European Journal of Clinical Nutrition*, 66(10), 1135-1140	Excluded based on inclusion and exclusion criteria: diet in general and primary outcome was cognitive decline
Luxwolda, M.F. Kuipers, R.S. Boersma, E.R. van Goor, S.A. Dijck-Brouwer, D.A. Bos, A.F. & Muskiet, F.A. 2014. DHA status is positively related to motor development in breastfed African and Dutch infants. *Nutritional Neuroscience*, 17(3), 97-103.	Excluded based on inclusion and exclusion criteria: DHA in RBC related to motor development
Miyake, Y. Sasaki, S,. Yokoyama, T. Tanaka, K. Ohya, Y. Fukushima, W. Saito, K. Ohfuji, S. & Kiyohara, C. 2006. Risk of postpartum depression in relation to dietary fish and fat intake in Japan: the Osaka Maternal and Child Health Study. *Psychological Medicine*, 36(12), 1727-1735.	Excluded based on inclusion and exclusion criteria: investigated the relationship of high-fat foods and specific types of fatty acids with the risk of PP depression.
Nisevic, J.R. Prpic, I. Kolic, I. Bazdaric, K. Tratnik, J.S. Prpic, I.S. Mazej, D. Spiric, Z. Barbone, F. & Horvat, M. 2019. Combined prenatal exposure to mercury and LCPUFA on newborn's brain measures and neurodevelopment at the age of 18 months. *Environmental Research*, 178, 108682.	Excluded based on inclusion and exclusion criteria: mercury and n-3
Poudel-Tandukar, Kalpana, *et al.* 2011. Long chain n-3 fatty acids intake, fish consumption and suicide in a cohort of Japanese men and women—The Japan Public Health Center-based (JPHC) Prospective Study. *Journal of Affective Disorders* 129.1-3: 282-288.	Excluded based on inclusion and exclusion criteria: n-3 and fish in relation to suicide; wrong outcome
Reeves, J. L., Otahal, P., Magnussen, C. G., Dwyer, T., Kangas, A. J., Soininen, P., & Smith, K. J. 2017. DHA mediates the protective effect of fish consumption on new episodes of depression among women. *British Journal of Nutrition*, 118(9), 743-749.	Excluded based on inclusion and exclusion criteria: n-3 and tyrosine in relation to depression
Tiainen, A. M. K., Männistö, S., Lahti, M., Blomstedt, P. A., Lahti, J., Perälä, M. M., & Eriksson, J. G. 2013. Personality and dietary intake–findings in the Helsinki birth cohort study. *PloS One*, 8(7), e68284.	Excluded based on inclusion and exclusion criteria: dietary pattern and personality, cross sectional study
Timonen, M., Horrobin, D., Jokelainen, J., Laitinen, J., Herva, A., & Räsänen, P. 2004. Fish consumption and depression: the Northern Finland 1966 birth cohort study. *Journal of Affective Disorders*, 82(3), 447-452.	Excluded based on inclusion and exclusion criteria: brief report
Tsai, A. C., Lucas, M., Okereke, O. I., O'Reilly, É. J., Mirzaei, F., Kawachi, I., & Willett, W. C. 2014. Suicide mortality in relation to dietary intake of n-3 and n-6 polyunsaturated fatty acids and fish: equivocal findings from 3 large US cohort studies. *American Journal of Epidemiology*, 179(12), 1458-1466.	Excluded based on inclusion and exclusion criteria: n-3 and suicide
Vaz, J. D. S., Kac, G., Emmett, P., Davis, J. M., Golding, J., & Hibbeln, J. R. 2013. Dietary patterns, n-3 fatty acids intake from seafood and high levels of anxiety symptoms during pregnancy: findings from the Avon Longitudinal Study of Parents and Children. *PLoS One*, 8(7), e67671.	Excluded based on inclusion and exclusion criteria: dietary patterns and n-3 from seafood and anxiety
Vuholm, S., Teisen, M. N., Mølgaard, C., Lauritzen, L., & Damsgaard, C. T. 2021. Sleep and physical activity in healthy 8–9-year-old children are affected by oily fish consumption in the FiSK Junior randomized trial. *European Journal of Nutrition*, 1-12.	Excluded based on inclusion and exclusion criteria: sleep is not an included outcome
Winpenny, E. M., van Harmelen, A. L., White, M., van Sluijs, E. M., & Goodyer, I. M. 2018. Diet quality and depressive symptoms in adolescence: no cross-sectional or prospective associations following adjustment for covariates. *Public Health Nutrition*, 21(13), 2376-2384.	Excluded based on inclusion and exclusion criteria: diet and fish data is cross-sectional data and depressive symptoms
Yang, Y., Kim, Y., & Je, Y. 2018. Fish consumption and risk of depression: Epidemiological evidence from prospective studies. *Asia-Pacific Psychiatry*, 10(4), e12335.	Excluded based on inclusion and exclusion criteria: review
Åberg, M. A., Åberg, N., Brisman, J., Sundberg, R., Winkvist, A., & Torén, K. 2009. Fish intake of Swedish male adolescents is a predictor of cognitive performance. *Acta Paediatrica*, 98(3), 555-560.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TABLE A3.15 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Appleton, K. M., Woodside, J. V., Yarnell, J. W. G., Arveiler, D., Haas, B., Amouyel, P. & PRIME Study Group. 2007. Depressed mood and dietary fish intake: direct relationship or indirect relationship as a result of diet and lifestyle?. *Journal of Affective Disorders*, 104(1-3), 217-223.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Appleton, K. M., Peters, T. J., Hayward, R. C., Heatherley, S. V., McNaughton, S. A., Rogers, P. J., & Kessler, D. 2007. Depressed mood and n-3 polyunsaturated fatty acid intake from fish: non-linear or confounded association?. *Social Psychiatry and Psychiatric Epidemiology*, 42, 100-104.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Astorg, P., Couthouis, A., Bertrais, S., Arnault, N., Meneton, P., Guesnet, P., & Hercberg, S. 2008. Association of fish and long-chain n-3 polyunsaturated fatty acid intakes with the occurrence of depressive episodes in middle-aged French men and women. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 78(3), 171-182.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Chuang, S. Y., Lo, Y. L., Wu, S. Y., Wang, P. N., & Pan, W. H. 2019. Dietary patterns and foods associated with cognitive function in Taiwanese older adults: the cross-sectional and longitudinal studies. *Journal of the American Medical Directors Association*, 20(5), 544-550.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Colangelo, L. A., He, K., Whooley, M. A., Daviglus, M. L., & Liu, K. 2009. Higher dietary intake of long-chain ω-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition*, 25(10), 1011-1019.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Daniels, J. L., Longnecker, M. P., Rowland, A. S., Golding, J., & ALSPAC Study Team. 2004. Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology*, 15(4), 394-402.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Davidson, P. W., Cory-Slechta, D. A., Thurston, S. W., Huang, L. S., Shamlaye, C. F., Gunzler, D., Myers, G.J. *et al.* 2011. Fish consumption and prenatal methylmercury exposure: cognitive and behavioral outcomes in the main cohort at 17 years from the Seychelles child development study. *Neurotoxicology*, 32(6), 711-717.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Demmelmair, H., Øyen, J., Pickert, T., Rauh-Pfeiffer, A., Stormark, K. M., Graff, I. E., Koletzko, B. *et al.* 2019. The effect of Atlantic salmon consumption on the cognitive performance of preschool children–a randomized controlled trial. *Clinical Nutrition*, 38(6), 2558-2568.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Devore, E. E., Grodstein, F., van Rooij, F. J., Hofman, A., Rosner, B., Stampfer, M. J., Breteler, M.M. *et al.* Dietary intake of fish and omega-3 fatty acids in relation to long-term dementia risk. *The American Journal of Clinical Nutrition*, 90(1), 170-176.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Elstgeest, L. E., Visser, M., Penninx, B. W., Colpo, M., Bandinelli, S., & Brouwer, I. A. 2019. Bidirectional associations between food groups and depressive symptoms: longitudinal findings from the Invecchiare in Chianti (InCHIANTI) study. *British Journal of Nutrition*, 121(4), 439-450.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Fischer, K., Melo van Lent, D., Wolfsgruber, S., Weinhold, L., Kleineidam, L., Bickel, H., ... & Wagner, M. 2018. Prospective associations between single foods, Alzheimer's dementia and memory decline in the elderly. *Nutrients*, 10(7), 852.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Gale, C. R., Robinson, S. M., Godfrey, K. M., Law, C. M., Schlotz, W., & O'Callaghan, F. J. 2008. Oily fish intake during pregnancy–association with lower hyperactivity but not with higher full-scale IQ in offspring. *Journal of Child Psychology and Psychiatry*, 49(10), 1061-1068.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Golding, J., Steer, C., Emmett, P., Davis, J. M., & Hibbeln, J. R. 2009. High levels of depressive symptoms in pregnancy with low omega-3 fatty acid intake from fish. *Epidemiology*, 20(4), 598-603.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Hamazaki, K., Matsumura, K., Tsuchida, A., Kasamatsu, H., Tanaka, T., Ito, M., & Inadera, H. 2020. Maternal dietary intake of fish and PUFAs and child neurodevelopment at 6 months and 1 year of age: a nationwide birth cohort—the Japan Environment and Children's Study (JECS). *American Journal of Clinical Nutrition*, 112(5), 1295-1303.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hamazaki, K., Matsumura, K., Tsuchida, A., Kasamatsu, H., Tanaka, T., Ito, M., & Inadera, H. 2020. Dietary intake of fish and n-3 polyunsaturated fatty acids and risk of postpartum depression: a nationwide longitudinal study–the Japan Environment and Children's Study (JECS). *Psychological Medicine*, 50(14), 2416-2424.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Handeland, K., Øyen, J., Skotheim, S., Graff, I. E., Baste, V., Kjellevold, M., Stormark, K. M. *et al.* 2017. Fatty fish intake and attention performance in 14–15 year old adolescents: FINS-TEENS-a randomized controlled trial. *Nutrition Journal*, 16, 1-10.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hansen, A. L., Dahl, L., Olson, G., Thornton, D., Grung, B., & Thayer, J. F. 2015. A long-term fatty fish intervention improved executive function in inpatients with antisocial traits and a history of alcohol and drug abuse. *Scandinavian Journal of Psychology*, 56(5), 467-474.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hedelin, M., Löf, M., Olsson, M., Lewander, T., Nilsson, B., Hultman, C. M., & Weiderpass, E. 2010. Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and the prevalence of psychotic-like symptoms in a cohort of 33 000 women from the general population. *BMC Psychiatry*, 10, 1-13.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hibbeln, J. R., Davis, J. M., Steer, C., Emmett, P., Rogers, I., Williams, C., & Golding, J. 2007. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *The Lancet*, 369(9561), 578-585.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Huang, T. L., Zandi, P. P., Tucker, K. L., Fitzpatrick, A. L., Kuller, L. H., Fried, L. P., Carlson, M.C. *et al.* 2005. Benefits of fatty fish on dementia risk are stronger for those without APOE ε4. *Neurology*, 65(9), 1409-1414.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Hysing, M., Kvestad, I., Kjellevold, M., Kolden Midtbø, L., Graff, I. E., Lie, Ø., Øyen, J. *et al.* 2018. Fatty fish intake and the effect on mental health and sleep in preschool children in FINS-KIDS, a randomized controlled trial. *Nutrients*, 10(10), 1478.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Julvez, J., Fernández-Barrés, S., Gignac, F., López-Vicente, M., Bustamante, M., Garcia-Esteban, R., Sunyer, J. *et al.* 2020. Maternal seafood consumption during pregnancy and child attention outcomes: a cohort study with gene effect modification by PUFA-related genes. *International Journal of Epidemiology*, 49(2), 559-571.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TABLE A3.15 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Julvez, J., Méndez, M., Fernandez-Barres, S., Romaguera, D., Vioque, J., Llop, S., Sunyer, J. *et al.* 2016. Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels. *American Journal of Epidemiology*, 183(3), 169-182.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kalmijn, S., Launer, L. J., Ott, A., Witteman, J. C., Hofman, A., & Breteler, M. M. 1997. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Annals of Neurology*, 42(5), 776-782.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kesse-Guyot, E., Peneau, S., Ferry, M., Jeandel, C., Hercberg, S., Galan, P.; SU.VI.Max 2 Research Group. 2011. Thirteen-year prospective study between fish consumption, long-chain n-3 fatty acids intakes and cognitive function. *The Journal of Nutrition, Health & Aging*, 15, 115-120.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kim, D. H., Grodstein, F., Rosner, B., Kang, J. H., Cook, N. R., Manson, J. E., Okereke, O. I. *et al.* 2013. Seafood types and age-related cognitive decline in the Women's Health Study. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 68(10), 1255-1262.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Kosti, R. I., Kasdagli, M. I., Kyrozis, A., Orsini, N., Lagiou, P., Taiganidou, F., & Naska, A. 2022. Fish intake, n-3 fatty acid body status, and risk of cognitive decline: a systematic review and a dose–response meta-analysis of observational and experimental studies. *Nutrition Reviews*, 80(6), 1445-1458.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Kvestad, I., Hysing, M., Kjellevold, M., Næss, S., Dahl, L., & Markhus, M. W. 2021. Maternal cod intake during pregnancy and infant development in the first year of life: secondary analyses from a randomized controlled trial. *The Journal of Nutrition*, 151(7), 1879-1885.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Larrieu, S., Letenneur, L., Helmer, C., Dartigues, J. F., & Barberger-Gateau, P. 2004. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. *The Journal of Nutrition, Health & Aging*, 8(3), 150-154.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Li, Y., Dai, Q., Ekperi, L. I., Dehal, A., & Zhang, J. 2011. Fish consumption and severely depressed mood, findings from the first national nutrition follow-up study. *Psychiatry Research*, 190(1), 103-109.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Liu, J., Cui, Y., Li, L., Wu, L., Hanlon, A., Pinto-Martin, J., Hibbeln, J. R. *et al.* 2017. The mediating role of sleep in the fish consumption–cognitive functioning relationship: a cohort study. *Scientific Reports*, 7(1), 1-9.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Lopez, L. B., Kritz-Silverstein, D., & Barrett-Connor, E. 2011. High dietary and plasma levels of the omega-3 fatty acid docosahexaenoic acid are associated with decreased dementia risk: the Rancho Bernardo study. *The Journal of Nutrition, Health & Aging*, 15, 25-31.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Lucas, M., Mirzaei, F., O'Reilly, E. J., Pan, A., Willett, W. C., Kawachi, I., Ascherio, A. *et al.* 2011. Dietary intake of n− 3 and n− 6 fatty acids and the risk of clinical depression in women: a 10-y prospective follow-up study. *The American Journal of Clinical Nutrition*, 93(6), 1337-1343.	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Markhus, M. W., Hysing, M., Midtbø, L. K., Nerhus, I., Næss, S., Aakre, I., Kjellevold, M. *et al.* 2021. Effects of two weekly servings of cod for 16 weeks in pregnancy on maternal iodine status and infant neurodevelopment: Mommy's Food, a randomized-controlled trial. *Thyroid*, 31(2), 288-298.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Mendez, M. A., Torrent, M., Julvez, J., Ribas-Fitó, N., Kogevinas, M., & Sunyer, J. 2009. Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years. *Public Health Nutrition*, 12(10), 1702-1710.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Morris, M.C., Evans, D.A., Tangney, C.C., Bienias, J.L., & Wilson, R.S. 2005. Fish consumption and cognitive decline with age in a large community study. *Archives of Neurology*, 62(12), 1849-1853.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Wilson, R. S., Schneider, J. *et al.* 2003. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Archives of Neurology*, 60(7), 940-946.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Ngabirano, L., Samieri, C., Feart, C., Gabelle, A., Artero, S., Duflos, C., Mura, T. *et al.* 2019. Intake of meat, fish, fruits, and vegetables and long-term risk of dementia and Alzheimer's disease. *Journal of Alzheimer's Disease*, 68(2), 711-722.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Nooyens, A. C., Van Gelder, B. M., Bueno-de-Mesquita, H. B., Van Boxtel, M. P., & Verschuren, W. M. 2018. Fish consumption, intake of fats and cognitive decline at middle and older age: the Doetinchem Cohort Study. *European Journal of Nutrition*, 57, 1667-1675.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Nozaki, S., Sawada, N., Matsuoka, Y. J., Shikimoto, R., Mimura, M., & Tsugane, S. 2021. Association between dietary fish and PUFA intake in midlife and dementia in later life: the JPHC Saku Mental Health Study. *Journal of Alzheimer's Disease*, 79(3), 1091-1104..	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Oken, E., Østerdal, M. L., Gillman, M. W., Knudsen, V. K., Halldorsson, T. I., Strøm, M., Olsen, S. F. *et al.* 2008. Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. *The American Journal of Clinical Nutrition*, 88(3), 789-796.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Øyen, J., Kvestad, I., Midtbø, L. K., Graff, I. E., Hysing, M., Stormark, K. M., Kjellevold, M. *et al.* 2018. Fatty fish intake and cognitive function: FINS-KIDS, a randomized controlled trial in preschool children. *BMC Medicine*, 16, 1-15.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Qin, B., Plassman, B. L., Edwards, L. J., Popkin, B. M., Adair, L. S., & Mendez, M. A. 2014. Fish intake is associated with slower cognitive decline in Chinese older adults. *The Journal of Nutrition*, 144(10), 1579-1585.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Samieri, C., Morris, M. C., Bennett, D. A., Berr, C., Amouyel, P., Dartigues, J. F., Grodstein, F. *et al.* 2018. Fish intake, genetic predisposition to Alzheimer disease, and decline in global cognition and memory in 5 cohorts of older persons. *American Journal of Epidemiology*, 187(5), 933-940.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Sanchez-Villegas, A., Henríquez, P., Figueiras, A., Ortuño, F., Lahortiga, F., & Martínez-González, M. A. 2007. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. *European Journal of Nutrition*, 46, 337-346..	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

TABLE A3.15 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Skotheim, S., Handeland, K., Kjellevold, M., Øyen, J., Frøyland, L., Lie, Ø., Dahl, L. *et al.* 2017. The effect of school meals with fatty fish on adolescents' self-reported symptoms for mental health: FINS-TEENS-a randomized controlled intervention trial. *Food & Nutrition Research*, 12;61(1)	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Smith, K. J., Sanderson, K., McNaughton, S. A., Gall, S. L., Dwyer, T., & Venn, A. J. 2014. Longitudinal associations between fish consumption and depression in young adults. *American Journal of Epidemiology*, 179(10), 1228-1235.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Solfrizzi, V., Custodero, C., Lozupone, M., Imbimbo, B. P., Valiani, V., Agosti, P., Panza, F. *et al.* 2017. Relationships of dietary patterns, foods, and micro-and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. *Journal of Alzheimer's Disease*, *59*(3), 815-849.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Strøm, M., Mortensen, E. L., Halldorsson, T. I., Thorsdottir, I., & Olsen, S. F. 2009. Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. *The American Journal of Clinical Nutrition*, *90*(1), 149-155.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Teisen, M. N., Vuholm, S., Niclasen, J., Aristizabal-Henao, J. J., Stark, K. D., Geertsen, S. S., Lauritzen, L. *et al.* 2020. Effects of oily fish intake on cognitive and socioemotional function in healthy 8–9-year-old children: The FiSK Junior randomized trial. *The American Journal of Clinical Nutrition*, 112(1), 74-83.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Tsurumaki, N., Zhang, S., Tomata, Y., Abe, S., Sugawara, Y., Matsuyama, S., & Tsuji, I. 2019. Fish consumption and risk of incident dementia in elderly Japanese: the Ohsaki cohort 2006 study. *British Journal of Nutrition*, 122(10), 1182-1191.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Valent, F., Mariuz, M., Bin, M., Mazej, D., Tognin, V., Tratnik, J., Barbone, F. *et al.* 2013. Associations of prenatal mercury exposure from maternal fish consumption and polyunsaturated fatty acids with child neurodevelopment: a prospective cohort study in Italy. *Journal of Epidemiology*, *23*(5), 360-370.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
van de Rest, O., Spiro III, A., Krall-Kaye, E., Geleijnse, J. M., de Groot, L. C., & Tucker, K. L. 2009. Intakes of (n-3) fatty acids and fatty fish are not associated with cognitive performance and 6-year cognitive change in men participating in the Veterans Affairs Normative Aging Study. *The Journal of Nutrition*, *139*(12), 2329-2336.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
van Gelder, B. M., Tijhuis, M., Kalmijn, S., & Kromhout, D. 2007. Fish consumption, n– 3 fatty acids, and subsequent 5-y cognitive decline in elderly men: the Zutphen Elderly Study. *The American Journal of Clinical Nutrition*, *85*(4), 1142-1147.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Vecchione, R., Vigna, C., Whitman, C., Kauffman, E. M., Braun, J. M., Chen, A., Lyall, K. *et al.* 2021. The association between maternal prenatal fish intake and child autism-related traits in the EARLI and HOME Studies. *Journal of Autism and Developmental Disorders*, *51*, 487-500.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Yang, Y., Kim, Y., & Je, Y. 2018. Fish consumption and risk of depression: Epidemiological evidence from prospective studies. *Asia-Pacific Psychiatry*, 10(4), e12335.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Zhou, F., Wu, F., Zou, S., Chen, Y., Feng, C., & Fan, G. 2016. Dietary, nutrient patterns and blood essential elements in Chinese children with ADHD. *Nutrients*, 8(6), 352.	Excluded for further assessment, as the primary study had already been assessed in VKM 2022

MORTALITY

TABLE A3.16 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "MORTALITY" BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 19)	Reason for exclusion
Zhang, B. Xiong, K. Cai, J. & Ma, A.G. 2020. Fish Consumption and Coronary Heart Disease: A Meta-Analysis. *Nutrients*, 12(8), 2278	Excluded, as the review has already been assessed in VKM 2022
Zhang, Z. Chen, G.C. Qin, Z.Z. Tong, X. Li, D.P. & Qin, L.Q. 2018. Poultry and Fish Consumption in Relation to Total Cancer Mortality: A Meta-Analysis of Prospective Studies. *Nutrition and Cancer-an International Journal*, 70(2), 204-212.	Excluded, as the review has already been assessed in VKM 2022
Zhao, L.G. Sun, J.W. Yang, Y. Ma, X. Wang, Y.Y. & Xiang, Y.B. 2016. Fish consumption and all-cause mortality: a meta-analysis of cohort studies. *European Journal of Clinical Nutrition*, 70(2):155-161.	Excluded, as the review has already been assessed in VKM 2022
Jiang, L. Wang, J.Y. Xiong, K. Xu, L. Zhang, B. & Ma, A.G. 2021. Intake of Fish and Marine n-3 Polyunsaturated Fatty Acids and Risk of Cardiovascular Disease Mortality: A Meta-Analysis of Prospective Cohort Studies. *Nutrients*, 13(7):2342.	Excluded, as the review has already been assessed in VKM 2022
Jayedi, A. Shab-Bidar, S. Eimeri, S. & Djafarian, K. 2018. Fish consumption and risk of all-cause and cardiovascular mortality: a dose-response meta-analysis of prospective observational studies. *Public Health Nutrition*, 21(7):1297-1306.	Excluded, as the review has already been assessed in VKM 2022
Schwingshackl, L. Schwedhelm, C. Hoffmann, G. Lampousi, A.M. Knuppel, S. Iqbal, K. Bechthold, A. Schlesinger, S. & Boeing, H. 2017. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *American Journal of Clinical Nutrition*, 105(6):1462-1473.	Excluded, as the review has already been assessed in VKM 2022
Kwok, C.S. Gulati, M. Michos, E.D. Potts, J. Wu, P. Watson, L. Loke, Y.K. Mallen, C. & Mamas, M.A. 2019. Dietary components and risk of cardiovascular disease and all-cause mortality: a review of evidence from meta-analyses. *European Journal of Preventive Cardiology*, 26(13):1415-1429.	Excluded, as the review has already been assessed in VKM 2022
Li, N. Wu, X.T. Zhuang, W. Xia, L. Chen, Y. Wu, C.C. Rao, Z.Y. Du, L. Zhao, R. Yi, M.S. *et al.* 2020. Fish consumption and multiple health outcomes: Umbrella review. *Trends in Food Science & Technology*, 99:273-283.	Excluded, as the review has already been assessed in VKM 2022
Mozaffarian, D. & Rimm, E.B. 2006. Fish intake, contaminants, and human health - Evaluating the risks and the benefits. *Jama-Journal of the American Medical Association*, 296(15):1885-1899.	Excluded, as the review has already been assessed in VKM 2022
Wan, Y. Zheng, J.S. Wang, F.L. & Li, D. 2017. Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies. *Asia Pacific Journal of Clinical Nutrition*, 26(5):939-956.	Excluded, as the review has already been assessed in VKM 2022
Jayedi, A. & Shab-Bidar, S. 2020. Fish Consumption and the Risk of Chronic Disease: An Umbrella Review of Meta-Analyses of Prospective Cohort Studies. *Advances in Nutrition*, 11(5):1123-1133.	Excluded, as the review has already been assessed in VKM 2022
Wang, C.C. Harris, W.S. Chung, M. Lichtenstein, A.H. Balk, E.M. Kupelnick, B. Jordan, H.S. & Lau, J. 2006. N-3 fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *American Journal of Clinical Nutrition*, 84(1):5-17.	Excluded based on inclusion and exclusion criteria: fish oil
Seyedrezazadeh, E. Moghaddam, M.P. Ansarin, K. Asghari Jafarabadi, M. Sharifi, A. Sharma, S. & Kolahdooz, F. 2019. Dietary Factors and Risk of Chronic Obstructive Pulmonary Disease: a Systemic Review and Meta-Analysis. *Tanaffos*, 18(4):294-309.	Excluded based on inclusion and exclusion criteria: wrong outcome (COPD)
Mozaffarian, D. 2008. Fish and n-3 fatty acids for the prevention of fatal coronary heart disease and sudden cardiac death. *American Journal of Clinical Nutrition*, 87(6):1991S-1996S.	Excluded based on inclusion and exclusion criteria:
de Lorgeril, M. Salen, P. Defaye, P. Mabo, P. & Paillard, F. 2001. Dietary prevention of sudden cardiac death. *European Heart Journal*, 23(4):277-285.	Excluded based on inclusion and exclusion criteria:
Aucoin, M. Cooley, K. Knee, C. Fritz, H. Balneaves, L.G. Breau, R. Fergusson, D. Skidmore, B. Wong, R. & Seely, D. 2016. Fish-Derived Omega-3 Fatty Acids and Prostate Cancer: A Systematic Review. *Integrative Cancer Therapies*, 16(1):32-62.	Excluded based on inclusion and exclusion criteria: omega-3
Bucher, H.C. Hengstler, P. Schindler, C. & Meier, G. 2002. N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. *American Journal of Medicine*, 112(4):298-304.	Excluded based on inclusion and exclusion criteria: omega-3
Zheng, J.S. Huang, T. Yu, Y.H. Hu, X.J. Yang, B. & Li, D. 2011. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutrition*, 15(4):725-737.	Excluded based on inclusion and exclusion criteria: review article
Nutrition Reviews. 1985. Mortality from Coronary Heart Disease Is Inversely Related to Fish Consumption in the Netherlands, *Nutrition Reviews*, 43(9):271–273.	Excluded based on inclusion and exclusion criteria: review

TABLE A3.17 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "MORTALITY"**

Study (n = 85)	Reason for exclusion
Appleby, P.N., Key, T.J., Thorogood, M., Burr, M.L. & Mann, J. 2002. Mortality in British vegetarians. *Public Health Nutr*, 5(1): 29-36.	Excluded based on inclusion and exclusion criteria: specific population group
Bergdahl, I.A., Ahlqwist, M., Barregard, L., Bjorkelund, C., Blomstrand, A., Skerfving, S., Sundh, V., Wennberg, M. & Lissner, L. 2013. Mercury in serum predicts low risk of death and myocardial infarction in Gothenburg women. *International Archives of Occupational and Environmental Health*, 86(1): 71-77.	Excluded based on inclusion and exclusion criteria: main outcome is mortality related to mercury in serum, and fish consumption is only a covariate
Biesbroek, S., Bueno-de-Mesquita, H.B., Peeters, P.H.M., Verschuren, W.M.M., van der Schouw, Y.T., Kramer, G.F.H., Tyszler, M. & Temme, E.H.M. 2014. Reducing our environmental footprint and improving our health: greenhouse gas emission and land use of usual diet and mortality in EPIC-NL: a prospective cohort study. *Environmental Health*, 13.	Excluded based on inclusion and exclusion criteria: mortality is only directly associated with greenhouse gas emission, and not fish intake
Bonaccio, M., Ruggiero, E., Di Castelnuovo, A., Costanzo, S., Persichillo, M., De Curtis, A., Cerletti, C. *et al.* 2017. Fish intake is associated with lower cardiovascular risk in a Mediterranean population: Prospective results from the Moli-sani study. *Nutrition Metabolism and Cardiovascular Diseases*, 27(10): 865-873.	Excluded based on inclusion and exclusion criteria: main outcome of fish intake is associated with CHD and stroke, not mortality
Breslow, R.A., Graubard, B.I., Sinha, R. & Subar, A.F. 2000. Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. *Cancer Causes & Control*, 11(5): 419-431.	Excluded based on inclusion and exclusion criteria: study does not discriminate between meat/poultry/fish
de Goede, J., Verschuren, W.M.M., Boer, J.M.A., Kromhout, D. & Geleijnse, J.M. 2012. Gender-Specific Associations of Marine n-3 Fatty Acids and Fish Consumption with 10-Year Incidence of Stroke. *Plos One*, 7(4).	Excluded based on inclusion and exclusion criteria: main outcome is fish intake associated with non-fatal stroke
Donat-Vargas, C., Bellavia, A., Berglund, M., Glynn, A., Wolk, A. & Akesson, A. 2020. Cardiovascular and cancer mortality in relation to dietary polychlorinated biphenyls and marine polyunsaturated fatty acids: a nutritional-toxicological aspect of fish consumption. *Journal of Internal Medicine*, 287(2): 197-209.	Excluded based on inclusion and exclusion criteria: mortality is associated with dietary polychlorinated biphenyls and marine polyunsaturated fatty acids
Erkkila, A.T., Lehto, S., Pyorala, K. & Uusitupa, M.I.J. 2003. n-3 fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. *American Journal of Clinical Nutrition*, 78(1): 65-71.	Excluded based on inclusion and exclusion criteria: mortality is associated with n-3 fatty acids in serum lipids, not fish consumption
Fresan, U., Martinez-Gonzalez, M.A., Segovia-Siapco, G., Sabate, J. & Bes-Rastrollo, M. 2020. A three-dimensional dietary index (nutritional quality, environment and price) and reduced mortality: The "Seguimiento Universidad de Navarra" cohort. *Preventive Medicine*, 137.	Excluded based on inclusion and exclusion criteria: based on dietary pattern, the sustainable diet index
Holmberg, S., Thelin, A. & Stiernstrom, E.L. 2009. Food Choices and Coronary Heart Disease: A Population Based Cohort Study of Rural Swedish Men with 12 Years of Follow-up. *International Journal of Environmental Research and Public Health*, 6(10): 2626-2638.	Excluded based on inclusion and exclusion criteria: main outcome is risk of coronary heart disease, and it is not specified by mortality
Ikeda, M., Yoshimoto, K., Yoshimura, T., Kono, S., Kato, H. & Kuratsune, M. 1983. A cohort study on the possible association between broiled fish intake and cancer. *Gan*, 74(5): 640-8.	Excluded based on inclusion and exclusion criteria: study only investigate intake of broiled fish
Khankari, N.K., Bradshaw, P.T., Steck, S.E., He, K., Olshan, A.F., Shen, J., Ahn, J. *et al.* 2015. Dietary intake of fish, polyunsaturated fatty acids, and survival after breast cancer: A population-based follow-up study on Long Island, New York. *Cancer*, 121(13): 2244-52.	Excluded based on inclusion and exclusion criteria: breast cancer patients
Konig, A., Bouzan, C., Cohen, J.T., Connor, W.E., Kris-Etherton, P.M., Gray, G.M., Lawrence, R.S., Savitz, D.A. & Teutsch, S.M. 2005. A quantitative analysis of fish consumption and coronary heart disease mortality. *American Journal of Preventive Medicine*, 29(4): 335-346.	Excluded based on inclusion and exclusion criteria: narrative review
Krieger, J.P., Cabaset, S., Pestoni, G., Rohrmann, S., Faeh, D. & Swiss Natl Cohort Study, G. 2018. Dietary Patterns Are Associated with Cardiovascular and Cancer Mortality among Swiss Adults in a Census-Linked Cohort. *Nutrients*, 10(3).	Excluded based on inclusion and exclusion criteria: dietary patterns
Kromhout, D., Bloemberg, B.P.M., Feskens, E.J.M., Hertog, M.G.L., Menotti, A. & Blackburn, H. 1996. Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality. *International Journal of Epidemiology*, 25(4): 753-759.	Excluded based on inclusion and exclusion criteria: dietary intake represents the availability of foods per country and not the foods actually consumed
Kutner, N.G., Clow, P.W., Zhang, R. & Aviles, X. 2002. Association of fish intake and survival in a cohort of incident dialysis patients. *American Journal of Kidney Diseases*, 39(5): 1018-1024.	Excluded based on inclusion and exclusion criteria: specific patient group, survival in dialysis patients is investigated
Leo, Q.J.N., Ollberding, N.J., Wilkens, L.R., Kolonel, L.N., Henderson, B.E., Le Marchand, L. & Maskarinec, G. 2016. Nutritional factors and non-Hodgkin lymphoma survival in an ethnically diverse population: the Multiethnic Cohort. *European Journal of Clinical Nutrition*, 70(1): 41-46.	Excluded based on inclusion and exclusion criteria: non-Hodgkin's lymphoma (NHL) survival is investigated
Levitan, E.B., Wolk, A. & Mittleman, M.A. 2009. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: a population-based prospective study of middle-aged and elderly men. *European Heart Journal*, 30(12): 1495-1500.	Excluded based on inclusion and exclusion criteria: main outcome is heart failure, and it does not discriminate between death and not
Levitan, E.B., Wolk, A. & Mittleman, M.A. 2010. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. *European Journal of Clinical Nutrition*, 64(6): 587-594.	Excluded based on inclusion and exclusion criteria: main outcome is heart failure, and it does not discriminate between death and not
Menotti, A., Kromhout, D., Blackburn, H., Fidanza, F., Buzina, R., Nissinen, A. & Seven Countries Study Res, G. 1999. Food intake patterns and 25-year mortality from coronary heart disease: Cross-cultural correlations in the Seven Countries Study. *European Journal of Epidemiology*, 15(6): 507-515.	Excluded based on inclusion and exclusion criteria: dietary patterns
Morris, M.C. Manson, J.E. Rosner, B. Buring, J.E. Willett, W.C. & Hennekens, C.H. 1995. Fish consumption and cardiovascular disease in the Physician's Health Study – a prospective study. *American Journal of Epidemiology*, 142(2):166-175.	Excluded based on inclusion and exclusion criteria: cardiovascular disease and not mortality
Nettleton, J.A., Steffen, L.M., Loehr, L.R., Rosamond, W.D. & Folsom, A.R. 2008. Incident Heart Failure Is Associated with Lower Whole-Grain Intake and Greater High-Fat Dairy and Egg Intake in the Atherosclerosis Risk in Communities (ARIC) Study. *Journal of the American Dietetic Association*, 108(11): 1881-1887.	Excluded based on inclusion and exclusion criteria: outcome is heart failure and does not discriminate between fatal and non-fatal

TABLE A3.17 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "MORTALITY" (cont.)**

Ohira, T., Iso, H., Yamagishi, K. & Tamakoshi, A. 2011. Fish, vegetable, and fruit intakes and mortality from pulmonary embolism among japanese men and women: the jacc (japan collaborative cohort study for evaluation of cancer risk) study. *Journal of Epidemiology and Community Health*, 65: A284-A284.	Excluded based on inclusion and exclusion criteria
Ohira, T., Iso, H., Yamagishi, K., Tamakoshi, A. & Grp, J.S. 2018. Fish Intake and Death From Pulmonary Embolisms Among Japanese Men and Women - The Japan Collaborative Cohort (JACC) Study. *Circulation Journal*, 82(8): 2063-2070.	Excluded based on inclusion and exclusion criteria: abstract from congress
Outzen, M., Tjonneland, A., Christensen, J. & Olsen, A. 2018. Fish consumption and prostate cancer risk and mortality in a Danish cohort study. *European Journal of Cancer Prevention*, 27(4): 355-360.	Excluded based on inclusion and exclusion criteria: mortality in persons diagnosed with prostate cancer
Pan, A., Sun, Q., Bernstein, A.M., Schulze, M.B., Manson, J.E., Stampfer, M.J., Willett, W.C. & Hu, F.B. 2012. Red Meat Consumption and Mortality Results From 2 Prospective Cohort Studies. *Archives of Internal Medicine*, 172(7): 555-563.	Excluded based on inclusion and exclusion criteria: investigates red meat and the replacement of red meat with fish, not fish intake solely
Papier, K., Appleby, P.N., Fensom, G.K., Knuppel, A., Perez-Cornago, A., Schmidt, J.A., Tong, T.Y.N. & Key, T.J. 2019. Vegetarian diets and risk of hospitalisation or death with diabetes in British adults: results from the EPIC-Oxford study. *Nutrition & Diabetes*, 9.	Excluded based on inclusion and exclusion criteria: vegetarians
Petermann-Rocha, F., Parra-Soto, S., Gray, S., Anderson, J., Welsh, P., Gill, J., Sattar, N., Ho, F.K., Celis-Morales, C. & Pell, J.P. 2021. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. *European Heart Journal*, 42(12): 1136-1143.	Excluded based on inclusion and exclusion criteria: vegetarians
Playdon, M.C., Nagle, C.M., Ibiebele, T.I., Ferrucci, L.M., Protani, M.M., Carter, J., Hyde, S.E. *et al.* 2017. Pre-diagnosis diet and survival after a diagnosis of ovarian cancer. *British Journal of Cancer*, 116(12): 1627-1637.	Excluded based on inclusion and exclusion criteria: survival after ovarian cancer diagnosis
Poudel-Tandukar, K., Nanri, A., Iwasaki, M., Mizoue, T., Matsushita, Y., Takahashi, Y., Noda, M., Inoue, M., Tsugane, S. & Japan Public Hlth Ctr-Based, P. 2011. Long chain n-3 fatty acids intake, fish consumption and suicide in a cohort of Japanese men and women - The Japan Public Health Center-based (JPHC) Prospective Study. *Journal of Affective Disorders*, 129(1-3): 282-288.	Excluded based on inclusion and exclusion criteria: suicide as outcome
Rodriguez, B.L., Sharp, D.S., Abbott, R.D., Burchfiel, C.M., Masaki, K., Chyou, P.H., Huang, B., Yano, K. & Curb, J.D. 1996. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. *Circulation*, 94(5): 952-6.	Excluded based on inclusion and exclusion criteria
Sala-Vila, A., Guasch-Ferré, M., Hu, F.B., Sánchez-Tainta, A., Bulló, M., Serra-Mir, M., López-Sabater, C. *et al.* 2016. Dietary α-Linolenic Acid, Marine ω-3 Fatty Acids, and Mortality in a Population With High Fish Consumption: Findings From the PREvención con Dieta MEDiterránea (PREDIMED) Study. *J Am Heart Assoc*, 5(1).	Excluded based on inclusion and exclusion criteria: focus on LCn-3 PUFA
Sasakabe, T., Wakai, K., Ukawa, S., Ando, M., Kawamura, T., Okabayashi, S., Tsushita, K., Ohira, H. & Tamakoshi, A. 2021. Food group intakes and all-cause mortality among a young older Japanese population of the same age: the New Integrated Suburban Seniority Investigation Project. *Nagoya Journal of Medical Science*, 83(1): 169-182.	Excluded based on inclusion and exclusion criteria: fish intake in relation to smoking
Sotomayor, C.G., Gomes-Neto, A.W., Gans, R.O.B., de Borst, M.H., Berger, S.P., Rodrigo, R., Navis, G.J., Touw, D.J. & Bakker, S.J.L. 2018. Fish Intake, Circulating Mercury and Mortality in Renal Transplant Recipients. *Nutrients*, 10(10).	Excluded based on inclusion and exclusion criteria: evaluates the impact from circulating mercury on impact from fish intake on mortality in renal transplant recipients
Sun, Y.B., Liu, B.Y., Snetselaar, L.G., Robinson, J.G., Wallace, R.B., Peterson, L.L. & Bao, W. 2019. Association of fried food consumption with all cause, cardiovascular, and cancer mortality: prospective cohort study. *British Medical Journal*, 364.	Excluded based on inclusion and exclusion criteria: investigates the impact of fried food consumption
Tsai, A.C., Lucas, M., Okereke, O.I., O'Reilly, E.J., Mirzaei, F., Kawachi, I., Ascherio, A. & Willett, W.C. 2014. Suicide Mortality in Relation to Dietary Intake of n-3 and n-6 Polyunsaturated Fatty Acids and Fish: Equivocal Findings From 3 Large US Cohort Studies. *American Journal of Epidemiology*, 179(12): 1458-1466.	Excluded based on inclusion and exclusion criteria: suicide as outcome
Van Blarigan, E.L., Fuchs, C.S., Niedzwiecki, D., Ye, X., Zhang, S., Song, M., Saltz, L.B. *et al.* 2018. Marine ω-3 Polyunsaturated Fatty Acid and Fish Intake after Colon Cancer Diagnosis and Survival: CALGB 89803 (Alliance). *Cancer Epidemiol Biomarkers Prev*, 27(4): 438-445.	Excluded based on inclusion and exclusion criteria: colon cancer recurrence/survival
Wang, Y., Jacobs, E.J., Shah, R.A., Stevens, V.L., Gansler, T. & McCullough, M.L. 2020. Red and Processed Meat, Poultry, Fish, and Egg Intakes and Cause-Specific and All-Cause Mortality among Men with Nonmetastatic Prostate Cancer in a US Cohort. *Cancer Epidemiology Biomarkers & Prevention*, 29(5): 1029-1038.	Excluded based on inclusion and exclusion criteria: cancer survival
Whelton, S.P., He, J., Whelton, P.K. & Muntner, P. 2004. Meta-analysis of observational studies on fish intake and coronary heart disease. *American Journal of Cardiology*, 93(9): 1119-1123.	Excluded based on inclusion and exclusion criteria: no CVD patients
Zhong, V.W., Allen, N.B., Greenland, P., Carnethon, M.R., Ning, H.Y., Wilkins, J.T., Lloyd-Jones, D.M. & Van Horn, L. 2021. Protein foods from animal sources, incident cardiovascular disease and all-cause mortality: a substitution analysis. *International Journal of Epidemiology*, 50(1): 223-233.	Excluded based on inclusion and exclusion criteria: pooled analysis of six prospective cohort studies of 29 682 US participants
Albert, C.M., Hennekens, C.H., O'Donnell, C.J., Ajani, U.A., Carey, V.J., Willett, W.C., Ruskin, J.N. & Manson, J.E. 1998. Fish consumption and risk of sudden cardiac death. *JAMA*, 279(1): 23-28.	Excluded, as the review has already been assessed in VKM 2022.
Ascherio, A., Rimm, E.B., Stampfer, M.J., Giovannucci, E.L. & Willett, W.C. 1995. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med*, 332(15): 977-82.	Excluded, as the review has already been assessed in VKM 2022.
Bellavia *et al.* 2017. Fish consumption and all-cause mortality in a cohort of Swedish men and women.	Excluded, as the review has already been assessed in VKM 2022.
Chavarro, J.E., Stampfer, M.J., Hall, M.N., Sesso, H.D. & Ma, J. 2008. A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. *American Journal of Clinical Nutrition*, 88(5): 1297-1303	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews (Szymanski *et al.*, 2010)
Daviglus, M.L., Stamler, J., Orencia, A.J., Dyer, A.R., Liu, K., Greenland, P., Walsh, M.K., Morris, D. & Shekelle, R.B. 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med*, 336(15): 1046-53.	Excluded, as the review has already been assessed in VKM 2022.

TABLE A3.17 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "MORTALITY" (cont.)**

de Goede, J., Geleijnse, J.M., Boer, J.M.A., Kromhout, D. & Verschuren, W.M.M. 2010. Marine (n-3) Fatty Acids, Fish Consumption, and the 10-Year Risk of Fatal and Nonfatal Coronary Heart Disease in a Large Population of Dutch Adults with Low Fish Intake. *Journal of Nutrition*, 140(5): 1023-1028	Excluded, as the review has already been assessed in VKM 2022.
Deng, A., Pattanaik, S., Bhattacharya, A., Yin, J., Ross, L., Liu, C. & Zhang, J. 2018. Fish consumption is associated with a decreased risk of death among adults with diabetes: 18-year follow-up of a national cohort. *Nutrition Metabolism and Cardiovascular Diseases*, 28(10): 1012-1020	Excluded, as the review has already been assessed in VKM 2022.
Engeset, D., Braaten, T., Teucher, B., Kuhn, T., Bueno-de-Mesquita, H., Leenders, M., Agudo, A. *et al.* 2015. Fish consumption and mortality in the European Prospective Investigation into Cancer and Nutrition cohort. *European Journal of Epidemiology*, 30(1): 57-70.	Excluded, as the review has already been assessed in VKM 2022.
Farvid, M.S., Malekshah, A.F., Pourshams, A., Poustchi, H., Sepanlou, S.G., Sharafkhah, M., Khoshnia, M. *et al.* 2017. Dietary Protein Sources and All-Cause and Cause-Specific Mortality: The Golestan Cohort Study in Iran. *American Journal of Preventive Medicine*, 52(2): 237-248..	Excluded, as the review has already been assessed in VKM 2022.
Feskens, E.J., Bowles, C.H. & Kromhout, D. 1993. Association between fish intake and coronary heart disease mortality. Differences in normoglycemic and glucose intolerant elderly subjects. *Diabetes Care*, 16(7): 1029-34.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (Jayedi *et al.*, 2020)
Folsom, A.R. & Demissie, Z. 2004. Fish intake, marine omega-3 fatty acids, and mortality in a cohort of postmenopausal women. *American Journal of Epidemiology*, 160(10): 1005-1010.	Excluded, as the review has already been assessed in VKM 2022.
Gillum, R.F., Mussolino, M.E. & Madans, J.H. 1996. The relationship between fish consumption and stroke incidence – The NHANES I epidemiologic follow-up study. *Archives of Internal Medicine*, 156(5): 537-542.	Excluded, as the review has already been assessed in VKM 2022.
Hengeveld, L.M., Praagman, J., Beulens, J.W.J., Brouwer, I.A., van der Schouw, Y.T. & Sluijs, I. 2018. Fish consumption and risk of stroke, coronary heart disease, and cardiovascular mortality in a Dutch population with low fish intake. *European Journal of Clinical Nutrition*, 72(7): 942-950.	Excluded, as the review has already been assessed in VKM 2022.
Hu, F.B. & Willett, W.C. 2002. Optimal diets for prevention of coronary heart disease. *Jama-Journal of the American Medical Association*, 288(20): 2569-2578..	Excluded, as the review has already been assessed in VKM 2022.
Jarvinen, R., Knekt, P., Rissanen, H. & Reunanen, A. 2006. Intake of fish and long-chain n-3 fatty acids and the risk of coronary heart mortality in men and women. *British Journal of Nutrition*, 95(4): 824-829	Excluded, as the review has already been assessed in VKM 2022.
Jayedi, A., Soltani, S., Abdolshahi, A. & Shab-Bidar, S. 2021. Fish consumption and the risk of cardiovascular disease and mortality in patients with type 2 diabetes: a dose-response meta-analysis of prospective cohort studies. *Critical Reviews in Food Science and Nutrition*, 61(10): 1640-1650.	Excluded, as the review has already been assessed in VKM 2022.
Kinjo, Y., Beral, V., Akiba, S., Key, T., Mizuno, S., Appleby, P., Yamaguchi, N., Watanabe, S. & Doll, R. 1999. Possible protective effect of milk, meat and fish for cerebrovascular disease mortality in Japan. *J Epidemiol*, 9(4): 268-74	Excluded, as the review has already been assessed in VKM 2022.
Kondo, K., Miura, K., Tanaka-Mizuno, S., Kadota, A., Arima, H., Okuda, N., Fujiyoshi, A. *et al.* 2019. Cardiovascular Risk Assessment Chart by Dietary Factors in Japan – NIPPON DATA80. *Circ J*, 83(6): 1254-1260.	Excluded, as the review has already been assessed in VKM 2022.
Kromhout, D., Bosschieter, E.B. & de Lezenne Coulander, C. 1985. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med*, 312(19): 1205-9.	Excluded, as the review has already been assessed in VKM 2022.
Letois, F., Mura, T., Scali, J., Gutierrez, L.A., Feart, C. & Berr, C. 2016. Nutrition and mortality in the elderly over 10 years of follow-up: the Three-City study. *British Journal of Nutrition*, 116(5): 882-889	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (SchwingshackI *et al.*, 2017)
Manger, M.S., Strand, E., Ebbing, M., Seifert, R., Refsum, H., Nordrehaug, J.E., Nilsen, D.W. *et al.* 2010. Dietary intake of n-3 long-chain polyunsaturated fatty acids and coronary events in Norwegian patients with coronary artery disease. *Am J Clin Nutr*, 92(1): 244-51.	Excluded, as the review has already been assessed in VKM 2022.
Mohan, D., Mente, A., Dehghan, M., Rangarajan, S., O'Donnell, M., Hu, W.H., Dagenais, G. *et al.* 2021. Associations of Fish Consumption With Risk of Cardiovascular Disease and Mortality Among Individuals With or Without Vascular Disease From 58 Countries. *Jama Internal Medicine*, 181(5): 631-649.	Excluded, as the review has already been assessed in VKM 2022.
Mozaffarian, D., Lemaitre, R.N., Kuller, L.H., Burke, G.L., Tracy, R.P. & Siscovick, D.S. 2003. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation*, 107(10): 1372-7.	Excluded, as the review has already been assessed in VKM 2022.
Nagata, C., Takatsuka, N. & Shimizu, H. 2002. Soy and fish oil intake and mortality in a Japanese community. *American Journal of Epidemiology*, 156(9): 824-831.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (SchwingshackI *et al.*, 2017)
Nahab, F., Pearson, K., Frankel, M.R., Ard, J., Safford, M.M., Kleindorfer, D., Howard, V.J. & Judd, S. 2016. Dietary fried fish intake increases risk of CVD: the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Public Health Nutrition*, 19(18): 3327-3336.	Excluded, as the review has already been assessed in VKM 2022.
Nakamura, Y., Hozawa, A., Turin, T.C., Takashima, N., Okamura, T., Hayakawa, T., Kita, Y. *et al.* 2009. Dietary Habits in Middle Age and Future Changes in Activities of Daily Living – NIPPON DATA80. *Gerontology*, 55(6): 707-713	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (Nakamura *et al.*, 2005).
Ness, A.R., Maynard, M., Frankel, S., Smith, G.D., Frobisher, C., Leary, S.D., Emmett, P.M. & Gunnell, D. 2005. Diet in childhood and adult cardiovascular and all-cause mortality: the Boyd Orr cohort. *Heart*, 91(7): 894-898..	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (Wan *et al.*, 2017 and Zhao *et al.*, 2016)
Oomen *et al.* 2000. Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands.	Excluded, as the review has already been assessed in VKM 2022.
Orencia, A.J. Daviglus, M.L. Dyer, A.R. Shekelle, R.B. & Stamler, J. 1996. Fish consumption and stroke in men - 30-year findings of the Chicago Western Electric Study. *Stroke*, 27:204-209.	Excluded, as the review has already been assessed in VKM 2022.

TABLE A3.17 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "MORTALITY" (cont.)**

Osler, M., Andreasen, A.H. & Hoidrup, S. 2003. No inverse association between fish consumption and risk of death from all-causes, and incidence of coronary heart disease in middle-aged, Danish adults. *Journal of Clinical Epidemiology*, 56(3): 274-279.	Excluded, as the review has already been assessed in VKM 2022.
Otsuka, R., Tange, C., Nishita, Y., Tomida, M., Kato, Y., Imai, T., Ando, F. & Shimokata, H. 2019. Fish and Meat Intake, Serum Eicosapentaenoic Acid and Docosahexaenoic Acid Levels, and Mortality in Community-Dwelling Japanese Older Persons. *International Journal of Environmental Research and Public Health*, 16(10).	Excluded, as the review has already been assessed in VKM 2022.
Owen, A.J., Magliano, D.J., O'Dea, K., Barr, E.L.M. & Shaw, J.E. 2016. Polyunsaturated fatty acid intake and risk of cardiovascular mortality in a low fish-consuming population: a prospective cohort analysis. *European Journal of Nutrition*, 55(4): 1605-1613.	Excluded, as the review has already been assessed in VKM 2022.
Sauvaget, C., Nagano, J., Allen, N., Grant, E.J. & Beral, V. 2003. Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *International Journal of Epidemiology*, 32(4): 536-543.	Excluded, as the review has already been assessed in VKM 2022.
Shao, M.Y., Jiang, C.Q., Zhang, W.S., Zhu, F., Jin, Y.L., Woo, J., Cheng, K.K., Lam, T.H. & Xu, L. 2021. Association of fish consumption with risk of all-cause and cardiovascular disease mortality: an 11-year follow-up of the Guangzhou Biobank Cohort Study. *European Journal of Clinical Nutrition*	Excluded, as the review has already been assessed in VKM 2022.
Takata, Y., Zhang, X., Li, H., Gao, Y.T., Yang, G., Gao, J., Cai, H., Xiang, Y.B., Zheng, W. & Shu, X.O. 2013. Fish intake and risks of total and cause-specific mortality in 2 population-based cohort studies of 134,296 men and women. *Am J Epidemiol*, 178(1): 46-57.	Excluded, as the review has already been assessed in VKM 2022.
Tomasallo, C., Anderson, H., Haughwout, M., Imm, P. & Knobeloch, L. 2010. Mortality among frequent consumers of Great Lakes sport fish. *Environmental Research*, 110(1): 62-69.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (Wan *et al*., 2017)
van den Brandt, P.A. 2019. Red meat, processed meat, and other dietary protein sources and risk of overall and cause-specific mortality in The Netherlands Cohort Study. *European Journal of Epidemiology*, 34(4): 351-369	Excluded, as the review has already been assessed in VKM 2022.
Villegas, R., Takata, Y., Murff, H. & Blot, W.J. 2015. Fish, omega-3 long-chain fatty acids, and all-cause mortality in a low-income US population: Results from the Southern Community Cohort Study. *Nutrition Metabolism and Cardiovascular Diseases*, 25(7): 651-658.	Excluded, as the review has already been assessed in VKM 2022.
Virtanen, H.E.K., Voutilainen, S., Koskinen, T.T., Mursu, J., Kokko, P., Ylilauri, M.P.T., Tuomainen, T.P., Salonen, J.T. & Virtanen, J.K. 2019. Dietary proteins and protein sources and risk of death: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr*, 109(5): 1462-1471	Excluded, as the review has already been assessed in VKM 2022.
Wallin, A., Orsini, N., Forouhi, N.G. & Wolk, A. 2018. Fish consumption in relation to myocardial infarction, stroke and mortality among women and men with type 2 diabetes: A prospective cohort study. *Clinical Nutrition*, 37(2): 590-596	Excluded, as the review has already been assessed in VKM 2022.
Yamagishi, K., Iso, H., Date, C., Fukui, M., Wakai, K., Kikuchi, S., Inaba, Y., Tanabe, N., Tamakoshi, A. & Grp, J.S. 2008. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women – The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study. *Journal of the American College of Cardiology*, 52(12): 988-996.	Excluded, as the review has already been assessed in VKM 2022.
Yuan, J.M., Ross, R.K., Gao, Y.T. & Yu, M.C. 2001. Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol*, 154(9): 809-16	Excluded, as the review has already been assessed in VKM 2022.
Zhang, Y., Zhuang, P., He, W., Chen, J.N., Wang, W.Q., Freedman, N.D., Abnet, C.C., Wang, J.B. & Jiao, J.J. 2018. Association of fish and long-chain omega-3 fatty acids intakes with total and cause-specific mortality: prospective analysis of 421 309 individuals. *J Intern Med*, 284(4): 399-417.	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022 (Jayedi *et al*., 2020)
Zhong, V.T.W., Van Horn, L., Greenland, P., Carnethon, M.R., Ning, H.Y., Wilkins, J.T., Lloyd-Jones, D.M. & Allen, N.B. 2020. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. *Jama Internal Medicine*, 180(4): 503-512	Excluded, as the review has already been assessed in VKM 2022.
Zhuang, P., Wang, W.Q., Wang, J., Zhang, Y. & Jiao, J.J. 2018. Current Level of Fish Consumption is Associated with Mortality in Chinese but not US Adults: New Findings From Two Nationwide Cohort Studies With 14 and 9.8 Years of Follow-Up. *Molecular Nutrition & Food Research*, 62(8)	Excluded, as the review has already been assessed in VKM 2022.

OVERWEIGHT AND OBESITY

TABLE A3.18 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "OBESITY AND OVERWEIGHT" DURING FULL-TEXT SCREENING BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 2)	Reason for exclusion
Liberali, R. Kupek, E. *&* Assis, M.A.A.D. 2020. Dietary patterns and childhood obesity risk: a systematic review. *Childhood Obesity*, 16(2):70-85.	Excluded based on inclusion and exclusion criteria: excluded since study focuses on childhood obesity and not general population. In addition, effects of seafood were not emphasized or specifically mentioned.
Schlesinger, S. Neuenschwander, M. Schwedhelm, C. Hoffmann, G. Bechthold, A. Boeing, H. *&* Schwingshackl, L. 2019. Food groups and risk of overweight, obesity, and weight gain: a systematic review and dose-response meta-analysis of prospective studies. *Advances in Nutrition*, 10(2):205-218.	Excluded, as the review has already been assessed in VKM 2022.
Bender, N. Portmann, M. Heg, Z. Hofmann, K. Zwahlen, M. *&* Egger, M. 2014. Fish or n3-PUFA intake and body composition: a systematic review and meta-analysis. *Obesity reviews*, 15(8):657-665.	Excluded, as the review has already been assessed in VKM 2022.

TABLE A3.19 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "OBESITY AND OVERWEIGHT"

Study (*n* = 28)	Reason for exclusion
Abete, I., Parra, D., Crujeiras, A.B., Goyenechea, E. *&* Martinez, J.A. 2008. Specific insulin sensitivity and leptin responses to a nutritional treatment of obesity via a combination of energy restriction and fatty fish intake. *J Hum Nutr Diet*, 21(6): 591-600	Excluded based on inclusion and exclusion criteria
Alkerwi, A., Sauvageot, N., Buckley, J.D., Donneau, A.F., Albert, A., Guillaume, M. *&* Crichton, G.E. 2015. The potential impact of animal protein intake on global and abdominal obesity: evidence from the Observation of Cardiovascular Risk Factors in Luxembourg (ORISCAV-LUX) study. *Public Health Nutrition*, 18(10): 1831-1838.	Excluded based on inclusion and exclusion criteria: cross-sectional study
Celis-Morales, C., Livingstone, K.M., Affleck, A., Navas-Carretero, S., San-Cristobal, R., Martinez, J.A., Marsaux, C.F.M. *et al.* 2018. Correlates of overall and central obesity in adults from seven European countries: findings from the Food4Me Study. *Eur J Clin Nutr*, 72(2): 207-219	Excluded based on inclusion and exclusion criteria: cross-sectional data
Fisk, H.L., Irvine, M., Miles, E.A., Lietz, G., Mathers, J.C., Packard, C.J., Armah, C.K. *et al.* 2018. Association of oily fish intake, sex, age, BMI and APOE genotype with plasma long-chain n-3 fatty acid composition. *Br J Nutr*, 120(1): 23-32.	Excluded based on inclusion and exclusion criteria: APOE genotype
Gunnarsdottir, I., Tomasson, H., Kiely, M., Martinez, J.A., Bandarra, N.M., Morais, M.G. *&* Thorsdottir, I. 2008. Inclusion of fish or fish oil in weight-loss diets for young adults: effects on blood lipids. *International Journal of Obesity*, 32(7): 1105-1112	Excluded based on inclusion and exclusion criteria: only biomarker
Ilesanmi-Oyelere, B.L., Coad, J., Roy, N.C. *&* Kruger, M.C. 2020. Dietary Patterns, Body Composition, and Bone Health in New Zealand Postmenopausal Women. *Frontiers in Nutrition*, 7	Excluded based on inclusion and exclusion criteria: dietary patterns
Inelmen, E.M., Toffanello, E.D., Enzi, G., Sergi, G., Coin, A., Busetto, L. *&* Manzato, E. 2008. Differences in dietary patterns between older and younger obese and overweight outpatients. *J Nutr Health Aging*, 12(1): 3-8	Excluded based on inclusion and exclusion criteria: focuses only on frequency of food pattern
Mori, T.A., Bao, D.Q., Burke, V., Puddey, I.B., Watts, G.F. *&* Beilin, L.J. 1999. Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *American Journal of Clinical Nutrition*, 70(5): 817-825	Excluded based on inclusion and exclusion criteria: only biomarker
Mori, T.A., Burke, V., Puddey, I.B., Shaw, J.E. *&* Beilin, L.J. 2004. Effect of fish diets and weight loss on serum leptin concentration in overweight, treated-hypertensive subjects. *J Hypertens*, 22(10): 1983-90.	Excluded based on inclusion and exclusion criteria: only biomarker
Panagiotakos, D.B., Zeimbekis, A., Boutziouka, V., Economou, M., Kourlaba, G., Toutouzas, P. *&* Polychronopoulos, E. 2007. Long-term fish intake is associated with better lipid profile, arterial blood pressure, and blood glucose levels in elderly people from Mediterranean islands (MEDIS epidemiological study). *Medical Science Monitor*, 13(7):CR307-CR312.	Excluded based on inclusion and exclusion criteria: only includes the effect of fish consumption on several biomarkers of cardiovascular-disease risk
Parra, D., Bandarra, N.M., Kiely, M., Thorsdottir, I. *&* Martinez, J.A. 2007. Impact of fish intake on oxidative stress when included into a moderate energy-restricted program to treat obesity. *European Journal of Nutrition*, 46(8): 460-467	Excluded based on inclusion and exclusion criteria
Ramel, A., Martinez, J.A., Kiely, M., Bandarra, N.M. *&* Thorsdottir, I. 2010. Effects of weight loss and seafood consumption on inflammation parameters in young, overweight and obese European men and women during 8 weeks of energy restriction. *European Journal of Clinical Nutrition*, 64(9): 987-993	Excluded based on inclusion and exclusion criteria
Ramel, A., Martinez, J.A., Kiely, M., Bandarra, N.M. *&* Thorsdottir, I. 2010. Moderate consumption of fatty fish reduces diastolic blood pressure in overweight and obese European young adults during energy restriction. *Nutrition*, 26(2): 168-174.	Excluded based on inclusion and exclusion criteria
Ramel, A. Jonsdottir, M.T. *&* Thorsdottir, I. 2009. Consumption of cod and weight loss in young overweight and obese adults on an energy reduced diet for 8-weeks. *Nutr Metab Cardiovasc Dis*, 19(10):690-6.	Excluded based on inclusion and exclusion criteria
Satija, A., Hu, F.B., Bowen, L., Bharathi, A.V., Vaz, M., Prabhakaran, D., Reddy, K.S. *et al.* 2015. Dietary patterns in India and their association with obesity and central obesity. *Public Health Nutrition*, 18(16): 3031-3041..	Excluded based on inclusion and exclusion criteria: dietary patterns linked to obesity
Schulze, M.B., Fung, T.T., Manson, J.E., Willett, W.C. *&* Hu, F.B. 2006. Dietary patterns and changes in body weight in women. *Obesity (Silver Spring)*, 14(8): 1444-53.	Excluded based on inclusion and exclusion criteria: dietary patterns and changes in body weight
Spencer, E.A., Appleby, P.N., Davey, G.K. *&* Key, T.J. 2003. Diet and body mass index in 38,000 EPIC-Oxford meat-eaters, fish-eaters, vegetarians and vegans. *International Journal of Obesity*, 27(6): 728-734	Excluded based on inclusion and exclusion criteria: cross-sectional analysis

TABLE A3.19 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "OBESITY AND OVERWEIGHT" (cont.)**

St-Jules, D.E. Watters, C.A. *&* Novotny, R. 2014. Estimation of fish intake in Asian and white female adolescents, and association with 2-year changes in body fatness and body fat distribution: the female adolescent maturation study. *J Acad Nutr Diet*, 114(4):543-51.	Excluded based on inclusion and exclusion criteria: cross-sectional analysis
Vázquez, C., Botella-Carretero, J.I., Corella, D., Fiol, M., Lage, M., Lurbe, E., Richart, C. *et al.* 2014. White fish reduces cardiovascular risk factors in patients with metabolic syndrome: the WISH-CARE study, a multicenter randomized clinical trial. *Nutr Metab Cardiovasc Dis*, 24(3): 328-35.	Excluded based on inclusion and exclusion criteria: only biomarker
Xu, X.Y., Shi, Z.M., Liu, G., Chang, D.N., Inglis, S.C., Hall, J.J., Schutte, A.E., Byles, J.E. *&* Parker, D. 2021. The Joint Effects of Diet and Dietary Supplements in Relation to Obesity and Cardiovascular Disease over a 10-Year Follow-Up: A Longitudinal Study of 69,990 Participants in Australia. *Nutrients*, 13(3)	Excluded based on inclusion and exclusion criteria: fish oil
Abete, I., Parra, D. *&* Martinez, J.A. 2009. Legume-, fish-, or high-protein-based hypocaloric diets: effects on weight loss and mitochondrial oxidation in obese men. *J Med Food*, 12(1): 100-8	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews
Huang, T., Wang, T.G., Heianza, Y., Wiggs, J., Sun, D.J.Y., Choi, H.K., Chai, J.F. *et al.* 2019. Fish and marine fatty acids intakes, the FADS genotypes and long-term weight gain: a prospective cohort study. *BMJ Open*, 9(7).	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Huang, T., Wang, T.G., Heianza, Y., Zheng, Y., Sun, D.J.Y., Kang, J.H., Pasquale, L.R. *et al.* 2019. Habitual consumption of long-chain n-3 PUFAs and fish attenuates genetically associated long-term weight gain. *American Journal of Clinical Nutrition*, 109(3): 665-673	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Jakobsen, M.U., Due, K.M., Dethlefsen, C., Halkjaer, J., Holst, C., Forouhi, N.G., Tjønneland, A. *et al.* 2012. Fish consumption does not prevent increase in waist circumference in European women and men. *Br J Nutr*, 108(5): 924-31..	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Jakobsen, M.U., Dethlefsen, C., Due, K.M., May, A.M., Romaguera, D., Vergnaud, A.C., Norat, T. *et al.* 2013. Fish consumption and subsequent change in body weight in European women and men. *British Journal of Nutrition*, 109(2): 353-362..	Excluded for further assessment, as the primary study had already been assessed in a systematic review that is included in VKM 2022
Ramel, A., Parra, D., Martinéz, J.A., Kiely, M. *&* Thorsdottir, I. 2009. Effects of seafood consumption and weight loss on fasting leptin and ghrelin concentrations in overweight and obese European young adults. *Eur J Nutr*, 48(2): 107-14	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Tapsell, L.C., Batterham, M.J., Charlton, K.E., Neale, E.P., Probst, Y.C., O'Shea, J.E., Thorne, R.L., Zhang, Q.S. *&* Louie, J.C.Y. 2013. Foods, nutrients or whole diets: effects of targeting fish and LCn3PUFA consumption in a 12mo weight loss trial. *Bmc Public Health*, 13	Excluded for further assessment, as the primary study had already been assessed in VKM 2022
Thorsdottir, I., Tomasson, H., Gunnarsdottir, I., Gisladottir, E., Kiely, M., Parra, M.D., Bandarra, N.M., Schaafsma, G. *&* Martinez, J.A. 2007. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *International Journal of Obesity*, 31(10): 1560-1566	Excluded for further assessment, as the primary study had already been assessed in one of the included systematic reviews

QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES

ALLERGY AND IMMUNOLOGY

TABLE A3.20 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8)

Di Giuseppe, D., Crippa, A. & Orsini, N. 2014. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Research & Therapy*, 16(5):446				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	yes	0.00
Q2	Protocol	yes/partial yes/no	yes	0.50
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	yes	1.00
Q5	Paired study selection	yes/no	yes	0.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	no	0.50
Q8	Description of included studies	yes/partial yes/no	partial yes	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	partial yes	1.00
Q10	Sources of funding for included studies	yes/no	yes	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	yes	0.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				**11.00**
Percent				**68.75**
Overall AMSTAR 2 judgement (confidence in the results)				**Moderate**
Include/exclude				**Include**

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Ierodiakonou, D., Garcia-Larsen, V., Logan, A., Groome, A., Cunha, S., Chivinge, J., Boyle, R. J. *et al.* 2016. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. *Jama*, 316(11):1181-1192.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, they included PICO	1.00
Q2	Protocol	yes/partial yes/no	Yes, their protocol was registered in PROSPERO	1.00
Q3	Explanation of included study design	yes/no	Yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes they searched the Cochrane Library, EMBASE, LILACS, MEDLINE, Web of Science, and http://apps.who.int/trialsearch from 1 January 1946 to 8 March 2016	1.00
Q5	Paired study selection	yes/no	No, it is not mentioned	0.00
Q6	Paired data extraction	yes/no	Yes, data were extracted in duplicate	1.00
Q7	List of excluded studies	yes/partial yes/no	No list was provided	0.00
Q8	Description of included studies	yes/partial yes/no	Yes, they explained the included articles in detail	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes, they used Cochrane Risk of Bias tool and the National Institute for Clinical Excellence methodological checklists for intervention and observational studies	1.00
Q10	Sources of funding for included studies	yes/no	No, they did not mention it	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes, random effects meta-analyses used generic inverse variance and Mantel-Haenszel methods for observational and intervention studies, respectively	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Yes, the considered RoB in individual studies	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes, the considered RoB in single studies	1.00
Q14	Heterogeneity assessed	yes/no	Yes, they explained the reasons for heterogeneity	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Yes, publication bias was assessed using funnel plots and the Egger test	1.00
Q16	Conflict of interest included	yes/no	Yes, all authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest	1.00
Total score				**13**
Percent				**81%**
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				**Moderate**
Include/exclude				**Include**

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Li, N., Wu, X., Zhuang, W., Xia, L., Chen, Y., Wu, C., Zhou, Y. *et al.* 2020. Fish consumption and multiple health outcomes: Umbrella review. *Trends in Food Science & Technology*, 99:273-283.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, they included PICO in their study.	1.00
Q2	Protocol	yes/partial yes/no	Partially yes, protocol was not established before study, but they had a methodology.	0.50
Q3	Explanation of included study design	yes/no	Yes, they performed eligibility criteria (2.3)	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes, they searched Embase, Medline, the Cochrane Database of Systematic Reviews and Web of Science.	1.00
Q5	Paired study selection	yes/no	No, not specified	0.00
Q6	Paired data extraction	yes/no	Yes, two independent investigators (NL and XW) extracted the following data separately for eligible articles	1.00
Q7	List of excluded studies	yes/partial yes/no	They did not provide the list of excluded articles.	0.00
Q8	Description of included studies	yes/partial yes/no	Yes, included studies with relevant reasoning are presented in tables.	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes, they used AMSTAR.	1.00
Q10	Sources of funding for included studies	yes/no	No, they did not.	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	N/A, no meta-analysis conducted	0.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	N/A, no meta-analysis conducted	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	They did not discuss RoB.	0.00
Q14	Heterogeneity assessed	yes/no	No, they did not provide. explanation for heterogeneity.	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	N/A, no meta-analysis conducted	0.00
Q16	Conflict of interest included	yes/no	Yes, the authors declare no competing interests.	1.00
Total score				**7.50**
Percent				**47%**
Percent (exclude n/a question)				**58%**
Overall AMSTAR 2 judgement (confidence in the results)				**Low**
Include/exclude				**Exclude**

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Venter, C., Agostoni, C., Arshad, S.H., Ben-Abdallah, M., Du Toit, G., Fleischer, D.M., O'Mahony, L. *et al.* 2020. Dietary factors during pregnancy and atopic outcomes in childhood: A systematic review from the European Academy of Allergy and Clinical Immunology. *Pediatric Allergy and Immunology*, 31(8):889-912.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, authors used PICO approach in their search and inclusion criteria.	1.00
Q2	Protocol	yes/partial yes/no	Partially yes, protocol was not established before study, but they had a methodology.	0.50
Q3	Explanation of included study design	yes/no	Yes, they used a flow chart.	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes, they searched three bibliographic databases (MEDLINE, EMBASE, and Web of Science).	1.00
Q5	Paired study selection	yes/no	Yes, for studies considered potentially relevant, full-text copies were obtained, and inclusion of the studies was discussed by CV, MBA, MP, and AM.	1.00
Q6	Paired data extraction	yes/no	Yes, data were extracted by three authors (AM, MBA, and MP).	1.00
Q7	List of excluded studies	yes/partial yes/no	Yes, reasons are mentioned.	1.00
Q8	Description of included studies	yes/partial yes/no	Yes, they described populations, interventions, comparators, outcomes and research designs.	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes, they used Cochrane Collaboration Risk of Bias tool for intervention trials and the National Institute for Clinical Excellence methodological checklist for cohort and case-control studies.	1.00
Q10	Sources of funding for included studies	yes/no	Yes, conflicts of interest were noted if industry was involved in any aspect of the study or if authors received funding.	1.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes, relevant statistics were used.	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Yes, risk of bias for cohort and case-control studies included assessment of: (a) selection bias, which was considered low if cases and controls were recruited from similar populations and had a similar attrition rate <20%; (b) assessment bias, which included blinding of outcome assessors and use of validated assessment tools; and (c) confounding bias (did study design and analysis account for relevant confounders?	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No.	0.00
Q14	Heterogeneity assessed	yes/no	Yes, the heterogeneity of the studies was calculated using the Cochran β2 and I2 statistics.	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Yes, in order to minimize publication bias, they performed a comprehensive search of the literature and included experts in the field to ensure that no relevant study was missed. They performed the Egger's test.	1.00
Q16	Conflict of interest included	yes/no	Yes, they declared no conflict of interest.	1.00
Total score				14.50
Percent				90.63
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Netting, M. J., Middleton, P. F. & Makrides, M. 2014. Does maternal diet during pregnancy and lactation affect outcomes in offspring? A systematic review of food-based approaches. *Nutrition*, 30(11-12):1225-1241.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, they included ICO but they did not explain the population considered in this study.	1.00
Q2	Protocol	yes/partial yes/no	Partially yes. Protocol was not established before study, but they had a methodology.	0.50
Q3	Explanation of included study design	yes/no	Yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partially yes, searched MEDLINE, EMBASE, and the Cochrane Library (last searched end of August 2011), more than 24 months until publication finished at 2014.	0.50
Q5	Paired study selection	yes/no	Yes, two authors independently assessed search results against study eligibility criteria.	1.00
Q6	Paired data extraction	yes/no	Yes, two authors also independently conducted data extraction for each included study.	1.00
Q7	List of excluded studies	yes/partial yes/no	Yes, one intervention trial and seven other studies were excluded [18–25].	1.00
Q8	Description of included studies	yes/partial yes/no	Yes, this systematic review included 42 studies (Table 1).	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes, they assessed the risk for bias using the methods outlined in the Cochrane Handbook for Reviews of Interventions.	1.00
Q10	Sources of funding for included studies	yes/no	No, they did not.	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes, where possible, the results of randomized controlled trials (RCTs) were pooled, using the meta-analysis program RevMan.	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Yes, the risk for bias assessments are described in Table 1 (association studies [26–76]) and in Table 2 (intervention studies. [26,29,32,34,36,39, 41,42,44,45,78]).	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes, they did consider risk of bias in interpretation.	1.00
Q14	Heterogeneity assessed	yes/no	Yes, they performed heterogeneity test but with no explanation on reasons.	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No, they did not mention that.	0.00
Q16	Conflict of interest included	yes/no	Yes, they explained the funding source in the acknowledgments.	1.00
Total score				13.00
Percent				81.25
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Kremmyda, L.S., Vlachava, M., Noakes, P.S., Diaper, N.D., Miles, E.A. & Calder, P.C. 2011. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. *Clinical reviews in allergy & immunology*, 41(1):36-66.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, they investigated PICO.	1.00
Q2	Protocol	yes/partial yes/no	No methodology	0.00
Q3	Explanation of included study design	yes/no	No explanation	0.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes, the studies were identified through Ovid Medline (1950– 2009) and PubMed (1950–2009) databases.	1.00
Q5	Paired study selection	yes/no	No, not mentioned.	0.00
Q6	Paired data extraction	yes/no	No, not mentioned.	0.00
Q7	List of excluded studies	yes/partial yes/no	No, not mentioned.	0.00
Q8	Description of included studies	yes/partial yes/no	Partial yes. They described them in tables but no follow up.	0.50
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	No RoB was performed.	0.00
Q10	Sources of funding for included studies	yes/no	No, they did not mention.	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	N/A, no meta analyses.	0.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	N/A, no meta analyses.	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No RoB was performed.	0.00
Q14	Heterogeneity assessed	yes/no	N/A, no meta analyses.	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No, not mentioned.	0.00
Q16	Conflict of interest included	yes/no	No declaration of conflict of interest.	0.00
Total score				2.50
Percent				15.63
Percent (exclude N/A question)				19.23
Overall AMSTAR 2 judgement (confidence in the results)				Critically low
Include/exclude				Excluded (narrative)

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Pattison, D.J., Harrison, R.A. & Symmons, D.P. 2004. The role of diet in susceptibility to rheumatoid arthritis: a systematic review. *The Journal of rheumatology*, 31(7):1310-1319.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, they included PICO in their criteria.	1.00
Q2	Protocol	yes/partial yes/no	Yes, the criteria were based on methodological issues relevant to nutritional epidemiology, expert knowledge, and published guidelines.	1.00
Q3	Explanation of included study design	yes/no	Yes, they used following criteria (1) an a priori hypothesis was given; (2) cases were ascertained using the ARA 19588 or 19879 criteria for diagnosis of RA; (3) cases and controls were comparable at baseline; (4) controls were randomly selected from the source of the population of the cases; (5) dietary assessment was undertaken prior to onset of symptoms, using a "validated" method of assessment and the same method was used for cases and controls; and (6) potential confounding factors were accounted for.	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes, they searched the Cochrane Database of Systematic Reviews, Medline OVID citations (1966 to 2003), Embase (1980 to 2003), and the ISI Web of Science (1981 to 2003).	1.00
Q5	Paired study selection	yes/no	Yes, two authors selected the articles.	1.00
Q6	Paired data extraction	yes/no	Yes, two authors extracted the data.	1.00
Q7	List of excluded studies	yes/partial yes/no	Yes, they listed excluded articles with justification.	1.00
Q8	Description of included studies	yes/partial yes/no	Yes, they described the included articles and explained them in details (see Table 1 and Table 2).	1.00
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes, explained in quality assessment and data extraction.	1.00
Q10	Sources of funding for included studies	yes/no	No, funding source was not investigated.	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted.	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted.	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	They did not perform RoB.	0.00
Q14	Heterogeneity assessed	yes/no	Yes, they explained the heterogeneity.	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted	N/A
Q16	Conflict of interest included	yes/no	They did not declare conflict of interest nor the funding source.	0.00
Total score				10.00
Percent				62.50
Percent (exclude n/a question)				76.9
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.20 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "ALLERGY AND IMMUNOLOGY" (*N* = 8) (cont.)**

Solman, L., Lloyd-Lavery, A., Grindlay, D.J.C., Rogers, N.K., Thomas, K.S. & Harman, K.E. 2019. What's new in atopic eczema? An analysis of systematic reviews published in 2016. Part 1: treatment and prevention. *Clinical and experimental dermatology*, 44(4):363-369.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	No clear inclusion criteria	0.00
Q2	Protocol	yes/partial yes/no	No protocol was used for review.	0.00
Q3	Explanation of included study design	yes/no	No clear inclusion criteria	0.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Not mentioned	0.00
Q5	Paired study selection	yes/no	Not mentioned	0.00
Q6	Paired data extraction	yes/no	Not mentioned	0.00
Q7	List of excluded studies	yes/partial yes/no	Not mentioned	0.00
Q8	Description of included studies	yes/partial yes/no	Yes, they explain the included studies.	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	No RoB was performed.	0.00
Q10	Sources of funding for included studies	yes/no	Yes, they investigated source of funding.	1.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted	0.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No RoB was performed.	0.00
Q14	Heterogeneity assessed	yes/no	N/A – no meta-analysis conducted	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	N/A – no meta-analysis conducted	0.00
Q16	Conflict of interest included	yes/no	Yes, they did declare conflict of interest and the funding source.	1.00
Total score				3.00
Percent				18.75
Percent (exclude N/A question)				23.08
Overall AMSTAR 2 judgement (confidence in the results)				Critically low
Include/exclude				Exclude

TABLE A3.21 **QUALITY ASSESSMENT (RISK OF BIAS) PF PRIMARY STUDIES FOR THE THEME "ALLERGY AND IMMUNOLOGY" (N = 22)**

Reference primary study (n = 22)	Quality assessment (risk of bias judgement)	Score
Acevedo, N., Frumento, P., Harb, H., Alhamwe, B.A., Johansson, C., Eick, L., Alm, J., Renz, H., Scheynius, A. & Potaczek, D.P. 2019. Histone Acetylation of Immune Regulatory Genes in Human Placenta in Association with Maternal Intake of Olive Oil and Fish Consumption. *International Journal of Molecular Sciences*, 20(5).	C	No details on fish intake. Maternal fish consumption was not clearly described in the analysis. Yes/no question if mother consumed fish during pregnancy.
Dunlop, A.L., Reichrtova, E., Palcovicova, L., Ciznar, P., Adamcakova-Dodd, A., Smith, S.J. & McNabb, S.J. 2006. Environmental and dietary risk factors for infantile atopic eczema among a Slovak birth cohort. *Pediatr Allergy Immunol*, 17(2): 103-11.	C	No clear research question was formulated; dietary pattern study; no details on fish intake
Goksor, E., Alm, B., Pettersson, R., Mollborg, P., Erdes, L., Aberg, N. & Wennergren, G. 2013. Early fish introduction and neonatal antibiotics affect the risk of asthma into school age. *Pediatric Allergy and Immunology*, 24(4): 339-344.	C	Unclear dietary information
Goksor, E., Alm, B., Thengilsdottir, H., Pettersson, R., Aberg, N. & Wennergren, G. 2011. Preschool wheeze – impact of early fish introduction and neonatal antibiotics. *Acta Paediatrica*, 100(12): 1561-1566.	C	Unclear dietary information, specific groups and use of antibiotics
González-Delgado, P., Caparrós, E., Moreno, M.V., Clemente, F., Flores, E., Velásquez, L., Rubio, G. & Fernández, J. 2016. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. *Pediatr Allergy Immunol*, 27(3): 269-75.	C	In vitro study. In vitro measurement of both cytokine production in peripheral blood mononuclear cells (PBMCs) and expression of HLADR in monocyte-derived dendritic cells stimulated with fish extracts.
Grieger, J.A., Pelecanos, A.M., Hurst, C., Tai, A. & Clifton, V.L. 2019. Pre-Conception Maternal Food Intake and the Association with Childhood Allergies. *Nutrients*, 11(8).	C	Missing to control for confounding factors
Hesselmar, B., Saalman, R., Rudin, A., Adlerberth, I. & Wold, A. 2010. Early fish introduction is associated with less eczema, but not sensitization, in infants. *Acta Paediatr*, 99(12): 1861-7.	C	Fish intake not reported
Papamichael, M.M., Katsardis, C., Lambert, K., Tsoukalas, D., Koutsilieris, M., Erbas, B. & Itsiopoulos, C. 2019. Efficacy of a Mediterranean diet supplemented with fatty fish in ameliorating inflammation in paediatric asthma: a randomised controlled trial. *Journal of Human Nutrition and Dietetics*, 32(2): 185-197	C	The study group has asthma
Papamichael, M.M., Itsiopoulos, C., Lambert, K., Katsardis, C., Tsoukalas, D. & Erbas, B. 2020. Sufficient vitamin D status positively modified ventilatory function in asthmatic children following a Mediterranean diet enriched with fatty fish intervention study. *Nutr Res*, 82: 99-109.	C	Investigation of the vitamin D status on lung function using participants in a RCT with fatty fish in asthma children.
Roberts, G., Golder, N. & Lack, G. 2002. Bronchial challenges with aerosolized food in asthmatic, food-allergic children. *Allergy*, 57(8): 713-7.	C	Patient group.
Storrø, O., Oien, T., Dotterud, C.K., Jenssen, J.A. & Johnsen, R. 2010. A primary health-care intervention on pre- and postnatal risk factor behavior to prevent childhood allergy. The Prevention of Allergy among Children in Trondheim (PACT) study. *BMC Public Health*, 10: 443.	C	Mix of study designs; prevention study; the study aimed to evaluate the impact of a primary prevention intervention program on risk behaviour for allergic diseases among children in a pre- and postnatal primary healthcare setting.
Uddenfeldt, M., Janson, C., Lampa, E., Leander, M., Norback, D., Larsson, L. & Rask-Andersen, A. 2010. High BMI is related to higher incidence of asthma, while a fish and fruit diet is related to a lower-Results from a long-term follow-up study of three age groups in Sweden. *Respiratory Medicine*, 104(7): 972-980.	C	Information about the fish was unclear. The aim was to investigate risk factors for asthma development in three different age groups (n = 8 150).
Ukleja-Sokolowska, N., Zbikowska-Gotz, M., Lis, K., Adamczak, R. & Bartuzi, Z. 2021. Assessment of TSLP, IL 25 and IL 33 in patients with shrimp allergy. *Allergy Asthma and Clinical Immunology*, 17(1).	C	Use of patient allergic to shrimps to assess allergic intermediate factors in blood
Urwin, H.J., Miles, E.A., Noakes, P.S., Kremmyda, L.S., Vlachava, M., Diaper, N.D., Godfrey, K.M., Calder, P.C., Vulevic, J. & Yaqoob, P. 2014. Effect of salmon consumption during pregnancy on maternal and infant faecal microbiota, secretory IgA and calprotectin. *Br J Nutr*, 111(5): 773-84.	C	Wrong outcome: faecal microbiota, IgA and calprotectin
Varraso, R., Fung, T.T., Barr, R.G., Hu, F.B., Willett, W. & Camargo, C.A. 2007. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US women. *American Journal of Clinical Nutrition*, 86(2): 488-495.	C	Dietary patterns studied in patient with chronic obstructive pulmonary disease

TABLE A3.21 **QUALITY ASSESSMENT (RISK OF BIAS) PF PRIMARY STUDIES FOR THE THEME "ALLERGY AND IMMUNOLOGY" (N = 22) (cont.)**

Reference primary study (n = 22)	Quality assessment (risk of bias judgement)	Score
Vasileiadou, S., Wennergren, G., Celind, F.S., Aberg, N., Pettersson, R., Alm, B. & Goksor, E. 2018. Eating fish and farm life reduce allergic rhinitis at the age of twelve. *Pediatric Allergy and Immunology*, 29(3): 283-289.	C	Study analyses the prevalence of risk factors and protective factors for allergic rhinitis. Only one question on fish intake.
Virtanen, S.M., Kaila, M., Pekkanen, J., Kenward, M.G., Uusitalo, U., Pietinen, P., Kronberg-Kippilä, C. *et al.* 2010. Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis. Br J Nutr, 103(2): 266-73.	C	Participants have increased risk of type 1 diabetes.
Wijga, A.H., Smit, H.A., Kerkhof, M., de Jongste, J.C., Gerritsen, J., Neijens, H.J., Boshuizen, H.C. & Brunekreef, B. 2003. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. *Thorax*, 58(7): 567-572.	C	Mothers were allergic. Children were examined at 2 years of food consumption and at 3 years for asthma symptoms. No result on fish is reported.
Woodman, R.J., Baghdadi, L.R., Shanahan, E.M., de Silva, I., Hodgson, J.M. & Mangoni, A.A. 2019. Diets high in n-3 fatty acids are associated with lower arterial stiffness in patients with rheumatoid arthritis: a latent profile analysis. *British Journal of Nutrition*, 121(2): 182-194	C	Participants have rheumatoid arthritis. Data on nutrients intake and not fish. Aim to identify patterns of fatty acids intake in RA patients.
Zapatero Remón, L., Alonso Lebrero, E., Martín Fernández, E. & Martínez Molero, M.I. 2005. Food-protein-induced enterocolitis syndrome caused by fish. *Allergol Immunopathol (Madr)*, 33(6): 312-6.	C	Report on 14 children with enterocolitis syndrome due to fish protein
Zeng, J., Wu, W., Tang, N., Chen, Y., Jing, J. & Cai, L. 2021. Maternal Dietary Protein Patterns During Pregnancy and the Risk of Infant Eczema: A Cohort Study. *Front Nutr*, 8: 608972	C	Study aim was to investigate the association between maternal dietary protein patterns during pregnancy and the risk of infant eczema. Dietary pattern study. Fish and red meat results are given together.
Zinn, C., Lopata, A., Visser, M. & Potter, P.C. 1997. The spectrum of allergy to South African bony fish (Teleosti). Evaluation by double-blind, placebo-controlled challenge. *S Afr Med J*, 87(2): 146-52.	C	Study tested different fish species by ingestion, skin prick test and RAST test in the participants with suspected fish allergy.

BIRTH AND GROWTH OUTCOMES

TABLE A3.22 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "BIRTH AND GROWTH" (N = 3)**

Reference primary study (*n* = 3)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Oken, E. Kleinman, K. P. Olsen, S. F. Rich-Edwards, J. W. & Gillman, M. W. 2004. Associations of seafood and elongated n-3 fatty acid intake with fetal growth and length of gestation: results from a US pregnancy cohort. *American journal of epidemiology*, 160(8):774-783.	B	
Olsen, S. F. Grandjean, P. Weihe, P. & Viderø, T. 1993. Frequency of seafood intake in pregnancy as a determinant of birth weight: evidence for a dose dependent relationship. *Journal of Epidemiology & Community Health*, 47(6):436-440.	C	Whale consumption is aggregated with fish consumption in exposure, and it is not possible to study the effects of fish consumption on health outcomes alone.
Zhao, R. Gao, Q. Xiong, T. Zhou, J. Wang, S. Zhang, Z. Hao, L. *et al.* 2022. Moderate freshwater fish intake, but not n-3 polyunsaturated fatty acids, is associated with a reduced risk of small for gestational age in a prospective cohort of Chinese pregnant women. *Journal of the Academy of Nutrition and Dietetics*, 122(4):722-730.	B	

BONE HEALTH

TABLE A3.23 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "BONE HEALTH" (N = 11)**

Reference primary study (*n* = 11)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Hirota, T., Kusu, T. & Hirota, K. 2005. Improvement of nutrition stimulates bone mineral gain in Japanese school children and adolescents. *Osteoporos Int*, 16(9): 1057-64.	B	
Tong, T. Y., Appleby, P. N., Armstrong, M. E., Fensom, G. K., Knuppel, A., Papier, K., Key, T. J. *et al.* 2020. Vegetarian and vegan diets and risks of total and site-specific fractures: results from the prospective EPIC-Oxford study. *BMC medicine*, 18, 1-15.	B	
Lucey, A. J., Paschos, G. K., Cashman, K. D., Martínéz, J. A., Thorsdottir, I., & Kiely, M. 2008. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. *The American Journal of Clinical Nutrition*, *87*(4), 1045-1052.	B	
Thacher, T. D., Bommersbach, T. J., Pettifor, J. M., Isichei, C. O., & Fischer, P. R. 2015. Comparison of limestone and ground fish for treatment of nutritional rickets in children in Nigeria. *The Journal of Pediatrics*, 167(1), 148-154.	B	
de Jonge, E. A., Rivadeneira, F., Erler, N. S., Hofman, A., Uitterlinden, A. G., Franco, O. H., & Kiefte-de Jong, J. C. 2018. Dietary patterns in an elderly population and their relation with bone mineral density: the Rotterdam Study. *European Journal of Nutrition*, 57, 61-73.	C	Use dietary pattern as exposure and not fish consumption explicitly
De Jonge, E. A., Kiefte-de Jong, J. C., De Groot, L. C., Voortman, T., Schoufour, J. D., Zillikens, M. C., ... & Rivadeneira, F. 2015. Development of a food group-based diet score and its association with bone mineral density in the elderly: the Rotterdam study. *Nutrients*, 7(8), 6974-6990.	C	Does not have fish intake as exposure alone, but within "a bone mineral density" diet consisting of several food groups.
Ishikawa-Takata, K. & Ohta, T. 2003. Relationship of lifestyle factors to bone mass in Japanese women. *J Nutr Health Aging*, 7(1):44-53.	C	Methodological weakness in the description of study design and population
Nieves, J. W., Barrett-Connor, E., Siris, E. S., Zion, M., Barlas, S., & Chen, Y. T. 2008. Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. *Osteoporosis International*, *19*, 673-679.	C	Fish intake used to estimate vitamin D intake, along with intake of milk, supplements and sun exposure. Intake of fish is not explicitly stated further in the paper, or used as an individual exposure variable.
Samieri, C., Ginder Coupez, V., Lorrain, S., Letenneur, L., Allès, B., Féart, C., Barberger-Gateau, P. *et al.* 2013. Nutrient patterns and risk of fracture in older subjects: results from the Three-City Study. *Osteoporosis International*, *24*, 1295-1305.	C	Excluded – dietary patterns
Graff, I. E., Øyen, J., Kjellevold, M., Frøyland, L., Gjesdal, C. G., Almås, B., Lie, Ø. *et al.* 2016. Reduced bone resorption by intake of dietary vitamin D and K from tailor-made Atlantic salmon: A randomized intervention trial. *Oncotarget*, *7*(43), 69200.	C	Tailor-made salmon; enriched with vitamin D
Kerstetter, J. E., Mitnick, M. E., Gundberg, C. M., Caseria, D. M., Ellison, A. F., Carpenter, T. O., & Insogna, K. L. 1999. Changes in bone turnover in young women consuming different levels of dietary protein. *The Journal of Clinical Endocrinology & Metabolism*, 84(3), 1052-1055.	C	Exposure was different levels of protein; no mention of fish

CANCER

TABLE A3.24 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CANCER" (*N* = 3)

Gao, Y., Ma, Y., Yu, M., Li, G., Chen, Y., Li, X., Wang, X. *et al.* 2022. Poultry and Fish Intake and Pancreatic Cancer Risk: A Systematic Review and Meta-Analysis. *Nutrition and Cancer*, 74(1):55-67.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	yes	1.00
Q2	Protocol	yes/partial yes/no	partial yes	0.50
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	partial yes	0.50
Q5	Paired study selection	yes/no	yes	1.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	no	0.00
Q8	Description of included studies	yes/partial yes/no	partial yes	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	partial yes	0.50
Q10	Sources of funding for included studies	yes/no	no	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	no	0.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				11.00
Percent				69%
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.24 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CANCER" (*N* = 3) (cont.)**

Jayedi, A. & Shab-Bidar, S. 2020. Fish consumption and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. *Advances in Nutrition*, 11(5):1123-1133.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	yes	1.00
Q2	Protocol	yes/partial yes/no	partial yes	0.50
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	partial yes	0.50
Q5	Paired study selection	yes/no	yes	1.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	yes	1.00
Q8	Description of included studies	yes/partial yes/no	partial yes	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	partial yes	0.50
Q10	Sources of funding for included studies	yes/no	yes	1.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	yes	1.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				14.00
Percent				87.50
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.24 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CANCER" (*N* = 3) (cont.)**

Kazemi, A., Barati-Boldaji, R., Soltani, S., Mohammadipoor, N., Esmaeilinezhad, Z., Clark, C. C., Akbarzadeh, M. *et al*. 2021. Intake of various food groups and risk of breast cancer: A systematic review and dose-response meta-analysis of prospective studies. *Advances in Nutrition*, 12(3):809-849.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	yes	1.00
Q2	Protocol	yes/partial yes/no	yes	1.00
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	yes	1.00
Q5	Paired study selection	yes/no	yes	1.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	no	0.00
Q8	Description of included studies	yes/partial yes/no	partial yes	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	partial yes	0.50
Q10	Sources of funding for included studies	yes/no	yes	1.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	yes	1.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				14.00
Percent				87.50
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.25 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "CANCER" (N = 10)**

Reference primary study (*n* = 10)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Aglago, E.K. Huybrechts, I. Murphy, N. Casagr, E., C. Nicolas, G. Pischon, T. Fedirko, V. Severi, G. Boutron-Ruault, M.C. *et al.* 2020. Consumption of Fish and Long-chain n-3 Polyunsaturated Fatty Acids Is Associated With Reduced Risk of Colorectal Cancer in a Large European Cohort. *Clin Gastroenterol Hepatol* 18:654-666. e656.	B	
Bradbury, K.E. Murphy, N. & Key, T.J. 2020. Diet and colorectal cancer in UK Biobank: a prospective study. *Int J Epidemiol*, 49:246-258.	B	
Cai, H. Sobue, T. Kitamura, T. Ishihara, J. Sawada, N. Iwasaki, M. Shimazu, T. & Tsugane, S. 2020. Association between meat and saturated fatty acid intake and lung cancer risk: The Japan Public Health Center-based prospective study. *Int J Cancer*, 147:3019-3028.	B	
Dianatinasab, M. Wesselius, A. de Loeij, T. Salehi-Abargouei, A. Yu, E.Y.W. Fararouei, M. Brinkman, M. *et al.* 2021. The association between meat and fish consumption and bladder cancer risk: a pooled analysis of 11 cohort studies. *Eur J Epidemiol*, 36:781-792.	B	
Etemadi, A. Abnet, C.C. Graubard, B.I. Beane-Freeman, L. Freedman, N.D. Liao, L. Dawsey, S.M. & Sinha, R. 2018. Anatomical subsite can modify the association between meat and meat compounds and risk of colorectal adenocarcinoma: Findings from three large US cohorts. *Int J Cancer*, 143:2261-2270.	B	
Hermans, K. van den Brandt, P.A. Loef, C. Jansen, R.L.H. & Schouten, L.J. 2021. Meat consumption and cancer of unknown primary (CUP) risk: results from The Netherlands cohort study on diet and cancer. *Eur J Nutr*, 60:4579-4593.	B	
Ma, Y. Yang, W. Li, T. Liu, Y. Simon, T.G. Sui, J. Wu, K. Giovannucci, E.L. Chan, A.T. & Zhang, X. 2019. Meat intake and risk of hepatocellular carcinoma in two large US prospective cohorts of women and men. *Int J Epidemiol*, 48:1863-1871.	B	
Makiuchi, T. Sobue, T. Kitamura, T. Ishihara, J. Sawada, N. Iwasaki, M. Yamaji, T. Shimazu, T. & Tsugane, S. 2019. Relationship between Meat/Fish Consumption and Biliary Tract Cancer: The Japan Public Health Center-Based Prospective Study. *Cancer Epidemiol Biomarkers Prev*, 29:95-102.	B	
Outzen, M. Tjønnel, A. Christensen, J. & Olsen, A. 2018. Fish consumption and prostate cancer risk and mortality in a Danish cohort study. *Eur J Cancer Prev,* 27:355-360.	B	
Zamani, S.A. McClain, K.M. Graubard, B.I. Liao, L.M. Abnet, C.C. Cook, M.B. & Petrick, J.L. 2020. Dietary Polyunsaturated Fat Intake in Relation to Head and Neck, Esophageal, and Gastric Cancer Incidence in the National Institutes of Health-AARP Diet and Health Study. *Am J Epidemiol*, 189:1096-1113.	B	

CARDIOVASCULAR DISEASES AND OUTCOMES

TABLE A3.26 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CARDIOVASCULAR DISEASES AND OUTCOMES" (*N*= 3)

Chowdhury, R. *et al.* 2012. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: systematic review and meta-analysis. *Bmj-British Medical Journal*, 345.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	yes	1.00
Q2	Protocol	yes/partial yes/no	yes	1.00
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	yes	1.00
Q5	Paired study selection	yes/no	yes	1.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	no	0.00
Q8	Description of included studies	yes/partial yes/no	yes	1.00
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	no	0.00
Q10	Sources of funding for included studies	yes/no	no	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	no	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	no	0.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				11.00
Percent				68.75
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.26 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CARDIOVASCULAR DISEASES AND OUTCOMES" (*N*= 3) (cont.)**

Li, N. *et al.* **2020. Fish consumption and multiple health outcomes: Umbrella review.** *Trends in Food Science & Technology*, **99:273-283.**				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	no	0.00
Q2	Protocol	yes/partial yes/no	yes	1.00
Q3	Explanation of included study design	yes/no	no	0.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	yes	1.00
Q5	Paired study selection	yes/no	no	0.00
Q6	Paired data extraction	yes/no	yes	1.00
Q7	List of excluded studies	yes/partial yes/no	yes	1.00
Q8	Description of included studies	yes/partial yes/no	no	0.00
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	no	0.00
Q10	Sources of funding for included studies	yes/no	no	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	no meta-analysis conducted	
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	no meta-analysis conducted	
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	no	0.00
Q14	Heterogeneity assessed	yes/no	no	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	no meta-analysis conducted	
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				5.00
Percent				31.25
Percent (exclude N/A question)				38.46
Overall AMSTAR 2 judgement (confidence in the results)				Critically low
Include/exclude				Exclude

TABLE A3.26 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "CARDIOVASCULAR DISEASES AND OUTCOMES" (*N*= 3) (cont.)**

Mente, A. *et al.* 2009. A Systematic Review of the Evidence Supporting a Causal Link Between Dietary Factors and Coronary Heart Disease. *Archives of Internal Medicine*, 169(7):659-669.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	yes	1.00
Q2	Protocol	yes/partial yes/no	partial yes	0.50
Q3	Explanation of included study design	yes/no	yes	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	partial yes	0.50
Q5	Paired study selection	yes/no	no	1.00
Q6	Paired data extraction	yes/no	no	0.00
Q7	List of excluded studies	yes/partial yes/no	yes	1.00
Q8	Description of included studies	yes/partial yes/no	yes	1.00
Q9	Risk of bias tool	yes/partial yes/no/includes only RCTs or NRSI	yes	1.00
Q10	Sources of funding for included studies	yes/no	no	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	yes	1.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	yes	1.00
Q14	Heterogeneity assessed	yes/no	yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	yes	1.00
Q16	Conflict of interest included	yes/no	yes	1.00
Total score				13.00
Percent				81.25
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.27 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "CARDIOVASCULAR DISEASES AND OUTCOMES" (N = 10)**

Reference primary study (*n* = 10)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Acosta, S., Johansson, A., & Drake, I. 2021. Diet and lifestyle factors and risk of atherosclerotic cardiovascular disease—a prospective cohort study. *Nutrients*, *13*(11), 3822.	B	
Frost, L. & Vestergaard, P. 2005. n–3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study1–3. *The American Journal of Clinical Nutrition*, *81*(1), 50-54.	B	
Gammelmark, A., Nielsen, M. S., Bork, C. S., Lundbye-Christensen, S., Overvad, K., & Schmidt, E. B. 2015. Fish Consumption and Adipose Tissue Content of Marine n-3 PUFA is Inversely Associated With Myocardial Infarction: A Danish Prospective Cohort Study. *Circulation*, *132*:A12418-A12418.	B	
Lajous, M., Willett, W. C., Robins, J., Young, J. G., Rimm, E., Mozaffarian, D., & Hernán, M. A. 2013. Changes in fish consumption in midlife and the risk of coronary heart disease in men and women. *American Journal of Epidemiology*, 178(3), 382-391.	B	
Lasota, A. N., Grønholdt, M. L. M., Bork, C. S., Lundbye-Christensen, S., Schmidt, E. B., & Overvad, K. 2019. Substitution of poultry and red meat with fish and the risk of peripheral arterial disease: a Danish cohort study. *European Journal of Nutrition*, 58, 2731-2739.	B	
Matheson, E. M., Mainous III, A. G., Hill, E. G., & Carnemolla, M. A. 2009. Shellfish consumption and risk of coronary heart disease. *Journal of the American Dietetic Association*, 109(8), 1422-1426.	B	
Petermann-Rocha, F., Parra-Soto, S., Gray, S., Anderson, J., Welsh, P., Gill, J., Pell, J. P. *et al.* 2021. Vegetarians, fish, poultry, and meat-eaters: who has higher risk of cardiovascular disease incidence and mortality? A prospective study from UK Biobank. *European Heart Journal*, *42*(12), 1136-1143.	B	
Tong, T. Y., Appleby, P. N., Bradbury, K. E., Perez-Cornago, A., Travis, R. C., Clarke, R., & Key, T. J. 2019. Risks of ischaemic heart disease and stroke in meat eaters, fish eaters, and vegetarians over 18 years of follow-up: results from the prospective EPIC-Oxford study. *BMJ*, *366*.	B	
Venø, S. K., Bork, C. S., Jakobsen, M. U., Lundbye-Christensen, S., Bach, F. W., McLennan, P. L., Overvad, K. *et al.* 2018. Substitution of fish for red meat or poultry and risk of ischemic stroke. *Nutrients*, *10*(11), 1648.	B	
Zhong, V. W., Allen, N. B., Greenland, P., Carnethon, M. R., Ning, H., Wilkins, J. T., Van Horn, L. *et al.* 2021. Protein foods from animal sources, incident cardiovascular disease and all-cause mortality: a substitution analysis. *International Journal of Epidemiology*, *50*(1), 223-233.	B	

TYPE 2 DIABETES

TABLE A3.28 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9)

Muley, A. Muley, P. & Shah, M. 2014. ALA, fatty fish or marine n-3 fatty acids for preventing DM?: a systematic review and meta-analysis. *Current diabetes reviews*, 10(3):158-165.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, assessed the population of >18 years (P) to find out if dietary intake of fish and n-3 PUFA (I) as compared to none or in lower quantile (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Not mentioned	0
Q3	Explanation of included study design	yes/no	They included prospective cohort studies only. They stated RCTs were not included as no studies were available.	0
Q4	Comprehensive literature search strategy	yes/partial yes/no	Searched three databases (PubMed, EMBASE and GOOGLE), and cross references from first yield were hand searched.	1
Q5	Paired study selection	yes/no	In triplicate	1
Q6	Paired data extraction	yes/no	In triplicate	1
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, but the studies are not listed.	0.5
Q8	Description of included studies	yes/partial yes/no	Country, follow-up, age, sex, exposure assessment, exposure type is explained.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	The internal validity of studies was assessed based on the Cochrane collaboration's tool for assessment of bias but no study was excluded for its quality regarding RoB.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	The internal validity of studies was assessed based on the Cochrane Collaboration's tool for assessment of bias, but no study was excluded for its quality regarding RoB.	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No	0
Q14	Heterogeneity assessed	yes/no	I^2 was used as a measure for heterogeneity, and is discussed.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No	0
Q16	Conflict of interest included	yes/no	The authors confirm that they have no conflict of interest.	1
Total score				10.5
Percent				66%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Tian, S., Xu, Q., Jiang, R., Han, T., Sun, C. & Na, L. 2017. Dietary protein consumption and the risk of type 2 diabetes: a systematic review and meta-analysis of cohort studies. *Nutrients*, 9(9):982.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to find out if dietary intake of fish protein (I) as compared to other protein sources (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Not mentioned	0
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Searched two databases (PubMed, EMBASE).	1
Q5	Paired study selection	yes/no	Not mentioned	0
Q6	Paired data extraction	yes/no	Not mentioned	0
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, but the studies are not listed.	0.5
Q8	Description of included studies	yes/partial yes/no	Adequately described in supplementary information	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Not mentioned	0
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Not mentioned	0
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Not mentioned	0
Q14	Heterogeneity assessed	yes/no	I^2 was used as a measure for heterogeneity.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Egger linear regression test and Begg rank correlation test were used to search for publication bias.	1
Q16	Conflict of interest included	yes/no	The authors declare no conflict of interest.	1
Total score				8.50
Percent				53
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Wallin, A., Di Giuseppe, D., Orsini, N., Patel, P.S., Forouhi, N.G. & Wolk, A. 2012. Fish consumption, dietary long-chain n-3 fatty acids, and risk of type 2 diabetes: systematic review and meta-analysis of prospective studies. *Diabetes care*, 35(4):918-929.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared to other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Yes – adhering to the PRISMA statement.	1
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Searched two databases (PubMed, EMBASE), and used reference lists from retrieved articles.	1
Q5	Paired study selection	yes/no	In duplicate	1
Q6	Paired data extraction	yes/no	In duplicate	1
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, and articles are found in the reference list.	0.5
Q8	Description of included studies	yes/partial yes/no	Country, follow-up, age, sex, exposure assessment, exposure type listed.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Newcastle-Ottawa Quality Assessment scale was used.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Quality score by Newcastle-Ottawa Quality Assessment scale was used.	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Discussed	1
Q14	Heterogeneity assessed	yes/no	I2 and Cochrane Q-test were used to evaluate heterogeneity.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed using Egger regression asymmetry test.	1
Q16	Conflict of interest included	yes/no	The authors declare no conflict of interest.	1
Total score				14.5
Percent				91%
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Wu, J.H., Micha, R., Imamura, F., Pan, A., Biggs, M.L., Ajaz, O., Mozaffarian, D. *et al.* 2012. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. *British journal of nutrition*, 107(S2):S214-S227.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Yes. The Meta-analyses of Observational studies in Epidemiology guidelines (MOOSE) was used.	1
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Searched three databases (MEDLINE, EMBASE, LILACS). Related articles were hand searched.	1
Q5	Paired study selection	yes/no	Title and abstracts were screened by one investigator. Two investigators assessed independently and in duplicate the full text.	1
Q6	Paired data extraction	yes/no	Data were extracted independently and in duplicate.	1
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, and articles are found in the reference list.	0.5
Q8	Description of included studies	yes/partial yes/no	Country, follow-up, age, sex, exposure assessment, exposure type listed.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Five criteria are described.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	MOOSE was used.	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Not mentioned	0
Q14	Heterogeneity assessed	yes/no	I2 was used to evaluate heterogeneity.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed by visual inspection of funnel plots and using Begg's test.	1
Q16	Conflict of interest included	yes/no	One of the authors reports research grant from the industry.	1
Total score				13.5
Percent				84%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Xun, P. *&* He, K. 2012. Fish consumption and incidence of diabetes: meta-analysis of data from 438,000 individuals in 12 independent prospective cohorts with an average 11-year follow-up. *Diabetes care*, 35(4):930-938.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared to other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Yes. The Meta-analyses of Observational studies in Epidemiology guidelines (MOOSE) was used.	1
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Only one database (PubMed) was used, but articles were also retrieved through Google and hand search of the references from retrieved articles.	0.5
Q5	Paired study selection	yes/no	Two investigators assessed independently.	1
Q6	Paired data extraction	yes/no	Not stated	0
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, and articles are found in the reference list.	1
Q8	Description of included studies	yes/partial yes/no	Country, follow-up, age, sex, exposure assessment, exposure type listed.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	MOOSE scoring was used.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Five criteria are described	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Discussed	1
Q14	Heterogeneity assessed	yes/no	Study selection is described	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed using Egger test.	1
Q16	Conflict of interest included	yes/no	The authors report no conflict of interest.	1
Total score				13.5
Percent				84%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Yanai, H., Hamasaki, H., Katsuyama, H., Adachi, H., Moriyama, S. & Sako, A. 2015. Effects of intake of fish or fish oils on the development of diabetes. Journal of clinical medicine research, 7(1):8.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared to other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	No information	0
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Not described	0
Q5	Paired study selection	yes/no	Not described	0
Q6	Paired data extraction	yes/no	Not described	0
Q7	List of excluded studies	yes/partial yes/no	Not described	0
Q8	Description of included studies	yes/partial yes/no	Country, age, sex, exposure assessment, exposure type are listed. Follow-up is missing.	0.5
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Not described	0
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted		N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted		N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Not mentioned	0
Q14	Heterogeneity assessed	yes/no	Heterogeneity is discussed	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted		N/A
Q16	Conflict of interest included	yes/no	The authors report no competing interest.	1
Total score				4.50
Percent				28.13
Percent (exclude n/a question)				34.62
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Zhang, M., Picard-Deland, E. & Marette, A. 2013. Fish and marine omega-3 polyunsaturated fatty acid consumption and incidence of type 2 diabetes: a systematic review and meta-analysis. *International journal of endocrinology*, 2013.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared to other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Not described	0
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Three databases (PubMed, OViD and EMBASE) were used, and cross references examined.	1
Q5	Paired study selection	yes/no	Two investigators assessed independently.	1
Q6	Paired data extraction	yes/no	Two investigators assessed independently.	1
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, but articles are not in the reference list.	0.5
Q8	Description of included studies	yes/partial yes/no	Country, follow-up, age, sex, exposure assessment, exposure type are listed.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Scoring system is described.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Three criteria are described.	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Discussed	1
Q14	Heterogeneity assessed	yes/no	An I2 was used to evaluate heterogeneity and heterogeneity is discussed.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed Egger's regression test and funnel plots.	1
Q16	Conflict of interest included	yes/no	The authors declare that there is no conflict of interest.	1
Total score				13.5
Percent				84%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.28 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)**

Zheng, J.S., Huang, T., Yang, J., Fu, Y.Q,. & Li, D. 2012. Marine N-3 polyunsaturated fatty acids are inversely associated with risk of type 2 diabetes in Asians: a systematic review and meta-analysis. *PLoS One.* 7(9)				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (I) as compared to other food (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Followed the MOOSE protocol.	1
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Five databases (PubMed, Embase, Cochrane, CNK1 and Chinese VIP database) were used.	1
Q5	Paired study selection	yes/no	Two investigators assessed independently.	1
Q6	Paired data extraction	yes/no	Not described	0
Q7	List of excluded studies	yes/partial yes/no	The reasons are given, but articles are not in the reference list.	0.5
Q8	Description of included studies	yes/partial yes/no	Follow-up, age, exposure assessment, exposure type and range are listed. Country and sex are missing.	0.5
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Stated in the supplementary Table 1 that this was done, but not described in the paper.	0
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described.	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Not described	0
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Not mentioned	0
Q14	Heterogeneity assessed	yes/no	An I^2 was used to evaluate heterogeneity. Heterogeneity is discussed.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed. Egger's regression test and Begg's funnel plots.	1
Q16	Conflict of interest included	yes/no	The authors declare that there is no conflict of interest.	1
Total score				10.0
Percent				63%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.28 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "DIABETES" (*N* = 9) (cont.)

Zhou, Y., Tian, C. & Jia, C. 2012. Association of fish and n-3 fatty acid intake with the risk of type 2 diabetes: a meta-analysis of prospective studies. *British Journal of Nutrition*, 108(3):408-417.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if high fish consumption (I) as compared to low consumption (C) reduced the risk of diabetes (O).	1
Q2	Protocol	yes/partial yes/no	Not described	0
Q3	Explanation of included study design	yes/no	Study selection is described.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Five databases (PubMed, Web of Science, CBM, VIP and CNK1) were used. References from retrieved references were hand searched.	1
Q5	Paired study selection	yes/no	Two investigators assessed independently.	1
Q6	Paired data extraction	yes/no	Two investigators assessed independently (stated in author contribution).	1
Q7	List of excluded studies	yes/partial yes/no	Not described	0
Q8	Description of included studies	yes/partial yes/no	Country, age, follow-up, sex, exposure assessment, exposure type and range are listed.	1
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Newcastle-Ottawa scale was used.	1
Q10	Sources of funding for included studies	yes/no	Not mentioned	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Adequately described	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Newcastle-Ottawa scale was used.	1
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Discussed	1
Q14	Heterogeneity assessed	yes/no	An I^2 and Q-test were used to evaluate heterogeneity. Heterogeneity is discussed.	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Potential publication bias was assessed Egger's test.	1
Q16	Conflict of interest included	yes/no	The authors declare that there is no conflict of interest.	1
Total score				13
Percent				81%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

TABLE A3.29 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TYPE 2 DIABETES" (*N* = 1)**

Reference primary study (*n* = 1)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Chen, Z. Franco, O.H. Lamballais, S. Ikram, M.A. Schoufour, J.D. Muka, T. *&* Voortman, T. 2020. Associations of specific dietary protein with longitudinal insulin resistance, prediabetes and type 2 diabetes: The Rotterdam Study. *Clinical nutrition*, 39(1):242-249.	B	

NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS

TABLE A3.30 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" (*N* = 3)

Ernst, E. 1999. Diet and dementia, is there a link? A systematic review. *Nutritional Neuroscience*, 2(1):1-6.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	No	0
Q2	Protocol	yes/partial yes/no	No	0
Q3	Explanation of included study design	yes/no	No	0
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partial yes	0.5
Q5	Paired study selection	yes/no	No	0
Q6	Paired data extraction	yes/no	No	0
Q7	List of excluded studies	yes/partial yes/no	No	0
Q8	Description of included studies	yes/partial yes/no	No	0
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No	0
Q10	Sources of funding for included studies	yes/no	No	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes	1
Q14	Heterogeneity assessed	yes/no	No	0
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q16	Conflict of interest included	yes/no	No	0
Total score				1.5
Percent				10%
Percent (exclude n/a question)				13%
Overall AMSTAR 2 judgement (confidence in the results)				Critically low
Include/exclude				Exclude

TABLE A3.30 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" (*N* = 3) (cont.)**

Murakami, K. *&* Sasaki, S. 2010. Dietary intake and depressive symptoms: a systematic review of observational studies. *Molecular nutrition & food research*, 54(4):471-488.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes	
Q2	Protocol	yes/partial yes/no	No, no risk of bias assessment	0
Q3	Explanation of included study design	yes/no	Yes	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	No, 1 database only	0
Q5	Paired study selection	yes/no	No	0
Q6	Paired data extraction	yes/no	No	0
Q7	List of excluded studies	yes/partial yes/no	No	0
Q8	Description of included studies	yes/partial yes/no	Partial yes	
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes	1
Q10	Sources of funding for included studies	yes/no	No	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No	0
Q14	Heterogeneity assessed	yes/no	No	0
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q16	Conflict of interest included	yes/no	Yes	1
Total score				3
Percent				19%
Percent (exclude n/a question)				23%
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.30 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" (*N* = 3) (cont.)**

Starling, P., Charlton, K., McMahon, A.T. & Lucas, C. 2015. Fish intake during pregnancy and foetal neurodevelopment—A systematic review of the evidence. *Nutrients*, 7(3):2001-2014.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Partial yes	0.5
Q2	Protocol	yes/partial yes/no	No	0
Q3	Explanation of included study design	yes/no	Yes	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partial yes	0.5
Q5	Paired study selection	yes/no	No	0
Q6	Paired data extraction	yes/no	No	0
Q7	List of excluded studies	yes/partial yes/no	No	0
Q8	Description of included studies	yes/partial yes/no	Partial yes	0.5
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No, no selection bias assessed	0
Q10	Sources of funding for included studies	yes/no	No	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes	1
Q14	Heterogeneity assessed	yes/no	No	0
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No meta-analysis	N/A
Q16	Conflict of interest included	yes/no	Yes	1
Total score				1.5
Percent				28%
Percent (exclude n/a question)				34%
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.31 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "NEURODEVELOPMENT AND NEUROLOGICAL DISORDERS" (*N* = 14)**

Reference primary study (*n* = 14)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Al-Ghannami, S.S. Al-Adawi, S. Ghebremeskel, K. Hussein, I.S. Min, Y. Jeyaseelan, L. Al-Oufi, H. S. *et al.* 2019. Randomized open-label trial of docosahexaenoic acid–enriched fish oil and fish meal on cognitive and behavioral functioning in Omani children. *Nutrition*, 57:167-172.	B	
Almeida, O.P. Norman, P. Hankey, G. Jamrozik, K. *&* Flicker, L. 2006. Successful mental health aging: results from a longitudinal study of older Australian men. *The American journal of geriatric psychiatry*, *14*(1):27-35.	C	Aim of determining the lifestyle and clinical factors associated with successful mental health aging in a cohort
Browne, J.C. Scott, K.M. *&* Silvers, K.M. 2006. Fish consumption in pregnancy and omega-3 status after birth are not associated with postnatal depression. *Journal of affective disorders*, *90*(2-3):131-139.	C	Investigates n-3 status postpartum and depression. Fish intake in pregnancy was dichotomized.
Danthiir, V. Hosking, D. Burns, N.R. Wilson, C. Nettelbeck, T. Calvaresi, E. Wittert, G.A. *et al.* 2014. Cognitive performance in older adults is inversely associated with fish consumption but not erythrocyte membrane n–3 fatty acids. *The Journal of nutrition*, *144*(3):311-320.	C	Study design
Emmett, P.M. Jones, L.R. *&* Golding, J. 2015. Pregnancy diet and associated outcomes in the Avon Longitudinal Study of Parents and Children. *Nutrition reviews*, *73*(suppl_3):154-174.	C	Reviews publications that have used ALSPAC data to report on diet during pregnancy relative to the growth and development of the offspring, as well as to some maternal outcomes
García-Esquinas, E. Ortolá, R. Banegas, J.R. Lopez-García, E. *&* Rodríguez-Artalejo, F. 2019. Dietary n-3 polyunsaturated fatty acids, fish intake and healthy ageing. *International Journal of Epidemiology*, *48*(6):1914-1924.	C	Response rate not included. Outcome/endpoint not relevant
Lehner, A. Staub, K. Aldakak, L. Eppenberger, P. Rühli, F. Martin, R.D. *&* Bender, N. 2020. Fish consumption is associated with school performance in children in a non-linear way: results from the German cohort study KiGGS. *Evolution, medicine, and public health*, (1):2-11.	C	Outcome not clearly formulated. A cohort-study but a cross-sectional study (not prospective).
Matsuoka, Y.J. Sawada, N. Mimura, M. Shikimoto, R. Nozaki, S. Hamazaki, K. Tsugane, S. *et al.* 2017. Dietary fish, n-3 polyunsaturated fatty acid consumption, and depression risk in Japan: a population-based prospective cohort study. *Translational psychiatry*, *7*(9):e1242-e1242.	C	Food frequency questionnaire not used at baseline, important confounders not identified and considered by the authors
Mesirow, M.S. Cecil, C. Maughan, B. *&* Barker, E. D. 2017. Associations between prenatal and early childhood fish and processed food intake, conduct problems, and co-occurring difficulties. *Journal of abnormal child psychology*, *45*:1039-1049.	B	
Nathanson, R. Hill, B. Skouteris, H. *&* Bailey, C. 2018. Antenatal diet and postpartum depressive symptoms: A prospective study. *Midwifery*, *62*:69-76.	C	Response rate not acceptable; fish intake question not included at baseline
Schiepers, O.J. de Groot, R.H. Jolles, J. *&* van Boxtel, M.P. 2009. Plasma phospholipid fatty acid status and depressive symptoms: association only present in the clinical range. *Journal of Affective Disorders*, 118(1-3):209-214.	C	Response rate at follow-up was very low (<10%); fish intake question not included at baseline
Shapouri-Moghaddam, A. Bagherniya, M. Ehteshamfar, S.M. Rahimi, H. *&* Safarian, M. 2017. High fish consumption decreased the likelihood of depressive symptoms in community-living older people: a randomized-controlled trial. *Journal of gerontology and geriatrics*, *65*:232-237.	C	Power calculation not reported; low participant number; study design maybe not suitable for the research hypothesis
Sharifan, P. Hosseini, M.S. *&* Sharifan, A. 2017. The interventional relationship between frequent fish consumption and depression symptoms in aging adults: A randomized controlled trial. *International Journal of Geriatric Psychiatry*, 32(12):e116-e122.	C	Recruited patients (have depression severity 10-29 BDI), included fish oil in intervention
van de Rest, O. Wang, Y. Barnes, L.L. Tangney, C. Bennett, D.A. *&* Morris, M.C. 2016. APOE ε4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. *Neurology*, 86(22):2063-2070.	C	Investigated if APOE e4 modifies the association between seafood and n-3 fatty acid intakes and domain-specific cognitive decline in a community-based, prospective study

MORTALITY

TABLE A3.32 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "MORTALITY" (*N* = 5)**

He, K., Song, Y., Daviglus, M.L., Liu, K., Van Horn, L., Dyer, A.R. *et al.* 2004. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*, 109(22):2705-11.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if fish consumption (>1-3/month, 1/week etc. (I) as compared to less (<1mo) (C) reduced the risk of CHD mortality (O).	1.00
Q2	Protocol	yes/partial yes/no	No, not mentioned.	0.00
Q3	Explanation of included study design	yes/no	Yes, study selection is described (included prospective cohort studies)	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	partial, two databases (Medline + EMBASE + language + search terms).	0.50
Q5	Paired study selection	yes/no	Yes, duplicate	1.00
Q6	Paired data extraction	yes/no	Yes, duplicate	1.00
Q7	List of excluded studies	yes/partial yes/no	Partial – the reasons are given, and articles are found in the reference list.	0.50
Q8	Description of included studies	yes/partial yes/no	Yes – country, follow-up, age, sex, exposure assessment, exposure type listed	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes – Beggs + Egger's.	0.00
Q10	Sources of funding for included studies	yes/no	No, not mentioned	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes – adequately described	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Yes Beggs + Egger's	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes	1.00
Q14	Heterogeneity assessed	yes/no	Yes, by a meta regression analysis.	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Yes, adequately described	1.00
Q16	Conflict of interest included	yes/no	No, not mentioned	0.00
Total score				9.50
Percent				59
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.32 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "MORTALITY" (*N* = 5) (cont.)**

Szymanski, K.M., Wheeler, D.C. & Mucci, L.A. 2010. Fish consumption and prostate cancer risk: a review and meta-analysis. *The American journal of clinical nutrition*, 92(5):1223-33.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if higher fish consumption (C) reduced the risk of prostate cancer mortality (O).	1.00
Q2	Protocol	yes/partial yes/no	Yes – protocol and guidelines	1.00
Q3	Explanation of included study design	yes/no	Yes. Study selection is described (prospective cohort studies).	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partial – three databases (Medline + EMBASE + ProQuest + search terms + ref. list).	0.50
Q5	Paired study selection	yes/no	Yes – duplicate	1.00
Q6	Paired data extraction	yes/no	Yes – duplicate	1.00
Q7	List of excluded studies	yes/partial yes/no	Partial. The reasons are given, and articles are found in the reference list.	0.50
Q8	Description of included studies	yes/partial yes/no	Yes. Country, follow-up, age, sex, exposure assessment, exposure type listed.	1.00
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No, not mentioned	0.00
Q10	Sources of funding for included studies	yes/no	No, not mentioned	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes, adequately described	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No, not mentioned	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No, not mentioned	0.00
Q14	Heterogeneity assessed	yes/no	Yes, adequately described	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Yes, by Egger and Begg + funnel plot	1.00
Q16	Conflict of interest included	yes/no	Yes. N conflict of interest is stated.	1.00
Total score				11.00
Percent				68.75
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.32 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "MORTALITY" (*N* = 5) (cont.)**

Lovegrove, C., Ahmed, K., Challacombe, B., Khan, M.S., Popert, R. & Dasgupta, P. 2015. Systematic review of prostate cancer risk and association with consumption of fish and fish-oils: analysis of 495,321 participants. *Int J Clin Pract*, 69(1):87-105.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if higher fish consumption (C) reduced the risk of prostate cancer mortality (O).	1.00
Q2	Protocol	yes/partial yes/no	No, not mentioned	0.00
Q3	Explanation of included study design	yes/no	No	0.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partial, PubMed and Ovid, Medline	0.50
Q5	Paired study selection	yes/no	Yes, duplicate	0.00
Q6	Paired data extraction	yes/no	No, no analysis performed	0.00
Q7	List of excluded studies	yes/partial yes/no	No	0.00
Q8	Description of included studies	yes/partial yes/no	Partial	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No	0.50
Q10	Sources of funding for included studies	yes/no	No	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis performed	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No, not performed	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No	0.00
Q14	Heterogeneity assessed	yes/no	Yes	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No	0.00
Q16	Conflict of interest included	yes/no	Yes	1.00
Total score				3.50
Percent				25.00
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.32 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "MORTALITY" (*N* = 5) (cont.)**

Marckmann, P. & Grønbæk, M. 1999. Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies. *Eur J Clin Nutr*, 53(8):585-90.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if higher fish consumption (C) reduced the risk CHD mortality (O).	1.00
Q2	Protocol	yes/partial yes/no	No, not mentioned	0.00
Q3	Explanation of included study design	yes/no	No	0.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	No, only MEDLINE	0.00
Q5	Paired study selection	yes/no	No	0.00
Q6	Paired data extraction	yes/no	No	0.00
Q7	List of excluded studies	yes/partial yes/no	No	0.00
Q8	Description of included studies	yes/partial yes/no	Partial	0.50
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No	0.50
Q10	Sources of funding for included studies	yes/no	No	0.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis performed.	N/A
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No meta-analysis performed.	N/A
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes, each study was scored for scientific quality 0-6 points.	1.00
Q14	Heterogeneity assessed	yes/no	No	0.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No	0.00
Q16	Conflict of interest included	yes/no	No	0.00
Total score				3.00
Percent				21.43
Percent (exclude N/A question)				
Overall AMSTAR 2 judgement (confidence in the results)				Low
Include/exclude				Exclude

TABLE A3.32 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS WITH AMSTAR 2 FOR "MORTALITY" (*N* = 5) (cont.)**

Geelen, A., Schouten, J.M., Kamphuis, C., Stam, B.E., Burema, J., Renkema, J.M., Kampman, E. *et al.* 2007. Fish consumption, n-3 fatty acids, and colorectal cancer: a meta-analysis of prospective cohort studies. *American journal of epidemiology*, 166(10):1116-1125.				
Question domain		**Categories of answers**	**Judgement**	**Score**
Q1	Inclusion of PICO	yes/no	Yes, assessed the general (P) to investigate if higher fish consumption (C) reduced the risk of cancer mortality (O).	1
Q2	Protocol	yes/partial yes/no	No	0
Q3	Explanation of included study design	yes/no	Yes	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes	0.5
Q5	Paired study selection	yes/no	No	0
Q6	Paired data extraction	yes/no	No	1
Q7	List of excluded studies	yes/partial yes/no	No	0
Q8	Description of included studies	yes/partial yes/no	Yes	0.5
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	No	0
Q10	Sources of funding for included studies	yes/no	No	0
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes	1
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	Yes	0
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	No	0
Q14	Heterogeneity assessed	yes/no	Yes	1
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	Yes	1
Q16	Conflict of interest included	yes/no	Yes	1
Total score				8
Percent				50%
Percent (exclude n/a question)				
Overall AMSTAR 2 judgement (confidence in the results)				Moderate
Include/exclude				Include

TABLE A3.33 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "MORTALITY" (N = 16)**

Reference primary study (*n* = 16)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Iso, H., Kobayashi, M., Ishihara, J., Sasaki, S., Okada, K., Kita, Y., Kokubo, Y. & Tsugane, S. 2006. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*, 113(2): 195-202.	B	
Iso, H. & Kubota, Y. 2007. Nutrition and Disease in the Japan Collaborative Cohort Study for Evaluation of Cancer. *Asian Pacific Journal of Cancer Prevention*, 8: 35-80.	C	The study mentions mortality, but data on this is not found in any of the tables, nor is the hazard ratio for fish intake and mortality found in the study.
Jin, X., Xiong, S., Yuan, C., Gong, E., Zhang, X., Yao, Y., Leng, Y., Niu, Z., Zeng, Y. & Yan, L.L. 2021. Apolipoprotein E Genotype, Meat, Fish, and Egg Intake in Relation to Mortality Among Older Adults: A Longitudinal Analysis in China. *Front Med (Lausanne)*, 8: 697389.	C	Energy intake not included/adjusted for + no response rate
Kromhout, D., Feskens, E.J. & Bowles, C.H. 1995. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol*, 24(2): 340-5.	C	The study design is not suited to test the research hypothesis, and number of participants too low
Kurozawa, Y., Ogimoto, I., Shibata, A., Nose, T., Yoshimura, T., Suzuki, H., Sakata, R. *et al.* 2004. Dietary habits and risk of death due to hepatocellular carcinoma in a large scale cohort study in Japan. Univariate analysis of JACC study data. *Kurume Med J*, 51(2): 141-9.	C	No confounders were adjusted for; energy level was not included; multiple testing was not adjusted for
Lapidus, L., Andersson, H., Bengtsson, C. & Bosaeus, I. 1986. Dietary habits in relation to incidence of cardiovascular disease and death in women: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Am J Clin Nutr*, 44(4): 444-8.	C	Study design not suited to test the research hypothesis; study mainly designed to test the impact of diet on myocardial infarction; and results on death only an additional endpoint and not presented other than mentioned in the result briefly
Lv, Y.B., Kraus, V.B., Gao, X., Yin, Z.X., Zhou, J.H., Mao, C., Duan, J. *et al.* 2020. Higher dietary diversity scores and protein-rich food consumption were associated with lower risk of all-cause mortality in the oldest old. *Clinical Nutrition*, 39(7): 2246-2254.	C	No detailed quantitative dietary intake evaluation performed; thus impossible to adjust for energy intake in the analyses
Mozaffarian, D., Stein, P.K., Prineas, R.J. & Siscovick, D.S. 2008. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. *Circulation*, 117(9): 1130-1137.	C	Study design not suited to test the research hypothesis; incidence of fatal CHD according to differences in HRV (heart rate variability)
Pertiwi, K., Küpers, L.K., de Goede, J., Zock, P.L., Kromhout, D. & Geleijnse, J.M. 2021. Dietary and Circulating Long-Chain Omega-3 Polyunsaturated Fatty Acids and Mortality Risk After Myocardial Infarction: A Long-Term Follow-Up of the Alpha Omega Cohort. *J Am Heart Assoc*: e022617.	B	
Smit, E., Garcia-Palmieri, M.R., Figueroa, N.R., McGee, D.L., Messina, M., Freudenheim, J.L. & Crespo, C.J. 2007. Protein and legume intake and prostate cancer mortality in Puerto Rican men. *Nutrition and Cancer-an International Journal*, 58(2): 146-152.	C	Study participants had very low intake/null consumers of seafood intake, and not suitable to determine the impact from seafood intake
Streppel, M.T., Ocke, M.C., Boshuizen, H.C., Kok, F.J. & Kromhout, D. 2008. Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study. *European Heart Journal*, 29(16): 2024-2030.	B	
Sun, Y., Liu, B., Rong, S., Zhang, J., Du, Y., Xu, G., Snetselaar, L.G., Wallace, R.B., Lehmler, H.J. & Bao, W. 2021. Association of Seafood Consumption and Mercury Exposure With Cardiovascular and All-Cause Mortality Among US Adults. *JAMA Netw Open*, 4(11): e2136367.	B	
Tabak, C., Feskens, E.J.M., Heederik, D., Kromhout, D., Menotti, A., Blackburn, H.W. & Seven Countries Study, G. 1998. Fruit and fish consumption: a possible explanation for population differences in COPD mortality (the seven countries study). *European Journal of Clinical Nutrition*, 52(11): 819-825.	C	Dietary information collected only in small random samples (8 – 49) of each cohort, not for each individual
Truong-Minh, P., Fujino, Y., Kubo, T., Ide, R., Tokui, N., Mizoue, T., Ogimoto, I., Matsuda, S. & Yoshimura, T. 2009. Fish intake and the risk of fatal prostate cancer: findings from a cohort study in Japan. *Public Health Nutrition*, 12(5): 609-613.	C	BMI and energy intake not included, nor mentioned as confounders
Walda, I.C., Tabak, C., Smit, H.A., Rasanen, L., Fidanza, F., Menotti, A., Nissinen, A., Feskens, E.J.M. & Kromhout, D. 2002. Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. *European Journal of Clinical Nutrition*, 56(7): 638-643.	B	
Yamagishi, K., Iso, H., Shimazu, T., Tamakoshi, A., Sawada, N., Matsuo, K., Ito, H. *et al.* 2019. Fish intake and risk of mortality due to aortic dissection and aneurysm: A pooled analysis of the Japan cohort consortium. *Clinical Nutrition*, 38(4): 1678-1683.	C	Important confounders not identified/ascertained and considered by authors

OVERWEIGHT AND OBESITY

TABLE A3.34 QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "OVERWEIGHT AND OBESITY" (N = 7)

Reference primary study (*n* = 7)	Quality assessment (risk of bias judgement) (A, B or C)	Eventual reason for grade C
Beulen, Y. *et al.* 2018. Quality of Dietary Fat Intake and Body Weight and Obesity in a Mediterranean Population: Secondary Analyses within the PREDIMED Trial. *Nutrients*, 10(12).	B	
Cade, J.E. *et al.* 2004. The UK Women's Cohort Study: comparison of vegetarians, fish-eaters and meat-eaters. *Public Health Nutrition*, 7(7):871-878.	C	Statistical analysis is not fully described; relevant confounders were not adequately handled.
Fatahi, S. *et al.* 2019. Effect of Weight Reduction Diets Containing Fish, Walnut or Fish plus Walnut on Cardiovascular Risk Factors in Overweight and Obese Women. *Archives of Iranian Medicine*, 22(10):574-583.	C	Research question is not clearly formulated; objective is to compare the effects of walnuts, fish and the combination of the two on cardiovascular risk factors
Riseberg, E. *et al.* 2022. Specific Dietary Protein Sources Are Associated with Cardiometabolic Risk Factors in the Boston Puerto Rican Health Study. *J Acad Nutr Diet*, 122(2):298-308.	C	Research question not clearly formulated
Rosell, M. *et al.* 2006. Weight gain over 5 years in 21 966 meat-eating, fish-eating, vegetarian, and vegan men and women in EPIC-Oxford. *International Journal of Obesity*, 30(9):1389-1396.	C	Analyses not adjusted for possible confounding factors
Smith, J.D. *et al.* 2015. Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. *American Journal of Clinical Nutrition*, 101(6):1216-1224.	B	
Tørris, C. Molin, M. & Småstuen, M.C. 2017. Lean Fish Consumption Is Associated with Beneficial Changes in the Metabolic Syndrome Components: A 13-Year Follow-Up Study from the Norwegian Tromsø Study. *Nutrients*, 9(3).	B	

MORTALITY

TABLE A3.35 **QUALITY ASSESSMENT (RISK OF BIAS) OF THE 2022 VKM REPORT WITH AMSTAR-2**

VKM (Norwegian Scientific Committee for Food and Environment). 2022. Benefit and risk assessment of fish in the Norwegian diet. Scientific Opinion of the Steering Committee of the Norwegian Scientific Committee for Food and Environment. Oslo.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, page 50 in report.	1.00
Q2	Protocol	yes/partial yes/no	Yes, published in 2020.	1.00
Q3	Explanation of included study design	yes/no	Yes, pages 53-54 in report.	1.00
Q4	Comprehensive literature search strategy	yes/partial yes/no	Yes, pages 51-52 in report	1.00
Q5	Paired study selection	yes/no	Yes, page 52 in report	1.00
Q6	Paired data extraction	yes/no	No	0.00
Q7	List of excluded studies	yes/partial yes/no	No	0.00
Q8	Description of included studies	yes/partial yes/no	Yes	1.00
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Yes	1.00
Q10	Sources of funding for included studies	yes/no	Yes	1.00
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	Yes	1.00
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No	0.00
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes, only included studies graded A or B	1.00
Q14	Heterogeneity assessed	yes/no	Yes	1.00
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No	0.00
Q16	Conflict of interest included	yes/no	Yes	1.00
Total score				12.00
Percent				75%
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE"

TABLE A3.36 **OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION"**

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Allergy and immunology					
Allergic rhinitis in children	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.32: systematic reviews, n = 2; primary studies, n = 3	Limited, no conclusion	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
Allergic rhinitis in children	Early fish introduction	VKM, 2022 Section 4.32: systematic reviews, n = 1; primary studies, n = 3	Limited, no conclusion	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
Allergic sensitization in children	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.33: systematic reviews, n = 2; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Allergic sensitization in children	Child total fish intake	VKM, 2022 Section 4.33: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
Asthma in children	Maternal total, fatty and lean intake in pregnancy	VKM, 2022 Section 4.31: systematic reviews, n = 3; primary studies, n = 4	Limited, no conclusion	Systematic reviews, n = 2; primary studies, n = 0	Limited, no conclusion
Eczema in children	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.29: systematic reviews, n = 2; primary studies, n = 8	Limited, suggestive (protective)	Systematic reviews, n = 2; primary studies, n = 0	Limited, no conclusion (downgraded from VKM, 2022)
Eczema in children	Child total fish intake	VKM, 2022 Section 4.29: systematic reviews, n = 1; primary studies, n = 2	Limited, suggestive (protective for intake in the first year of life, but not later)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective for intake in the first year of life, but not later)
Multiple sclerosis	Total fish intake	VKM, 2022 Section 4.34: systematic reviews, n = 1; primary studies, n = 2	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective)
Rheumatoid arthritis	Total fish intake	VKM, 2022 Section 4.16: systematic reviews, n = 1; primary studies, n = 6	Limited, suggestive (protective)	Systematic reviews, n = 2; primary studies, n = 0	Limited, no conclusion (downgraded from VKM 2022)
Birth and growth outcomes					
Preterm birth	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.23: systematic reviews, n = 1; primary studies, n = 11 (including one pooled analysis consisting of n = 13 unique European cohort studies)	Probable (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Probable (protective effect)
Preterm birth	Maternal fatty fish intake in pregnancy	VKM, 2022 Section 4.23: systematic reviews, n = 1; primary studies, n = 4 (including one pooled analysis consisting of n = 11 European unique cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Preterm birth	Maternal lean fish intake in pregnancy	VKM, 2022 Section 4.23: systematic reviews, n = 1; primary studies, n = 4 (including one pooled analysis consisting of n = 10 European unique cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Small for gestational age	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.24: systematic reviews, n = 1; primary studies, n = 9 (including one pooled analysis consisting of n = 11 European cohort studies)	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective)
Small for gestational age	Maternal fatty fish intake in pregnancy	VKM, 2022 Section 4.24: systematic reviews, n = 1; primary studies, n = 5 (including one pooled analysis consisting of n = 11 European cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion

TABLE A3.36 **OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)**

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Small for gestational age	Maternal lean fish intake in pregnancy	VKM, 2022 Section 4.24: systematic reviews, n = 1; primary studies, n = 4 (including one pooled analysis consisting of n = 10 European cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Birth weight	Maternal total, fatty and lean fish intake in pregnancy	VKM, 2022 Section 4.26: systematic reviews, n = 0; primary studies, n = 13 (including one pooled analysis consisting of n = 13 European cohort studies)	Limited, suggestive (positive association)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (positive association)
Birth weight	Maternal fatty fish intake in pregnancy	VKM, 2022 Section 4.26: systematic reviews, n = 0; primary studies, n = 4 (including one pooled analysis consisting of n = 11 European cohort studies)	Limited, suggestive (positive association)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (positive association)
Birth weight	Maternal lean fish intake in pregnancy	VKM, 2022 Section 4.26: systematic reviews, n = 0; primary studies, n = 3 (including one pooled analysis consisting of n = 10 European cohort studies)	Limited, suggestive (positive association)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (positive association)
Low birth weight	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.25: systematic reviews, n = 1; primary studies, n = 10 (including one pooled analysis consisting of n = 13 European cohort studies)	Probable (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Probable (protective effect)
Low birth weight	Maternal fatty fish intake in pregnancy	VKM, 2022 Section 4.25: systematic reviews, n = 1; primary studies, n = 4 (including one pooled analysis consisting of n = 13 European cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Low birth weight	Maternal lean fish intake in pregnancy	VKM, 2022 Section 4.25: systematic reviews, n = 1; primary studies, n = 3 (including one pooled analysis consisting of n = 12 European cohort studies)	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
High birth weight	Maternal total, fatty and lean fish intake in pregnancy	VKM, 2022 Section 4.25: systematic reviews, n = 0; primary studies, n = 1 (including one pooled analysis consisting of n = 13 European cohort studies)	Limited, suggestive (increased risk)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (increased risk)
Birth length	Maternal total, fatty and lean fish intake in pregnancy	VKM, 2022 Section 4.27: systematic reviews, n = 0; primary studies, n = 6	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Head circumference	Maternal total, fatty and lean fish intake in pregnancy	VKM, 2022 Section 4.27: systematic reviews, n = 0; primary studies, n = 6	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Bone health					
Hip fracture	Total fish intake	VKM, 2022 Section 4.21: systematic reviews, n = 1; primary studies, n = 5	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective)
Cancer					
Liver cancer	Total fish intake	WCRF, 2018	Limited, suggestive (protective) (from WCRF, 2018)	Systematic reviews, n = 1; primary studies, n = 0	Limited, suggestive (protective)
Colorectal cancer	Total fish intake	WCRF, 2018	Limited, suggestive (protective) (from WCRF, 2018)	Systematic reviews, n = 0; primary studies, n = 3	Limited, suggestive (protective)
Nasopharyngeal cancer	Cantonese-style salted fish	WCRF, 2018	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 0	Strong evidence (increased risk)

TABLE A3.36 **OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)**

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Pancreatic cancer	Total fish intake	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
Breast cancer	Total fish intake	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
CVD					
Total cardiovascular disease	Total fish intake	VKM, 2022 Section 4.2: systematic reviews, n = 0; primary studies, n = 8	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 2	Limited, suggestive (protective effect)
Total cardiovascular disease	Fatty fish intake	VKM, 2022 Section 4.2: systematic reviews, n = 0; primary studies, n = 3	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Total cardiovascular disease	Lean fish intake	VKM, 2022 Section 4.2: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
CHD	Total fish intake	VKM, 2022 Section 4.3: systematic reviews, n = 3; Umbrella reviews, n = 2; primary studies, n = 9	Probable (protective effect)	Systematic reviews, n = 1; primary studies, n = 5	Probable (protective effect)
CHD	Fatty fish intake	VKM, 2022 Section 4.3: systematic reviews, n = 0; primary studies, n = 4	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective effect)
CHD	Lean fish intake	VKM, 2022 Section 4.3: systematic reviews, n = 0; primary studies, n = 4	Limited, suggestive (no effect)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (no effect)
CHD	Shellfish	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion
Myocardial infarction	Total fish intake	VKM, 2022 Section 4.4: systematic reviews, n = 2; Umbrella review, n = 1; primary studies, n = 8	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 2	Limited, suggestive (protective effect)
Myocardial infarction	Fatty fish intake	VKM, 2022 Section 4.4: systematic reviews, n = 0; primary studies, n = 4	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective effect)
Myocardial infarction	Lean fish intake	VKM, 2022 Section 4.4: systematic reviews, n = 0; primary studies, n =4	Limited, suggestive (no effect)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (no effect)
Total stroke	Total fish intake	VKM, 2022 Section 4.5: systematic reviews, n = 5; umbrella reviews, n = 4; primary studies, n = 14	Probably (protective effect)	Systematic reviews, n = 1; primary studies, n = 2	Probably (protective effect)
Total stroke	Fatty fish intake	VKM, 2022 Section 4.5: systematic reviews, n = 2; primary studies, n = 7	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective effect)
Total stroke	Lean fish intake	VKM, 2022 Section 4.5: systematic reviews, n = 2; primary studies, n = 7	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective effect)
Total stroke	Shellfish	VKM, 2022 Section 4.5: systematic reviews, n = 1; primary studies, n = 0	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Ischemic stroke	Total fish intake	VKM, 2022 Section 4.5: systematic reviews, n = 3; primary studies, n = 8	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 2	Limited, suggestive (protective effect)
Haemorrhagic stroke	Total fish intake	VKM, 2022 Section 4.5: systematic reviews, n = 3; primary studies, n = 8	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective effect)
Atrial fibrillation	Total fish intake	VKM, 2022 Section 4.6: systematic reviews, n = 1; primary studies, n = 5	Limited, suggestive (adverse effect)	Systematic reviews, n = 0; primary studies = 1	Limited, suggestive (adverse effect)

TABLE A3.36 **OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)**

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Atrial fibrillation	Fatty fish intake	VKM, 2022 Section 4.6: systematic reviews, n = 1; primary studies, n = 4	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Atrial fibrillation	Lean fish intake	VKM, 2022 Section 4.6: systematic reviews, n = 1; primary studies, n = 3	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective effect)
Heart failure	Total fish intake	VKM, 2022 Section 4.6: systematic reviews, n = 1; primary studies, n = 4	Limited, suggestive (protective effect)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective effect)
Venous thromboembolism	Total fish intake	VKM, 2022 Section 4.6: systematic reviews, n = 0; primary studies, n = 3	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Peripheral arterial disease	Total fish intake	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion
Peripheral arterial disease	Fatty fish intake	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion
Peripheral arterial disease	Lean fish intake	Not included in VKM, 2022	Not included in VKM, 2022	Systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion
Type 2 diabetes					
Type 2 diabetes	Total fish intake	VKM, 2022 Section 4.15: systematic reviews, n = 3; umbrella review, n = 1; primary studies, n = 16	Limited, no conclusion	Systematic reviews, n = 6; primary studies, n = 1	Limited, no conclusion
Type 2 diabetes	Fatty fish intake	VKM, 2022 Section 4.15: systematic reviews, n = 2; primary studies, n = 7	Limited, no conclusion	Systematic reviews, n = 2; primary studies, n = 0	Limited, no conclusion
Type 2 diabetes	Lean fish intake	VKM, 2022 Section 4.15: systematic reviews, n = 2; primary studies, n = 7	Limited, suggestive (no association)	Systematic reviews, n = 2; primary studies, n = 0	Limited, suggestive (no association)
Mortality					
Alzheimer's disease mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
CVD mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 2; primary studies, n = 18	Probable (protective)	Systematic reviews, n = 0; primary studies, n = 4	Probable (protective)
Total heart disease mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 2; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
CHD mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 2; primary studies, n = 18	Probable (protective)	Systematic reviews, n = 1; primary studies, n = 3	Probable (protective)
CHD mortality	Total fatty fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
CHD mortality	Total lean fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Myocardial infarction (MI) mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 5	Probable (protective)	Systematic reviews, n = 0; primary studies, n = 0	Probable (protective)
Stroke mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 12	Probable (protective)	Systematic reviews, n = 0; primary studies, n = 0	Probable (protective)
Ischemic stroke mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 6	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective)

TABLE A3.36 OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Haemorrhagic stroke mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 6	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive (protective)
Type 2 diabetes mortality	Total fish intake	VKM, 2022 Section 4.7: systematic reviews, n = 0; primary studies, n = 4	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Colorectal cancer mortality	Total fish intake	Not included in VKM report	Not included in VKM report	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
Prostate cancer-specific mortality	Total fish intake	Not included in VKM report	Not included in VKM report	Systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion
All-cause mortality	Total fish intake	VKM, 2022 Section 4.8: systematic reviews, n = 5; primary studies, n = 23	Probable (protective)	Systematic reviews, n = 0; primary studies, n = 2	Probable (protective)
All-cause mortality	Fatty fish intake	VKM, 2022 Section 4.8: systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
All-cause mortality	Fatty lean fish intake	VKM, 2022 Section 4.8: systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Neurodevelopment and neurological diseases					
Neurodevelopment in children	Maternal total fish intake in pregnancy	VKM, 2022 Section 4.9: systematic reviews, n = 1; primary studies, n = 22	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective)
Neurodevelopment in children	Maternal fatty fish intake in pregnancy	VKM, 2022 Section 4.9: systematic reviews, n = 0; primary studies, n = 4	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Neurodevelopment in children	Maternal lean fish intake in pregnancy	VKM, 2022 Section 4.9: systematic reviews, n = 0; primary studies, n = 5	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Neurodevelopment in children	Child total fish intake	VKM, 2022 Section 4.9: systematic reviews, n = 1; primary studies, n = 4	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective)
Neurodevelopment in children	Child fatty fish intake	VKM, 2022 Section 4.9: systematic reviews, n = 1; primary studies, n = 6	Limited, suggestive (protective)	Systematic reviews, n = 0; primary studies, n = 1	Limited, suggestive (protective)
Neurodevelopment in children	Child lean fish intake	VKM, 2022 Section 4.9: systematic reviews, n = 1; primary studies, n = 0	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Total fish intake	VKM, 2022 Section 4.13: systematic reviews, n = 4; umbrella review, n = 1; primary studies, n = 21	Probable (protective effect)	Systematic reviews, n = 0; primary studies, n = 0	Probable (protective effect)
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Fatty fish intake	VKM, 2022 Section 4.13: systematic reviews, n = 0; primary studies, n = 2	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Lean fish intake	VKM, 2022 Section 4.13: systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Depression and post-partum depression	Total fish intake	VKM, 2022 Section 4.14: systematic reviews, n = 4; umbrella reviews, n = 2; primary studies, n = 13	Limited, suggestive	Systematic reviews, n = 0; primary studies, n = 0	Limited, suggestive

TABLE A3.36 **OVERVIEW OF THE LITERATURE INCLUDED IN THE FINAL "WEIGHT OF EVIDENCE" FROM THE 2022 VKM REPORT AND THE SYSTEMATIC LITERATURE SEARCH FOR ALL THE HEALTH OUTCOMES IN "EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION" (cont.)**

Health outcome	Fish consumption	Literature included in 2022 VKM report in the "weight of evidence" conclusion (number of systematic reviews and primary studies in VKM, 2022)	Conclusion "weight of evidence" 2022 VKM report	Literature included in the systematic literature search in the final "weight of evidence" conclusion (number of systematic reviews and primary studies)	Final conclusion "weight of evidence" in background report (including VKM, 2022 and updated literature search)
Depression and post-partum depression	Fatty fish intake	VKM, 2022 Section 4.14: systematic reviews, n = 0; primary studies, n = 1	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Depression and post-partum depression	Lean fish intake	VKM, 2022 Section 4.14: systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 0	Limited, no conclusion
Obesity in adults					
Obesity in adults	Total fish intake	VKM, 2022 Section 4.18: systematic reviews, n = 1; primary studies, n = 3	Limited, no conclusion	Systematic reviews, n = 0; primary studies, n = 3	Limited, no conclusion

APPENDIX 4
TOXIC EFFECTS OF DIOXINS AND dl-PCBs

LITERATURE SEARCH STRATEGY

TABLE A4.1 LITERATURE SEARCH STRATEGY FOR THE SYSTEMATIC REVIEW "TOXIC EFFECTS OF DIOXINS AND dl-PCBs" IN PUBMED

Database: PubMed
Date of literature search: 16 December 2021
Literature search string:
((((((((("journal article"[Publication Type]) OR "review"[Publication Type]) OR "scientific integrity review"[Publication Type]) OR "meta analysis"[Publication Type]) OR research[Publication Type]) OR review, systematic[MeSH Terms]) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh])) AND ((((((((((((((((tetrachlorodibenzodioxin[MeSH Terms]) OR 2,3,7,8 tetrachlorodibenzo p dioxin[MeSH Terms]) OR tcdd[MeSH Terms]) OR dioxins[MeSH Terms]) OR polychlorinated biphenyls[MeSH Terms]) OR pcbs[MeSH Terms]) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]))) OR ((((((((((Tetrachlorodibenzodioxin[Title/Abstract]) OR "2,3,7,8 tetrachlorodibenzo p dioxin"[Title/Abstract]) OR TCDD*[Title/Abstract]) OR PCDD*[Title/Abstract]) OR PCDF*[Title/Abstract]) OR "Polychlorinated dibenzofuran"[Title/Abstract]) OR dioxin*[Title/Abstract]) OR "polychlorinated biphenyl*"[Title/Abstract]) OR PCB[Title/Abstract]) OR PCBs[Title/Abstract]) OR (TEQ[Title/Abstract] OR "total equivalen*"[Title/Abstract])) OR coplanar[Title/Abstract] OR "Polychlorinated dibenzodioxin"[Title/Abstract])) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]))) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]))) AND (english[Language] AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh])) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh]))))) AND ((((((((cohort study OR cohort studies[MeSH Terms])) OR (case control study OR case control studies[MeSH Terms])) OR adverse effects[MeSH Terms]) OR (cross sectional study OR cross sectional studies[MeSH Terms])) OR case reports[MeSH Terms] OR blood [MeSH Terms] OR hormones [MeSH Terms] OR serum [MeSH Terms] OR urine [MeSH Terms] OR semen[MeSH Terms])) OR (epidemiolog*[Title/Abstract] OR "cohort study"[Title/Abstract] OR "cohort studies"[Title/Abstract] OR "case control study"[Title/Abstract] OR "case control studies"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "observational study"[Title/Abstract] OR "observational studies"[Title/Abstract] OR "case series"[Title/Abstract]OR "cross sectional study"[Title/Abstract] OR "cross sectional studies"[Title/Abstract] OR "case report"[Title/Abstract]OR "case reports"[Title/Abstract] OR urine[Title/Abstract] OR serum[Title/Abstract] OR plasma [Title/Abstract] OR haema*[Title/Abstract] OR hema [Title/Abstract] OR blood [Title/Abstract] OR sperm [Title/Abstract] OR semen[Title/Abstract] OR hormone*[Title/Abstract] OR reproduct*[Title/Abstract]))) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh])) AND (english[Language] AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh])) AND ("2016/07/05"[PDat] : "2021/12/16"[PDat]) AND Humans[Mesh]))))
Total hits: 1 193

TABLE A4.2 **LITERATURE SEARCH STRATEGY FOR THE SYSTEMATIC REVIEW "TOXIC EFFECTS OF DIOXINS AND dl-PCBs" IN PUBMED**

Database: Web of Science			
Date of literature search: 16 December 2021			
# Search group	Literature search string	Search history and limitations in search	Total hits
#1 Exposure	(Tetrachlorodibenzodioxin OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin" OR TCDD OR dioxin* OR "polychlorinated biphenyl*" OR PCB$ OR TEQ OR "total equivalen*" OR coplanar OR PCDD$ OR PCDF$ OR "Polychlorinated dibenzofuran" OR Polychlorinated dibenzodioxins) (Topic)	(Tetrachlorodibenzodioxin OR "2,3,7,8-Tetrachlorodibenzo-p-dioxin" OR TCDD OR dioxin* OR "polychlorinated biphenyl*" OR PCB$ OR TEQ OR "total equivalen*" OR coplanar OR PCDD$ OR PCDF$ OR "Polychlorinated dibenzofuran" OR Polychlorinated dibenzodioxins) (Topic) and Proceedings Papers or Meeting Abstracts or Editorial Materials or Letters or Book Chapters or News Items or Poetry or Retractions or Biographical-Items or Book Reviews or Reprints or Retracted Publications or Withdrawn Publication (Exclude – Document Types) and Chinese or Korean or Spanish or Portuguese or German or Polish or French or Japanese or Russian or Italian or Turkish or Malay or Czech or Ukrainian or Croatian or Indonesian or Slovak (Exclude – Languages) Timespan: 2016-07-05 to 2021-12-13 (publication date)	19 995
#2 Population	(human OR women OR men OR child*)	(human OR women OR men OR child*) (Topic) and Meeting Abstracts or Editorial Materials or Book Reviews or Letters or Proceedings Papers or Book Chapters or News Items or Retractions or Biographical-Items or Poetry or Retracted Publications or Art Exhibit Reviews or Film Reviews or Reprints or Fiction, Creative Prose or Record Reviews or Music Performance Review or Theater Reviews or TV Review, Radio Review Videos or Dance Performance Reviews or Item Withdrawal or Bibliographies or Withdrawn Publication or Hardware Reviews or Excerpts or Software Reviews or Database Reviews (Exclude – Document Types) and Spanish or Portuguese or Russian or German or French or Turkish or Chinese or Italian or Polish or Korean or Czech or Croatian or Hungarian or Ukrainian or Japanese or Slovenian or Slovak or Unspecified or Malay or Indonesian or Norwegian or Greek or Bulgarian or Afrikaans or Catalan or Dutch or Lithuanian or Arabic or Icelandic or Estonian or Serbian or Swedish or Persian or Danish or Galician or Welsh or Basque or Eskimo or Georgian or Latin or Samoan or Zulu or Hebrew or Urdu (Exclude – Languages) Timespan: 2016-07-05 to 2021-12-13 (publication date)	1 894 550
#3	#1 AND #2	Timespan: 2016-07-05 to 2021-12-13 (Publication Date)	3 692
#4 Outcome	(epidemiolog* OR "cohort stud*" OR "case control stud* " OR "adverse effect*" OR "observational stud*" OR "case serie*" OR "case report*" OR "cross sectional stud*" OR urine OR serum OR plasma OR haema* OR hema* OR blood OR sperm OR semen OR hormone* OR reproduct*)	(epidemiolog* OR "cohort stud*" OR "case control stud* " OR "adverse effect*" OR "observational stud*" OR "case serie*" OR "case report*" OR "cross sectional stud*" OR urine OR serum OR plasma OR haema* OR hema* OR blood OR sperm OR semen OR hormone* OR reproduct*) (Topic) and Meeting Abstracts or Editorial Materials or Letters or Proceedings Papers or Book Chapters or Book Reviews or News Items or Retractions or Retracted Publications or Biographical-Items or Reprints or Poetry or Film Reviews or Hardware Reviews or Withdrawn Publication or Art Exhibit Reviews or Bibliographies or Music Performance Review or Fiction, Creative Prose or Item Withdrawal or Record Reviews or Excerpts or TV Review, Radio Review Videos or Meeting Summary or Software Reviews or Theater Reviews (Exclude – Document Types) and Spanish or German or French or Russian or Portuguese or Chinese or Turkish or Polish or Korean or Italian or Hungarian or Czech or Japanese or Ukrainian or Indonesian or Greek or Slovak or Croatian or Icelandic or Norwegian or Arabic or Malay or Dutch or Persian or Slovenian or Unspecified or Catalan or Danish or Welsh or Esperanto or Afrikaans or Bulgarian or Estonian or Serbian or Galician or Lithuanian or Eskimo or Swedish or Serbo Croatian or Basque or Hebrew or Samoan (Exclude – Languages) Timespan: 2016-07-05 to 2021-12-13 (publication date)	1 739 115
#5	#3 AND #4	Timespan: 2016-07-05 to 2021-12-13 (publication date)	1 577

LIST OF EXCLUDED RECORDS DURING FULL-TEXT SCREENING

TABLE A4.3 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 32)	Reason for exclusion
Aghaei, M., Janjani, H., Yousefian, F., Jamal, A., & Yunesian, M. 2019. Association between ambient gaseous and particulate air pollutants and attention deficit hyperactivity disorder (ADHD) in children; a systematic review. *Environmental Research*, *173*, 135-156.	None of the included studies published after 2016 were relevant for our purpose.
Cano-Sancho, G., Ploteau, S., Matta, K., Adoamnei, E., Louis, G. B., Mendiola, J., Antignac, J.P. *et al.* 2019. Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: Systematic review and meta-analysis. *Environment International*, *123*, 209-223.	Only one of the included 17 studies in the review was relevant for our purpose (and this was included in the primary studies).
Edwards, D., Voronina, A., Attwood, K., & Grand'Maison, A. 2021. Association between occupational exposures and sarcoma incidence and mortality: systematic review and meta-analysis. *Systematic Reviews*, *10*, 1-19.	Studies that are relevant for our purpose were published before 2009.
Ennour-Idrissi, K., Ayotte, P., & Diorio, C. 2019. Persistent organic pollutants and breast cancer: a systematic review and critical appraisal of the literature. *Cancers*, *11*(8), 1063.	Only one of the included studies in the review was relevant for our purpose (and this was included in the primary studies).
Fernández-Martínez, N. F., Ching-Lopez, A., de Labry Lima, A. O., Salamanca-Fernández, E., Pérez-Gómez, B., Jiménez-Moleón, J. J., Rodríguez-Barranco, M. *et al.* 2020. Relationship between exposure to mixtures of persistent, bioaccumulative, and toxic chemicals and cancer risk: A systematic review. *Environmental Research*, *188*, 109787.	None of the included studies were relevant for our purpose.
Fiolet, T., Mahamat-Saleh, Y., Frenoy, P., Kvaskoff, M., & Mancini, F.R. 2021. Background exposure to polychlorinated biphenyls and all-cause, cancer-specific, and cardiovascular-specific mortality: A systematic review and meta-analysis. *Environment International*, *154*, 106663.	None of the included studies were relevant for our purpose (mono-ortho only).
Kadawathagedara, M, de Lauzon-Guillain, B. & Botton, J. 2018. Environmental contaminants and child's growth. *J Dev Orig Health Dis*, 9:632-641.	Not a systematic review.
Kahn, L. G., Harley, K. G., Siegel, E. L., Zhu, Y., Factor-Litvak, P., Porucznik, C. A., Program Collaborators for Environmental Influences on Child Health Outcomes Program. *et al.* 2021. Persistent organic pollutants and couple fecundability: a systematic review. *Human Reproduction Update*, *27*(2), 339-366.	None of the included studies were relevant for our purpose.
Lefebvre, T., Fréour, T., Ploteau, S., Le Bizec, B., Antignac, J. P., & Cano-Sancho, G. 2021. Associations between human internal chemical exposure to Persistent Organic Pollutants (POPs) and In Vitro Fertilization (IVF) outcomes: Systematic review and evidence map of human epidemiological evidence. *Reproductive Toxicology*, *105*, 184-197.	Only one of the included studies in the review was relevant for our purpose (and this is included in the primary studies).
Mallozzi, M., Leone, C., Manurita, F., Bellati, F., & Caserta, D. 2017. Endocrine disrupting chemicals and endometrial cancer: an overview of recent laboratory evidence and epidemiological studies. *International Journal of Environmental Research and Public Health*, *14*(3), 334.	All studies included in the review were published before 2016.
Matta, K., Koual, M., Ploteau, S., Coumoul, X., Audouze, K., Le Bizec, B., ... & Cano-Sancho, G. 2021. Associations between exposure to organochlorine chemicals and endometriosis: a systematic review of experimental studies and integration of epidemiological evidence. *Environmental Health Perspectives*, *129*(7), 076003.	Only included animal studies.
Meltzer, G. Y., Watkins, B. X., Vieira, D., Zelikoff, J. T., & Boden-Albala, B. 2020. A systematic review of environmental health outcomes in selected American Indian and Alaska Native populations. *Journal of racial and ethnic health disparities*, *7*, 698-739.	Only one of the included studies in the review was relevant for our purpose (and this is included in the primary studies).
Mouly, T. A., & Toms, L. M. L. 2016. Breast cancer and persistent organic pollutants (excluding DDT): a systematic literature review. *Environmental Science and Pollution Research*, *23*, 22385-22407.	Includes only studies published between 2006 and 2015.
Nelson, W., Liu, D. Y., Yang, Y., Zhong, Z. H., Wang, Y. X., & Ding, Y. B. 2020. In utero exposure to persistent and nonpersistent endocrine-disrupting chemicals and anogenital distance. A systematic review of epidemiological studies. *Biology of Reproduction*, *102*(2), 276-291.	Studies that were relevant for our purpose were published before 2016.
Peinado, F. M., Artacho-Cordón, F., Barrios-Rodríguez, R., & Arrebola, J. P. 2020. Influence of polychlorinated biphenyls and organochlorine pesticides on the inflammatory milieu. A systematic review of in vitro, in vivo and epidemiological studies. *Environmental Research*, *186*, 109561.	Not relevant papers according to criteria.
Poole, C.J.M. & Basu, S. 2017. Systematic Review: Occupational illness in the waste and recycling sector. *Occup Med (Lond)*, 67:626-636.	Includes only studies published between 1997 and 2015.
Raffetti, E., Donat-Vargas, C., Mentasti, S., Chinotti, A., & Donato, F. 2020. Association between exposure to polychlorinated biphenyls and risk of hypertension: A systematic review and meta-analysis. *Chemosphere*, *255*, 126984.	Only four of the included studies were relevant for our purpose (and these were included in the primary studies).
Ribeiro, C. M., Beserra, B. T. S., Silva, N. G., Lima, C. L., Rocha, P. R. S., Coelho, M. S., Amato, A. A. *et al.* 2020. Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis. *BMJ Open*, *10*(6), e033509.	Only two of the included studies were relevant for our purpose (and these are included in the primary studies).

LIST OF EXCLUDED RECORDS DURING FULL-TEXT SCREENING

TABLE A4.3 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)

Study (n = 32)	Reason for exclusion
Rivollier, F. Krebs, M.O. & Kebir, O. 2019. Perinatal Exposure to Environmental Endocrine Disruptors in the Emergence of Neurodevelopmental Psychiatric Diseases: A Systematic Review. *International Journal of Environmental Research and Public Health*, 16:19.	Only two of the included 47 studies in the review were relevant for our purpose (and these were included in the primary studies).
Rocha, P. R. S., Oliveira, V. D., Vasques, C. I., Dos Reis, P.E.D., & Amato, A.A. 2021. Exposure to endocrine disruptors and risk of breast cancer: a systematic review. *Critical Reviews In Oncology/Hematology*, *161*, 103330.	Only one of the included studies in the review was relevant for our purpose (and this is included in the primary studies).
Singh, N. Ogunseitan, O.A. & Tang, Y.Y. 2021. Systematic review of pregnancy and neonatal health outcomes associated with exposure to e-waste disposal. *Critical Reviews in Environmental Science and Technology*, 51:2424-2448.	Only two of the included 27 studies in the review were relevant for our purpose (and these are included in the primary studies).
Sirohi, D. Al Ramadhani, R. & Knibbs, L.D. 2021. Environmental exposures to endocrine disrupting chemicals (EDCs) and their role in endometriosis: a systematic literature review. *Rev Environ Health*, 36:101-115.	Only one of the included 29 studies in the review was relevant for our purpose (and this is included in the primary studies).
Tsai, M. S., Chen, M. H., Lin, C. C., Liu, C. Y., & Chen, P.C. 2019. Children's environmental health based on birth cohort studies of Asia (2)–air pollution, pesticides, and heavy metals. *Environmental research*, *179*, 108754.	No relevant studies included, as the study did not cover dioxins and dl-PCBs.
Tsai, M. S., Chen, M. H., Lin, C. C., Ng, S., Hsieh, C. J., Liu, C. Y., Chen, P. C. *et al.* 2017. Children's environmental health based on birth cohort studies of Asia. *Science of the Total Environment*, *609*, 396-409.	Includes only studies published before 2015.
Wan, M.L.Y. Co, V.A. & El-Nezami, H. 2021. Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. *Critical Reviews in Food Science and Nutrition*, 28.	None of the included studies in the review was relevant for our purpose.
Wang, Y., Hollis-Hansen, K., Ren, X., Qiu, Y., & Qu, W. J. O. R. 2016. Do environmental pollutants increase obesity risk in humans?. *Obesity reviews*, *17*(12), 1179-1197.	Only included studies published before 2016.
Wikoff, D. S., Urban, J. D., Ring, C., Britt, J., Fitch, S., Budinsky, R., & Haws, L. C. 2021. Development of a range of plausible noncancer toxicity values for 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin based on effects on sperm count: Application of systematic review methods and quantitative integration of dose response using meta-regression. *Toxicological Sciences*, *179*(2), 162-182.	Mainly focuses on animal studies.
Xu, J., Ye, Y., Huang, F., Chen, H., Wu, H., Huang, J., Wu, Y. *et al.* 2016. Association between dioxin and cancer incidence and mortality: a meta-analysis. *Scientific Reports*, *6*(1), 1-17.	All studies were published before 2015.
Zani, C., Ceretti, E., Covolo, L., & Donato, F. 2017. Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of cutaneous melanoma and non-Hodgkin lymphoma. *Chemosphere*, *183*, 97-106.	All studies were published before 2015.
Zeinomar, N., Oskar, S., Kehm, R. D., Sahebzeda, S., & Terry, M. B. 2020. Environmental exposures and breast cancer risk in the context of underlying susceptibility: A systematic review of the epidemiological literature. *Environmental research*, *187*, 109346.	Only two of the included studies were relevant for our purpose (and these are included in the primary studies).
Zeng, Z., Ngai, S., Wang, Q., Liang, W., & Huo, X. 2021. Early-life exposure to widespread environmental toxicants and children's health risks: A focus on the post-vaccination antibody potency or immunoglobulin levels. *Science of The Total Environment*, *781*, 146714.	No relevant studies were included.
Zou, H., Lin, Y., Yang, L., Ou, C., Geng, F., Wang, Y., Sun, Y. *et al.* 2019. Neonatal weight and prenatal exposure to polychlorinated biphenyls: a meta-analysis. *Asian Pacific Journal of Cancer Prevention: APJCP*, *20*(11), 3251.	All studies were published before 2015.

TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA**

Study (n = 283)
Abellan, A. *et al.* 2019. Prenatal exposure to organochlorine compounds and lung function during childhood. *Environ Int*, 131:105049.
Alampi, J.D. *et al.* 2021. Association Between Gestational Exposure to Toxicants and Autistic Behaviors Using Bayesian Quantile Regression. *American Journal of Epidemiology*, 190(9):1803-1813.
Aminov, Z. *et al.* 2016. Diabetes Prevalence in Relation to Serum Concentrations of Polychlorinated Biphenyl (PCB) Congener Groups and Three Chlorinated Pesticides in a Native American Population. *Environ Health Perspect*, 124(9):1376-83.
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TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

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TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

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TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

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TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

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TABLE A4.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECT OF DIOXINS AND dl-PCBs" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

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TABLE A4.5 PRIMARY STUDIES EXCLUDED AS THEY HAD ALREADY BEEN ASSESSED IN THE DIOXIN RISK ASSESSMENTS IN EFSA 2018

Study (n = 11)
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QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS IN "TOXIC EFFECTS OF DIOXINS AND dl-PCBs"

TABLE A4.6 QUALITY ASSESSMENT (RISK OF BIAS) OF THE RISK ASSESSMENT REPORT OF DIOXINS FROM (EFSA, 2018) WITH THE QUALITY ASSESSMENT TOOL AMSTAR 2

EFSA. 2018. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA Journal*, 16(11):e05333.				
Question domain		Categories of answers	Judgement	Score
Q1	Inclusion of PICO	yes/no	Yes, defined population, intervention (exposure), control group and outcome	1
Q2	Protocol	yes/partial yes/no	Yes, protocol published in 2016.	1
Q3	Explanation of included study design	yes/no	Yes, included both human and animal studies as there is a low number of human studies available.	1
Q4	Comprehensive literature search strategy	yes/partial yes/no	Partial yes	0.5
Q5	Paired study selection	yes/no	Yes	1
Q6	Paired data extraction	yes/no	Yes	1
Q7	List of excluded studies	yes/partial yes/no	Yes	1
Q8	Description of included studies	yes/partial yes/no	Partial yes	0.5
Q9	Risk-of-bias tool	yes/partial yes/no/includes only RCTs or NRSI	Partial yes	0.5
Q10	Sources of funding for included studies	yes/no	Yes	1
Q11	Appropriate statistical methods in meta-analysis	yes/no/no meta-analysis conducted	No meta-analyses conducted	n/a
Q12	Impact of risk of bias in meta-analysis	yes/no/no meta-analysis conducted	No meta-analyses conducted	n/a
Q13	Impact of risk of bias in individual studies when interpreting results	yes/no	Yes, OHAT analyses included.	1
Q14	Heterogeneity assessed	yes/no	Not mentioned in the report.	0
Q15	Publication bias assessed	yes/no/no meta-analysis conducted	No meta-analyses conducted	n/a
Q16	Conflict of interest included	yes/no	Yes, implicit in being an EFSA expert.	1
Total score				10.5
Percent				66%
Percent (exclude n/a questions)				81%
Overall AMSTAR 2 judgement (confidence in the results)				High
Include/exclude				Include

QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES

TABLE A4.7 QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs", USING THE QUALITY ASSESSMENT TOOL OF THE OHAT (OFFICE OF HEALTH ASSESSMENT AND TRANSLATION)

Study	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Alvarez-Silvares E, Fernández-Cruz T, Domínguez-Vigo P, *et al.* 2021. Association between placenta concentrations polybrominated and polychlorinated biphenyls and gestational diabetes mellitus: a case-control study in northwestern Spain. *Environ Sci Pollut Res Int*, 28:10292-10301.	- -	+ +	+ +	-	-	-	-	Tier 2
Alvarez-Silvares E, Rubio-Cid P, Gonzalez-Gomez X, *et al.* 2021. Determination of organic pollutants in meconium and its relationship with fetal growth. Case control study in Northwestern Spain. *Journal of Perinatal Medicin*e, 49:884-896.	-	-	+ +	+	+	-	- -	Tier 2
Ames J, Warner M, Brambilla P, *et al.* 2018. Neurocognitive and physical functioning in the Seveso Women's Health Study. *Environ Res*, 162:55-62.	-	-	+	+	-	+	-	Tier 2
Ames, J., Warner, M., Mocarelli, P., *et al.* 2018. AHR gene-dioxin interactions and birthweight in the Seveso Second Generation Health Study. *Int J Epidemiol*, 7:1992-2004.	-	+	+	+	+ +	+ +	+	Tier 2
Ames, J, Warner, M, Siracusa C, *et al.* 2019. Prenatal dioxin exposure and neuropsychological functioning in the Seveso Second Generation Health Study. *Int J Hyg Environ Health*, 222:425-433.	-	+	+ +	+	+ +	+ +	+ +	Tier 2
Aminov, Z. & Carpenter, D.O. 2020. Serum concentrations of persistent organic pollutants and the metabolic syndrome in Akwesasne Mohawks, a Native American community. *Environ Pollut*, 260:114004.	+	+ +	- -	+	+ +	+ +	+ +	Tier 2
Anh LT, Kido T, Seijiro HB, *et al.* 2017. A relationship in adrenal androgen levels between mothers and their children from a dioxin-exposed region in Vietnam. *Science of the Total Environment*, 607:32-41.	- -	-	+ +	-	+ +	+ +	-	Tier 2
Baba T, Ito S, Yuasa M, *et al.* 2018. Association of prenatal exposure to PCDD/Fs and PCBs with maternal and infant thyroid hormones: The Hokkaido Study on Environment and Children's Health. *Sci Total Environ*, 615:1239-1246.	+ +	+	+	+	-	+ +	+	Tier 1
Boda H, Nghi TN, Nishijo M, *et al.* 2018. Prenatal dioxin exposure estimated from dioxins in breast milk and sex hormone levels in umbilical cord blood in Vietnamese newborn infants. *Science of the Total Environment*, 615:1312-1318.	+	+ +	+ +	+	+	+ +	+ +	Tier 1
Burns JS, Williams PL, Sergeyev O, *et al.* 2020. Associations of peri-pubertal serum dioxins and polychlorinated biphenyls with growth and body composition among Russian boys in a longitudinal cohort. *Int J Hyg Environ Health*, 223:228-237.	-	+	+	+	+	+	-	Tier 2
Chessa MA, La Placa M, Patrizi A, *et al.* 2021. Chloracne: a case series on cutaneous expression of CYP1A1 as diagnostic biomarker. *Clin Exp Dermatol*, 46:896-900.	- -	-	-	-	+	+ +	-	Tier 3
Chu CP, Wu SW, Huang YJ, *et al.* 2019. Neuroimaging signatures of brain plasticity in adults with prenatal exposure to polychlorinated biphenyls: Altered functional connectivity on functional MRI. *Environ Pollut*, 250:960-968.	-	-	+	+	+	+ +	-	Tier 2
Collins JJ, Bodner KM, Aylward LL, *et al.* 2016. Mortality risk among workers with exposure to dioxins. *Occup Med (Lond)*, 66:706-712.	- -	-	-	-	-	-	-	Tier 3
Donat-Vargas C, Moreno-Franco B, Laclaustra M, *et al.* 2020. Exposure to dietary polychlorinated biphenyls and dioxins, and its relationship with subclinical coronary atherosclerosis: The Aragon Workers' Health Study. *Environ Int*, 136:105433.	+	-	+ +	+	+	+	+	Tier 2
Dong JJ, Ruan MC, Hang JG, *et al.* 2020. The relationship between perinatal exposure to dioxins and serum steroid hormone levels in preschool-aged children at an e-waste region in China. *Int J Hyg Environ Health*, 229:113580.	-	-	+ +	+	+	+	-	Tier 2
Eskenazi B, Ames J, Rauch S, *et al.* 2021. Dioxin exposure associated with fecundability and infertility in mothers and daughters of Seveso, Italy. *Hum Reprod*, 36:794-807.	+	+	-	+ +	+ +	-	+	Tier 2
Fukushi J, Tsushima H, Matsumoto Y, *et al.* 2019. Influence of dioxin-related compounds on physical function in Yusho incident victims. *Heliyon*, 5:7.	-	+ +	+	+	+ +	+ +	-	Tier 2

TABLE A4.7 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs", USING THE QUALITY ASSESSMENT TOOL OF THE OHAT (OFFICE OF HEALTH ASSESSMENT AND TRANSLATION) (cont.)**

Study	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Henriquez-Hernandez LA, Boada LD, Perez-Arellano JL, *et al.* 2016. Relationship of polychlorinated biphenyls (PCBs) with parasitism, iron homeostasis, and other health outcomes: Results from a cross-sectional study on recently arrived African immigrants. *Environmental Research*, 50:549-556.	-	-	-	-	+	+	-	Tier 3
Huang CY, Lee CC, Chang JW, *et al.* 2017. Association Between Dioxin and Metabolic Syndrome by Age and Sex in an Endemic Area of Exposure in Taiwan. *Epidemiology*, 28:S82-s88.	-	+ +	+	+	+ +	+ +	-	Tier 2
Hui LL, Lam HS, Lau EYY, *et al.* 2016. Prenatal dioxin exposure and neurocognitive development in Hong Kong 11-year-old children. *Environ Res*, 150:205-212.	+	-	+	-	+	+ +	-	Tier 2
Kelsey KT, Rytel M, Dere E, *et al.* 2019. Serum dioxin and DNA methylation in the sperm of operation ranch hand veterans exposed to Agent Orange. *Environ Health*, 18:91.	+	-	-	+	+ +	+	-	Tier 2
Kobayashi S, Sata F, Miyashita C, *et al.* 2017. Dioxin-metabolizing genes in relation to effects of prenatal dioxin levels and reduced birth size: The Hokkaido study. *Reprod Toxicol*, 67:111-116.	+ +	+ +	+ +	+ +	+ +	+ +	+ +	Tier 1
Kondo H, Tanio K, Nagaura Y, *et al.* 2018. Sleep disorders among Yusho patients highly intoxicated with dioxin-related compounds: A 140-case series. *Environ Res*, 166:261-268.	-	+ +	+	+ +	+	+	-	Tier 2
Koual M, Cano-Sancho G, Bats AS, *et al.* 2019. Associations between persistent organic pollutants and risk of breast cancer metastasis. *Environ Int*, 132:105028.	+	+ +	+ +	+ +	+ +	+ +	+ +	Tier 1
Lambertino A, Persky V, Freels S, *et al.* 2021. Associations of PCBS, dioxins and furans with follicle-stimulating hormone and luteinizing hormone in postmenopausal women: National Health and Nutrition Examination Survey 1999-2002. *Chemosphere*, 262:128309.	+	+ +	+	+	+	+ +	-	Tier 1
Leijs MM, Esser A, Amann PM, *et al.* 2018. Hyperpigmentation and higher incidence of cutaneous malignancies in moderate-high PCB- and dioxin exposed individuals. *Environ Res*, 164:221-228.	-	+	+	+	-	+	+	Tier 2
Leijs MM, Koppe JG, Olie K, *et al.* 2018. Exposure to Environmental Contaminants and Lung Function in Adolescents-Is There a Link? *Int J Environ Res Public*, Health 2018.	-	+	+	-	-	+	-	Tier 2
Li ZM, Albrecht M, Fromme H, *et al.* 2020. Persistent Organic Pollutants in Human Breast Milk and Associations with Maternal Thyroid Hormone Homeostasis. *Environ Sci Technol*, 54:1111-1119.	+	+	+	+	+	+ +	+	Tier 1
Li ZM, Hernandez-Moreno D, Main KM, *et al.* 2018. Association of In Utero Persistent Organic Pollutant Exposure With Placental Thyroid Hormones. *Endocrinology*, 159:3473-3481.	+	+	+	+	+	+	-	Tier 1
Liang YS, Tang Z, Jiang YS, *et al.* 2021. Lipid metabolism disorders associated with dioxin exposure in a cohort of Chinese male workers revealed by a comprehensive lipidomics study. *Environment International*, 155:10.	+	-	+	+	+	-	-	Tier 2
Liang YS, Tang Z, Jiang YS, *et al.* 2020. Serum metabolic changes associated with dioxin exposure in a Chinese male cohort. *Environment International*, 143:9.	+	-	+	+	+	-	-	Tier 2
Lim JE, Lee S, Lee S, *et al.* 2018. Serum persistent organic pollutants levels and stroke risk. *Environ Pollut*, 233:855-861.	-	+	+ +	-	+	-	-	Tier 2
Lim JE, Nam C, Yang J, *et al.* 2017. Serum persistent organic pollutants (POPs) and prostate cancer risk: A case-cohort study. *Int J Hyg Environ Health*, 220:849-856.	+	+ +	+ +	-	+ +	-	-	Tier 1
Liu X, Zhang L, Li JG, *et al.* 2019. Relative Effect Potency Estimates for Dioxin-Like Compounds in Pregnant Women with Gestational Diabetes Mellitus and Blood Glucose Outcomes Based on a Nested Case-control Study. *Environmental Science & Technology*, 53:7792-7802.	+ +	+ +	+ +	+ +	+	+ +	+ +	Tier 1
Luong HV, Tai P, Nishijo M, *et al.* 2018. Association of dioxin exposure and reproductive hormone levels in men living near the Bien Hoa airbase, Vietnam. *Science of the Total Environment*, 628:484-489.	+	+ +	+	+ +	+ +	+ +	-	Tier 1

TABLE A4.7 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs", USING THE QUALITY ASSESSMENT TOOL OF THE OHAT (OFFICE OF HEALTH ASSESSMENT AND TRANSLATION) (cont.)**

Study	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Mannetje AT, Eng A, Walls C, *et al.* 2018. Morbidity in New Zealand pesticide producers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Environ Int*, 110:22-31.	-	+	+	+ +	-	+ +	-	Tier 2
Matovu H, Li ZM, Henkelmann B, *et al.* 2021. Multiple persistent organic pollutants in mothers' breastmilk: Implications for infant dietary exposure and maternal thyroid hormone homeostasis in Uganda, East Africa. *Sci Total Environ*, 770:145262.	-	+	+	+	-	+ +	-	Tier 2
Matta K, Vigneau E, Cariou V, *et al.* 2020. Associations between persistent organic pollutants and endometriosis: A multipollutant assessment using machine learning algorithms. *Environ Pollut*, 260:114066.	-	+	+ +	+	+ +	+ +	-	Tier 2
Mattonet K, Nowack-Weyers N, Vogel V, *et al.* 2022. Prenatal exposure to endocrine disrupting chemicals is associated with altered DNA methylation in cord blood. *Epigenetics*, 17(9):935-952.	-	+	+	+ +	+ +	+ +	-	Tier 2
McBride D, Lovelock K, Shepherd D, *et al.* 2016. Community exposure to hazardous site remediation in rural New Zealand: an exposed-referent study of serum dioxins and health effects. *Aust N Z J Public Health*, 40:412-417.	+	- -	+	+ +	+	-	-	Tier 2
McBride DI, Collins JJ, Bender TJ, *et al.* 2018. Cohort study of workers at a New Zealand agrochemical plant to assess the effect of dioxin exposure on mortality. *BMJ Open*, 8:e019243.	-	-	+	+	+	+	+	Tier 2
Miyashita C, Araki A, Mitsui T, *et al.* 2018. Sex-related differences in the associations between maternal dioxin-like compounds and reproductive and steroid hormones in cord blood: The Hokkaido study. *Environ Int*, 117:175-185.	+ +	+ +	+	-	+ +	+ +	+ +	Tier 1
Miyashita C, Bamai YA, Araki A, *et al.* 2018. Prenatal exposure to dioxin-like compounds is associated with decreased cord blood IgE and increased risk of wheezing in children aged up to 7years: The Hokkaido study. *Sci Total Environ*, 610:191-199.	-	+ +	-	-	+ +	+ +	+	Tier 2
Nghiem GT, Nishijo M, Pham TN, *et al.* 2019. Adverse effects of maternal dioxin exposure on fetal brain development before birth assessed by neonatal electroencephalography (EEG) leading to poor neurodevelopment; a 2-year follow-up study. *Sci Total Environ*, 667:718-729.	-	+ +	+ +	-	+ +	+ +	-	Tier 2
Nguyen ATN, Nishijo M, Pham TT, *et al.* 2018. Sex-specific effects of perinatal dioxin exposure on eating behavior in 3-year-old Vietnamese children. *BMC Pediatr*, 18:213.	-	+ +	+	-	+	+ +	-	Tier 2
Nwanaji-Enwerem JC, Jenkins TG, Colicino E, *et al.* 2020. Serum dioxin levels and sperm DNA methylation age: Findings in Vietnam war veterans exposed to Agent Orange. *Reproductive Toxicology*, 96:27-35.	-	-	-	- -	+ +	+ +	-	Tier 3
Oanh NTP, Kido T, Honma S, *et al.* 2018. Androgen disruption by dioxin exposure in 5-year-old Vietnamese children: Decrease in serum testosterone level. *Sci Total Environ*, 640:466-474.	+	+	+ +	-	+	+ +	+	Tier 1
Oyama Y, Phuc HD, Honma S, *et al.* 2021. Decreased serum testosterone levels associated with 17 beta-hydroxysteroid dehydrogenase activity in 7-year-old children from a dioxin-exposed area of Vietnam. *Science of the Total Environment*, 783:11.	+	+	+	-	+	+ +	+	Tier 1
Pan WY, Yin SS, Ye XQ, *et al.* 2019. Supporting dataset and methods for serum concentrations of selected persistent organic pollutants measured in women with primary ovarian insufficiency. *Data in Brief*, 26:11.	- -	+ +	+ +	+	+ +	+ +	+ +	Tier 2
Patel CJ, Manrai AK, Corona E, *et al.* 2017. Systematic correlation of environmental exposure and physiological and self-reported behaviour factors with leukocyte telomere length. *Int J Epidemiol*, 46:44-56.	+	-	+	-	+	+ +	- -	Tier 2
Paul R, Moltó J, Ortuño N, *et al.* 2017. Relationship between serum dioxin-like polychlorinated biphenyls and post-testicular maturation in human sperm. *Reprod Toxicol*, 73:312-321.	+	+ +	+ +	+	+ +	+ +	-	Tier 1
Pavuk M, Serio TC, Cusack C, *et al.* 2019. Hypertension in Relation to Dioxins and Polychlorinated Biphenyls from the Anniston Community Health Survey Follow-Up. *Environ Health Perspect*, 127:127007.	-	+	+	-	-	+	-	Tier 2
Pelcl T, Skrha J, Jr. Prazny M, *et al.* 2018. Diabetes, Cardiovascular Disorders and 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Body Burden in Czech Patients 50 Years After the Intoxication. *Basic Clin Pharmacol Toxicol*, 123:356-359.	-	+	+	-	+	+ +	- -	Tier 2
Pelclova D, Navratil T, Vlckova S, *et al.* 2018. Exhaled breath condensate biomarkers reflect systemic changes in patients with chronic dioxin intoxication. *Monatshefte Fur Chemie*, 149:1579-1586.	-	+	+	-	+	+ +	- -	Tier 2

TABLE A4.7 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs", USING THE QUALITY ASSESSMENT TOOL OF THE OHAT (OFFICE OF HEALTH ASSESSMENT AND TRANSLATION) (cont.)**

Study	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Pelclova D, Urban P, Fenclova Z, *et al.* 2018. Neurological and Neurophysiological Findings in Workers with Chronic 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Intoxication 50 Years After Exposure. *Basic Clin Pharmacol Toxicol*, 122:271-277.	-	+	+	-	+	+ +	- -	Tier 2
Petriello MC, Charnigo R, Sunkara M, *et al.* 2018. Relationship between serum trimethylamine N-oxide and exposure to dioxin-like pollutants. *Environ Res*, 162:211-218.	+	+	-	+	+ +	-	-	Tier 2
Petrosino V, Motta G, Tenore G, *et al.* 2018. The role of heavy metals and polychlorinated biphenyls (PCBs) in the oncogenesis of head and neck tumors and thyroid diseases: a pilot study. *Biometals*, 31:285-295.	- -	- -	-	- -	-	- -	- -	Tier 3
Pham NT, Nishijo M, Nghiem TTG, *et al.* 2021. Effects of perinatal dioxin exposure on neonatal electroencephalography (EEG) activity of the quiet sleep stage in the most contaminated area from Agent Orange in Vietnam. *Int J Hyg Environ Health*, 232:113661.	+	+	+	+	+	+	-	Tier 1
Pham The T, Pham Ngoc T, Hoang Van T, *et al.* 2020. Effects of perinatal dioxin exposure on learning abilities of 8-year-old children in Vietnam. *Int J Hyg Environ Health*, 223:132-141.	-	-	-	+	+	-	-	Tier 3
Pham TN, Nishijo M, Pham TT, *et al.* 2020. Dioxin exposure and sexual dimorphism of gaze behavior in prepubertal Vietnamese children living in Da Nang, a hot spot for dioxin contamination. *Science of the Total Environment*, 749:10.	-	+	-	+	+	+	-	Tier 2
Pilsner JR, Shershebnev A, Medvedeva YA, *et al.* 2018. Peripubertal serum dioxin concentrations and subsequent sperm methylome profiles of young Russian adults. *Reprod Toxicol*, 78:40-49.	-	-	-	-	-	-	- -	Tier 3
Rahbar MH, Swingle HM, Christian MA, *et al.* 2017. Environmental Exposure to Dioxins, Dibenzofurans, Bisphenol A, and Phthalates in Children with and without Autism Spectrum Disorder Living near the Gulf of Mexico. *Int J Environ Res Public Health*, 14(11):1425	- -	+ +	+ +	-	+ +	+ +	- -	Tier 2
Rytel MR, Butler R, Eliot M, *et al.* 2021. DNA methylation in the adipose tissue and whole blood of Agent Orange-exposed Operation Ranch Hand veterans: a pilot study. *Environ Health*, 20:43.	-	+	+	- -	+ +	+	-	Tier 2
Samer CF, Gloor Y, Rollason V, *et al.* 2020. Cytochrome P450 1A2 activity and incidence of thyroid disease and cancer after chronic or acute exposure to dioxins. *Basic Clin Pharmacol Toxicol*, 126:296-303.	-	- -	-	+	+	+	- -	Tier 3
Shi LL, Wang MQ, Nakayama SF, *et al.* 2020. The association between dioxins and steroid hormones in general adult males: a cross-sectional study in an e-waste region of China. *Environ Sci Pollut Res Int*, 27:26511-26519.	+	+ +	+ +	+	+	+	+	Tier 1
Slama N, Warner M, Mocarelli P, *et al.* 2019. The 2nd to 4th digit length ratio (2D:4D) among children of Seveso women exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Early Hum Dev*, 131:45-50.	-	-	- -	+	+	+ +	+	Tier 3
Sun XL, Kido T, Honma S, *et al.* 2017. The relationship between dioxins exposure and risk of prostate cancer with steroid hormone and age in Vietnamese men. *Sci Total Environ*, 595:842-848.	+	+	+ +	+ +	+	+ +	-	Tier 1
Sun XL, Okamoto R, Kido T, *et al.* 2020. Association of dioxin in maternal breast milk and salivary steroid hormone levels in preschool children: A five-year follow-up study of a Vietnam cohort. *Chemosphere*, 241:124899.	-	+ +	+	-	+	+	-	Tier 2
Tai PT, Nishijo M, Nghi TN, *et al.* 2016. Effects of Perinatal Dioxin Exposure on Development of Children during the First 3 Years of Life. *J Pediatr*, 175:159-166.e152.	-	+	+	-	+	+	-	Tier 2
Van Luong H, Tai PT, Nishijo M, *et al.* 2018. Association of dioxin exposure and reproductive hormone levels in men living near the Bien Hoa airbase, Vietnam. *Sci Total Environ*, 628:484-489.	-	+ +	+	+	+	+	-	Tier 2
Vermeir G, Covaci A, Van Larebeke N, *et al.* 2021. Neurobehavioural and cognitive effects of prenatal exposure to organochlorine compounds in three year old children. *BMC Pediatr*, 21:99.	+	+	-	-	+	+	-	Tier 2
Vu HT, Nishijo M, Pham TN, *et al.* 2021. Effects of perinatal dioxin exposure on mirror neuron activity in 9-year-old children living in a hot spot of dioxin contamination in Vietnam. *Neuropsychologia*, 161:108001.	-	+	-	+ +	-	+	-	Tier 2
Wang Z, Hang JG, Feng H, *et al.* 2019. Effects of perinatal dioxin exposure on development of children: a 3-year follow-up study of China cohort. *Environ Sci Pollut Res Int*, 26:20780-20786.	-	-	+ +	+ +	-	+	-	Tier 2

TABLE A4.7 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FOR THE THEME "TOXIC EFFECTS OF DIOXINS AND dl-PCBs", USING THE QUALITY ASSESSMENT TOOL OF THE OHAT (OFFICE OF HEALTH ASSESSMENT AND TRANSLATION) (cont.)**

Study	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Warner M, Rauch S, Ames J, *et al.* 2019. In utero dioxin exposure and cardiometabolic risk in the Seveso Second Generation Study. *Int J Obes (Lond)*, 43:2233-2243.	+	+	+	+	+	+	+	Tier 1
Warner M, Rauch S, Ames J, *et al.* 2020. Prenatal dioxin exposure and thyroid hormone levels in the Seveso second generation study. *Environ Res*, 183:109280.	+	+	+	+	+	+	+	Tier 1
Warner M, Rauch S, Brambilla P, *et al.* 2020. Prenatal dioxin exposure and glucose metabolism in the Seveso Second Generation study. *Environ Int*, 134:105286.	+	+	+	+	+	+	+	Tier 1
Xu P, Chen Z, Wu L, *et al.* 2019. Health risk of childhood exposure to PCDD/Fs emitted from a municipal waste incinerator in Zhejiang, China. *Sci Total Environ*, 689:937-944.	- -	+	+	+	+	+	-	Tier 2
Ye M, Warner M, Mocarelli P, *et al.* 2018. Prenatal exposure to TCDD and atopic conditions in the Seveso second generation: a prospective cohort study. *Environ Health*, 17:22.	-	-	+	+ +	+	+	+	Tier 2
Zhang Z, He J, Shi T, *et al.* 2019. Associations between polychlorinated dibenzo-dioxins and polychlorinated dibenzo-furans exposure and oxidatively generated damage to DNA and lipid. *Chemosphere*, 227:237-246.	-	-	+	+	+	+	-	Tier 2
Zhang Z, Zhou M, He J, *et al.* 2020. Polychlorinated dibenzo-dioxins and polychlorinated dibenzo-furans exposure and altered lung function: The mediating role of oxidative stress. *Environ Int*, 137:105521.	-	-	+	+	+	+	-	Tier 2

APPENDIX 5
TOXIC EFFECTS OF MeHg

LITERATURE SEARCH STRATEGY

TABLE A5.1 LITERATURE SEARCH STRATEGY FOR THE REVIEW "TOXIC EFFECTS OF MeHg" IN PUBMED AND WEB OF SCIENCE

Database: PubMed
Date of literature search: 15 December 2021
Literature search string:
(((((((("journal article"[Publication Type]) OR "review"[Publication Type]) OR "scientific integrity review"[Publication Type]) OR "meta analysis"[Publication Type]) OR "systematic review"[Publication Type])) AND ("2010/01/01"[PDat] : "2022/12/31"[PDat])) AND Humans[Mesh]) AND (("methylmercury compounds"[MeSH Terms]) OR (methylmercury[Title/Abstract] OR MeHg[Title/Abstract] OR methyl-Hg[Title/Abstract] OR CH3Hg[Title/Abstract] OR mercury[MeSH Terms] OR mercury[Title/Abstract]) AND ("2010/01/01"[PDat] : "2022/12/31"[PDat])) AND (epidemiolog*[Title/Abstract] OR "cohort study"[Title/Abstract] OR "cohort studies"[Title/Abstract] OR "case control study"[Title/Abstract] OR "case control studies"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "observational study"[Title/Abstract] OR "observational studies"[Title/Abstract] OR "case series"[Title/Abstract] OR "cross sectional study"[Title/Abstract] OR "cross sectional studies"[Title/Abstract] OR "case report"[Title/Abstract]OR "case reports"[Title/Abstract]) AND (english[Language])
Total hits: 928
Database: Web of Science
Date of literature search: 15 December 2021
Literature search string:
TS=((methylmercury OR MeHg OR methyl-Hg OR CH3Hg OR CH3Hg OR mercur*) AND (epidemiolog* OR "cohort stud*" OR "case control stud*" OR "adverse effect*" OR "observational stud*" OR "case serie*" OR "case report*" OR "cross sectional stud*")) AND DOP=(2010-01-01/2022-12-31)
Search filters: Including only document types (articles and review articles)
Total hits: 1 834

TABLE A5.2 **UPDATED LITERATURE SEARCH STRATEGY FOR THE REVIEW "TOXIC EFFECTS OF MeHg" IN PUBMED AND WEB OF SCIENCE**

Database: PubMed
Date of literature search: 14 November 2022
Literature search string:
(((((((("journal article"[Publication Type]) OR "review"[Publication Type]) OR "scientific integrity review"[Publication Type]) OR "meta analysis"[Publication Type]) OR "systematic review"[Publication Type])) AND ("2010/01/01"[PDat] : "2021/12/15"[PDat])) AND Humans[Mesh]) AND (("methylmercury compounds"[MeSH Terms]) OR (methylmercury[Title/Abstract] OR MeHg[Title/Abstract] OR methyl-Hg[Title/Abstract] OR CH3Hg[Title/Abstract] OR mercury[MeSH Terms] OR mercury[Title/Abstract]) AND ("2010/01/01"[PDat] : "2021/12/15"[PDat]))) AND (epidemiolog*[Title/Abstract] OR "cohort study"[Title/Abstract] OR "cohort studies"[Title/Abstract] OR "case control study"[Title/Abstract] OR "case control studies"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "observational study"[Title/Abstract] OR "observational studies"[Title/Abstract] OR "case series"[Title/Abstract] OR "cross sectional study"[Title/Abstract] OR "cross sectional studies"[Title/Abstract] OR "case report"[Title/Abstract] OR "case reports"[Title/Abstract] OR "systematic review"[Title/Abstract] OR "meta anal*"[Title/Abstract] OR "meta-anal*"[Title/Abstract]) AND (english[Language])
Search filters: Include only article types (reviews, systematic reviews and meta-analysis)
Total hits: 242
Database: Web of Science
Date of literature search: 14 November 2022
Literature search string:
TS=((methylmercury OR MeHg OR methyl-Hg OR CH3Hg OR CH3Hg OR mercur*) AND (epidemiolog* OR "cohort stud*" OR "case control stud*" OR "adverse effect*" OR "observational stud*" OR "case serie*" OR "case report*" OR "cross sectional stud*" OR "systematic review" OR "meta anal*" OR "meta-anal*")) AND DOP=(2010-01-01/2021-12-15)
Search filters: Including only document types (review articles)
Total hits: 330

RECORDS EXCLUDED DURING FULL-TEXT SCREENING

TABLE A5.3 SYSTEMATIC REVIEWS EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg" BASED ON INCLUSION AND EXCLUSION CRITERIA

Study (n = 9)	Reason for exclusion
Feng, L. Li, P. *&* Feng, X. 2021. Methylmercury bioaccumulation in rice and health effects: A systematic review. *Current Opinion in Environmental Science & Health*, 23:100285:	Excluded based on inclusion and exclusion criteria: not a systematic review.
Grandjean, P. *&* Landrigan, P.J. 2014. Neurobehavioural effects of developmental toxicity. T*he lancet neurology*, 13(3):330-338.	Excluded based on inclusion and exclusion criteria: not a systematic review.
Ke, T. Tinkov, A.A. Skalny, A.V. Bowman, A.B. Rocha, J.B. Santamaria, A. *&* Aschner, M. 2021. Developmental exposure to methylmercury and ADHD, a literature review of epigenetic studies. *Environmental Epigenetics*, 7(1):dvab014.	Excluded based on inclusion and exclusion criteria: not a systematic review.
Perez-Fernandez, C. Flores, P. *&* Sánchez-Santed, F. 2019. A systematic review on the influences of neurotoxicological xenobiotic compounds on inhibitory control. *Frontiers in Behavioral Neuroscience*, 13:139.	The systematic review also included animal studies and the results or discussion do not distinguish between animal and human studies.
Sheehan, M.C. Burke, T.A. Navas-Acien, A. Breysse, P.N. McGready, J. *&* Fox, M.A. 2014. Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: a systematic review. *Bulletin of the World Health Organization*, 92:254-269F.	Excluded based on inclusion and exclusion criteria: no health outcome included.
Spiller, P. Hibbeln, J.R. Myers, G. Vannice, G. Golding, J. Crawford, M.A., Carlson, S.E. *et al.* 2019. An abundance of seafood consumption studies presents new opportunities to evaluate effects on neurocognitive development. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, 151:8-13.	Excluded based on inclusion and exclusion criteria: not a systematic review.
Vianna, A.D.S. Matos, E.P.D. Jesus, I.M.D. Asmus, C.I.R.F. *&* Câmara, V.D.M. 2019. Human exposure to mercury and its hematological effects: a systematic review. *Cad Saude Publica*, 11;35(2)	Excluded based on inclusion and exclusion criteria: The systematic review had included n = 80 studies, where of n = 48 of these are case-reports (a study type that is an exclusion criteria). Also, of the 80 included studies, 75 were graded as weak in the quality assessment.
Wang, M.D. Little, J. Gomes, J. Cashman, N.R. *&* Krewski, D. 2017. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. *Neurotoxicology*, 61:101-130.	Excluded based on inclusion and exclusion criteria: In the section regarding Hg, no specific human studies are included. They have only mentioned Hg in the discussion and this refers to case-reports.
Zheng, L. Y. Sanders, A. P. Saland, J. M. Wright, R. O. *&* Arora, M. 2017. Environmental exposures and pediatric kidney function and disease: A systematic review. *Environmental research*, 158:625-648.	Excluded based on inclusion and exclusion criteria: Have included n = 5 studies assessing Hg, but all of these compare Hg exposure from amalgam vs. composite use in RCTs. Not relevant exposure (as per criteria).

TABLE A5.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg" BASED ON INCLUSION AND EXCLUSION CRITERIA**

Study (n = 45)	Reason for exclusion
Al-Saleh, I. 2021. Health risk assessment of trace metals through breast milk consumption in Saudi Arabia. *Biological Trace Element Research*, 199(12):4535-4545.	Excluded based on inclusion and exclusion criteria: no health outcome measured
Aranda, N. Valls, R.M. Romeu, M. Sánchez-Martos, V. Albaladejo, R. Fernández-Castillejo, S., Giralt, M. *et al.* 2017. Consumption of seafood and its estimated heavy metals are associated with lipid profile and oxidative lipid damage on healthy adults from a Spanish Mediterranean area: A cross-sectional study. *Environmental research*, 156:644-651.	Excluded based on inclusion and exclusion criteria: no Hg measurements in participants
Bellinger, D.C. 2012. Comparing the population neurodevelopmental burdens associated with children's exposures to environmental chemicals and other risk factors. *Neurotoxicology*, 33(4):641-643.	Excluded based on inclusion and exclusion criteria: individual health outcome not measured (only population based).
Bellinger, D.C. 2012. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environmental Health Perspectives*, 120(4):501-507.	Excluded based on inclusion and exclusion criteria: a review, but not a systematic review or meta-analysis.
Berky, A.J., Ryde, I.T., Feingold, B., Ortiz, E.J. Wyatt, L.H., Weinhouse, C., Pan, W.K. *et al.* 2019. Predictors of mitochondrial DNA copy number and damage in a mercury-exposed rural Peruvian population near artisanal and small-scale gold mining: An exploratory study. *Environmental and molecular mutagenesis*, 60(2):197-210.	Excluded based on inclusion and exclusion criteria: no health outcome measured.
Budtz-Jørgensen, E. Debes, F., Weihe, P. *&* Grandjean, P. 2010. Structural equation models for meta-analysis in environmental risk assessment. *Environmetrics*, 21(5):510-527.	Excluded based on inclusion and exclusion criteria: statistical method paper
Butler, L.J., Janulewicz, P.A., Carwile, J.L., White, R.F. Winter, M.R. *&* Aschengrau, A. 2017. Childhood and adolescent fish consumption and adult neuropsychological performance: An analysis from the Cape Cod Health Study. *Neurotoxicology and teratology*, 61:47-57.	Excluded based on inclusion and exclusion criteria: no Hg measurements
Butts, C.D., Bloom, M.S., McGough, A., Lenhart, N., Wong, R. Mok-Lin, E., Fujimoto, V.Y. *et al.* 2020. Seafood consumption is associated with higher follicular fluid arsenic (As) and mercury (Hg) concentrations in women undergoing in vitro fertilization (IVF). *Environmental Research*, 188:109753.	Excluded based on inclusion and exclusion criteria: no health outcome measured
Carneiro, M.F.H., Grotto, D. *&* Barbosa Jr, F. 2014. Inorganic and methylmercury levels in plasma are differentially associated with age, gender, and oxidative stress markers in a population exposed to mercury through fish consumption. *Journal of Toxicology and Environmental Health*, Part A, 77(1-3):69-79.	Excluded based on inclusion and exclusion criteria: no health outcome measured (only oxidative stress)
Carwile, J.L., Butler, L.J., Janulewicz, P.A., Winter, M.R. *&* Aschengrau, A. 2016. Childhood fish consumption and learning and behavioral disorders. *International journal of environmental research and public health*, 13(11):1069.	Excluded based on inclusion and exclusion criteria: no assessment of Hg exposure
Chevrier, C., Warembourg, C., Gaudreau, E., Monfort, C., Le Blanc, A., Guldner, L. *&* Cordier, S. 2013. Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. *Epidemiology*, 24(2):251-260.	Excluded based on inclusion and exclusion criteria: Hg only included as a co-exposure in paper
Davidson, P.W., Myers, G.J. *&* Shamlaye, C. 2020. Principles of studying low-level neurotoxic exposures in children: using the Seychelles Child Development Study of methyl mercury as a prototype. *NeuroToxicology*, 81:307-314.	Excluded based on inclusion and exclusion criteria: method paper using the Seychelles study as an example.
de Marco, K.C., Braga, G.U. *&* Barbosa Jr, F. 2011. Determination of the effects of eNOS gene polymorphisms (T-786C and Glu298Asp) on nitric oxide levels in a methylmercury-exposed population. *Journal of Toxicology and Environmental Health*, Part A, 74(20):1323-1333.	Excluded based on inclusion and exclusion criteria: no health outcome included (only nitric oxide levels)
Diaz, S.M., Palma, R. M., Muñoz, M. N., Becerra-Arias, C. *&* Fernández Niño, J. A. 2020. Factors associated with high mercury levels in women and girls from the Mojana region, Colombia, 2013–2015. International *Journal of Environmental Research and Public Health*, 17(6):1827.	Excluded based on inclusion and exclusion criteria: Hg exposure from gold mining areas
Dos Santos Freitas, J., Lacerda, E.M., da Silva Martins, I.C.V., Rodrigues Jr, D., Bonci, D.M., Cortes, M.I., da Silva Souza, G. *et al.* 2018. Cross-sectional study to assess the association of color vision with mercury hair concentration in children from Brazilian Amazonian riverine communities. *Neurotoxicology*, 65:60-67.	Excluded based on inclusion and exclusion criteria: Hg exposure from contaminated areas
Engström, K.S., Wennberg, M., Strömberg, U., Bergdahl, I. A., Hallmans, G., Jansson, J.H., Broberg, K. *et al.* 2011. Evaluation of the impact of genetic polymorphisms in glutathione-related genes on the association between methylmercury or n-3 polyunsaturated long chain fatty acids and risk of myocardial infarction: a case-control study. *Environmental health*, 10(1):1-8.	Excluded based on inclusion and exclusion criteria: association between Hg exposure and health outcome not measured
Franken, C., Koppen, G., Lambrechts, N., Govarts, E., Bruckers, L., Den Hond, E., Schoeters, G. *et al.* 2017. Environmental exposure to human carcinogens in teenagers and the association with DNA damage. *Environmental research*, 152:165-174.	Excluded based on inclusion and exclusion criteria: health outcome not measured (only DNA damage)
Ginsberg, G., Sonawane, B., Nath, R. *&* Lewandowski, P. 2014. Methylmercury-induced inhibition of paraoxonase-1 (PON1)—Implications for cardiovascular risk. Journal of Toxicology and *Environmental Health, Part A*, 77(17):1004-1023.	Excluded based on inclusion and exclusion criteria: not a human study (only mechanistic)
Golding, J., Steer, C.D., Hibbeln, J.R., Emmett, P.M., Lowery, T. *&* Jones, R. 2013. Dietary predictors of maternal prenatal blood mercury levels in the ALSPAC birth cohort study. *Environmental health perspectives*, 121(10):1214-1218.	Excluded based on inclusion and exclusion criteria: health outcome not measured

TABLE A5.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Study (n = 45)	Reason for exclusion
Gump, B.B., MacKenzie, J.A., Dumas, A.K., Palmer, C., D. Parsons, P.J., Segu, Z.M., Bendinskas, K.G. *et al.* 2012. Fish consumption, low-level mercury, lipids, and inflammatory markers in children. *Environmental research*, 112:204-211.	Excluded based on inclusion and exclusion criteria: health outcome not measured
Hara, N., Saito, H., Takahashi, K. *&* Takeda, M. 2013. Lower urinary tract symptoms in patients with Niigata Minamata disease: A case–control study 50 years after methyl mercury pollution. *International journal of urology*, 20(6):610-615.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured
Inoue, S., Yorifuji, T., Tsuda, T. *&* Doi, H. 2012. Short-term effect of severe exposure to methylmercury on atherosclerotic heart disease and hypertension mortality in Minamata. *Science of the total environment*, 417:291-293.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured
Julvez, J., Davey Smith, G., Ring, S. *&* Grandjean, P. 2019. A birth cohort study on the genetic modification of the association of prenatal Methylmercury with child cognitive development. *American journal of epidemiology*, 188(10):1784-1793.	Excluded based on inclusion and exclusion criteria: Hg exposure in blood, hair or toenails not measured (only cord tissue)
Kim, H., Lee, J., Woo, H.D., Kim, D.W., Oh, J.H., Chang, H.J., Kim, J. *et al.* 2020. Dietary mercury intake and colorectal cancer risk: A case-control study. *Clinical Nutrition*, 39(7):2106-2113.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured directly in participants.
Kong, H.K., Gan, C.F., Xiong, M., Kwok, K.W.H., Lui, G.C.S., Li, P., Lo, S.C.L. *et al.* 2019. Chronic methylmercury exposure induces production of prostaglandins: evidence from a population study and a rat dosing experiment. *Environmental Science & Technology*, 53(13):7782-7791.	Excluded based on inclusion and exclusion criteria: health outcome not measured
Kuras, R. Kozlowska, L. Reszka, E. Wieczorek, E. Jablonska, E. Gromadzinska, J., Wasowicz, W. *et al.* 2019. Environmental mercury exposure and selenium-associated biomarkers of antioxidant status at molecular and biochemical level. A short-term intervention study. *Food and Chemical Toxicology*, 130:187-198.	Excluded based on inclusion and exclusion criteria: health outcome not measured (only biomarker)
Lee, P.H. *&* Burstyn, I. 2016. Identification of confounder in epidemiologic data contaminated by measurement error in covariates. *BMC medical research methodology*, 16:1-18.	Excluded based on inclusion and exclusion criteria: statistical method paper
Leung, Y.K., Ouyang, B., Niu, L., Xie, C., Ying, J., Medvedovic, M., Ho, S.M. 2018. Identification of sex-specific DNA methylation changes driven by specific chemicals in cord blood in a Faroese birth cohort. *Epigenetics*, 13(3):290-300.	Excluded based on inclusion and exclusion criteria: health outcome not measured (only DNA methylation)
Little, M., Achouba, A., Dumas, P., Ouellet, N., Ayotte, P. *&* Lemire, M. 2019. Determinants of selenoneine concentration in red blood cells of Inuit from Nunavik (Northern Québec, Canada). *Environment international*, 127:243-252.	Excluded based on inclusion and exclusion criteria: health outcome not measured (focus on selenium)
Maeda, E., Murata, K., Kumazawa, Y., Sato, W., Shirasawa, H., Iwasawa, T., Terada, Y. *et al.* 2019. Associations of environmental exposures to methylmercury and selenium with female infertility: A case–control study. *Environmental research*, 168:357-363.	Excluded based on inclusion and exclusion criteria: health outcome not measured (focus on selenium)
Monastero, R.N., Karimi, R., Nyland, J.F., Harrington, J., Levine, K. *&* Meliker, J.R. 2017. Mercury exposure, serum antinuclear antibodies, and serum cytokine levels in the Long Island Study of Seafood Consumption: A cross-sectional study in NY, USA. *Environmental research*, 156:334-340.	Excluded based on inclusion and exclusion criteria: health outcome not measured
Morris, M.C., Brockman, J., Schneider, J.A., Wang, Y., Bennett, D.A., Tangney, C.C. *&* van de Rest, O. 2016. Association of seafood consumption, brain mercury level, and APOE β4 status with brain neuropathology in older adults. *JAMA*, 315(5):489-497.	Excluded based on inclusion and exclusion criteria: exposure in blood, hair or toenails not measured (Hg measured in the brain during autopsy)
Nyland, J.F., Wang, S.B., Shirley, D.L., Santos, E.O., Ventura, A.M., de Souza, J.M. *&* Silbergeld, E.K. 2011. Fetal and maternal immune responses to methylmercury exposure: a cross-sectional study. *Environmental Research*, 111(4):584-589.	Excluded based on inclusion and exclusion criteria: health outcome not measured (only biomarker)
Nyland, J.F., Fillion, M., Barbosa Jr, F., Shirley, D.L., Chine, C., Lemire, M., Silbergeld, E.K. *et al.* 2011. Biomarkers of methylmercury exposure immunotoxicity among fish consumers in Amazonian Brazil. *Environmental Health Perspectives*, 119(12):1733-1738.	Excluded based on inclusion and exclusion criteria: health outcome not measured (only biomarker)
Sá, A.B., Simone, C., Oliveira, C.S.B.D., Lima, A.A.D.S., Borges, B.E.S., Santos, G.D.F.S., Pinheiro, M.D.C.N. *et al.* 2019. Fish consumption frequency and lipid peroxidation in the riverside population of Lower Tocantins, Pará. Nutrición Clínica y Dietética Hospitalaria, 39(1): 64-68	Excluded based on inclusion and exclusion criteria: health outcome not measured
Schoeman, K., Tanaka, T., Bend, J.R. *&* Koren, G. 2010. Hair mercury levels of women of reproductive age in Ontario, Canada: implications to fetal safety and fish consumption. *The Journal of Pediatrics*, 157(1):127-131.	Excluded based on inclusion and exclusion criteria: health outcome not measured
Sheehan, M.C. Burke, T.A. Breysse, P.N. Navas-Acien, A. McGready, J. *&* Fox, M.A. 2012. Association of markers of chronic viral hepatitis and blood mercury levels in US reproductive-age women from NHANES 2001–2008: a cross-sectional study. *Environmental Health*, 11(1):1-11.	Excluded based on inclusion and exclusion criteria: Hg exposure only included as a confounding variable
Vejrup, K., Brantsæter, A.L., Knutsen, H.K., Magnus, P., Alexander, J., Kvalem, H.E., Haugen, M. *et al.* 2014. Prenatal mercury exposure and infant birth weight in the Norwegian Mother and Child Cohort Study. *Public health nutrition*, 17(9):2071-2080.	Excluded based on inclusion and exclusion criteria: Hg exposure only calculated from intake, not biomarker exposure

TABLE A5.4 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg" BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Study (n = 45)	Reason for exclusion
Vejrup, K., Schjølberg, S., Knutsen, H.K., Kvalem, H.E., Brantsæter, A.L., Meltzer, H.M., Haugen, M. *et al.* 2016. Prenatal methylmercury exposure and language delay at three years of age in the Norwegian Mother and Child Cohort Study. *Environment international*, 92, 63-69.	Excluded based on inclusion and exclusion criteria: Hg exposure only calculated from intake, not biomarker exposure
Wang, Y. Goodrich, J. M., Werner, R., Gillespie, B., Basu, N. *&* Franzblau, A. 2013. Relationship of estimated dietary intake of n-3 polyunsaturated fatty acids from fish with peripheral nerve function after adjusting for mercury exposure. *Science of the total environment*, 454, 73-78.	Excluded based on inclusion and exclusion criteria: Hg exposure only included as a confounding variable
Yeter, D., Portman, M.A., Aschner, M., Farina, M., Chan, W.C., Hsieh, K.S. *&* Kuo, H.C. 2016. Ethnic Kawasaki disease risk associated with blood mercury and cadmium in US children. *International journal of environmental research and public health*, 13(1):101.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured
Yorifuji, T., Tsuda, T., Inoue, S., Takao, S., Harada, M. *&* Kawachi, I. 2013. Critical appraisal of the 1977 diagnostic criteria for Minamata disease. *Archives of Environmental & Occupational Health*, 68(1):22-29.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured
Yorifuji, T. *&* Tsuda, T. 2016. Epidemiological studies of neurological signs and symptoms and blood pressure in populations near the industrial methylmercury contamination at Minamata, Japan. *Archives of environmental & occupational health*, 71(4):231-236.	Excluded based on inclusion and exclusion criteria: Hg exposure not measured
Zeilmaker, M.J., Hoekstra, J., van Eijkeren, J.C., de Jong, N., Hart, A., Kennedy, M., Gunnlaugsdottir, H. 2013. Fish consumption during child bearing age: A quantitative risk–benefit analysis on neurodevelopment. *Food and Chemical Toxicology*, 54, 30-34.	Excluded based on inclusion and exclusion criteria: Hg exposure only calculated from intake, not biomarker exposure
Zijlmans, W., Wickliffe, J., Hindori-Mohangoo, A., MacDonald-Ottevanger, S., Ouboter, P., Landburg, G., Lichtveld, M. *et al.* 2020. Caribbean Consortium for Research in Environmental and Occupational Health (CCREOH) Cohort Study: Influences of complex environmental exposures on maternal and child health in Suriname. *BMJ open*, 10(9):e034702.	Excluded based on inclusion and exclusion criteria: Description of an ongoing study

TABLE A5.5 **PRIMARY STUDIES EXCLUDED AS THEY HAD ALREADY BEEN ASSESSED IN ONE OF THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH "TOXIC EFFECT OF MeHg"**

Primary studies assessed (n = 44)	Primary study assessed in systematic review
Barbone, F., Rosolen, V., Mariuz, M., Parpinel, M., Casetta, A., Sammartano, F., Horvat, M. *et al.* 2019. Prenatal mercury exposure and child neurodevelopment outcomes at 18 months: Results from the Mediterranean PHIME cohort. *International journal of hygiene and environmental health*, 222(1):9-21.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Bulka, C.M., Persky, V.W., Daviglus, M.L., Durazo-Arvizu, R.A. *&* Argos, M. 2019. Multiple metal exposures and metabolic syndrome: A cross-sectional analysis of the National Health and Nutrition Examination Survey 2011–2014. *Environmental research*, 168:397-405.	Excluded, as the primary study has already been assessed in an included systematic review (Xu *et al.*, 2021)
Deroma, L., Parpinel, M., Tognin, V., Channoufi, L., Tratnik, J., Horvat, M., Barbone, F. 2013. Neuropsychological assessment at school-age and prenatal low-level exposure to mercury through fish consumption in an Italian birth cohort living near a contaminated site. *International journal of hygiene and environmental health*, 216(4):486-493.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Downer, M.K., Martínez-González, M.A., Gea, A., Stampfer, M., Warnberg, J., Ruiz-Canela, M., PREDIMED Study Investigators *et al.* 2017. Mercury exposure and risk of cardiovascular disease: a nested case-control study in the PREDIMED (PREvention with MEDiterranean Diet) study. *BMC Cardiovascular Disorders*, 17:1-11.	Excluded, as the primary study has already been assessed in an included systematic review (Chowdhury *et al.* 2019 and Hu *et al.* 2018)
Ettinger, A.S., Bovet, P., Plange-Rhule, J., Forrester, T.E., Lambert, E.V., Lupoli, N., Luke, A. *et al.* 2014. Distribution of metals exposure and associations with cardiometabolic risk factors in the "Modeling the Epidemiologic Transition Study". *Environmental Health*, 131-15.	Excluded, as the primary study has already been assessed in an included systematic review (Roy *et al.*, 2017)
Giacoppo, S., Galuppo, M., Calabrβ, R.S., D'Aleo, G., Marra, A., Sessa, E., Mazzon, E. *et al.* 2014. Heavy metals and neurodegenerative diseases: an observational study. *Biological trace element research*, 161:151-160.	Excluded, as the primary study has already been assessed in an included systematic review (Sarihi *et al.*, 2021)
Golding, J., Hibbeln, J.R., Gregory, S.M., Iles-Caven, Y., Emond, A. *&* Taylor, C.M. 2017. Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: a British prebirth cohort study. *International journal of hygiene and environmental health*, 220(7):1161-1167.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Golding, J., Rai, D., Gregory, S., Ellis, G., Emond, A., Iles-Caven, Y., Taylor, C. *et al.* 2018. Prenatal mercury exposure and features of autism: a prospective population study. *Molecular autism*, 9:1-9.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Govarts, E., Remy, S., Bruckers, L., Den Hond, E., Sioen, I., Nelen, V., Schoeters, G. 2016. Combined effects of prenatal exposures to environmental chemicals on birth weight. *International journal of environmental research and public health*, 13(5):495.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al.*, 2021)
Gregory, S., Iles-Caven, Y., Hibbeln, J.R., Taylor, C.M. *&* Golding, J. 2016. Are prenatal mercury levels associated with subsequent blood pressure in childhood and adolescence? The Avon prebirth cohort study. *BMJ open*, 6(10):e012425.	Excluded, as the primary study has already been assessed in an included systematic review (Gallego-Vinas *et al.*, 2019)
Gustin, K., Barman, M., Stråvik, M., Levi, M., Englund-Ögge, L., Murray, F., Kippler, M. *et al.* 2020. Low-level maternal exposure to cadmium, lead, and mercury and birth outcomes in a Swedish prospective birth-cohort. *Environmental Pollution*, 2651:14986.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al.*, 2021)
Hu, Y., Chen, L., Wang, C., Zhou, Y., Zhang, Y., Wang, Y., Tian, Y. *et al.* 2016. Prenatal low-level mercury exposure and infant neurodevelopment at 12 months in rural northern China. *Environmental Science and Pollution Research*, 23:12050-12059.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Hu, X.F., Laird, B.D., *&* Chan, H.M., 2017. Mercury diminishes the cardiovascular protective effect of omega-3 polyunsaturated fatty acids in the modern diet of Inuit in Canada. *Environmental research*, 152470-477.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018 and Hu *et al.*, 2021)
Jeppesen, C., Valera, B., Nielsen, N.O., Bjerregaard, P. *&* Jørgensen, M.E. 2015. Association between whole blood mercury and glucose intolerance among adult Inuit in Greenland. *Environmental research*, 143192-197.	Excluded, as the primary study has already been assessed in an included systematic review (Roy *et al.*, 2017 and Xu *et al.*, 2021)
Julvez, J., Méndez, M., Fernandez-Barres, S., Romaguera, D., Vioque, J., Llop, S., Sunyer, J. 2016. Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels. *American journal of epidemiology*, 183(3):169-182.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Kalish, B.T., Rifas-Shiman, S.L., Wright, R.O., Amarasiriwardena, C.J., Jayawardene, I., Gillman, M.W., Oken, E. 2014. Associations of prenatal maternal blood mercury concentrations with early and mid-childhood blood pressure: a prospective study. *Environmental research*, 133:327-333.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018 and Gallego-Vinas *et al.*, 2019)
Kim, K.N., Bae, S., Park, H.Y., Kwon, H.J. *&* Honga, Y.C. 2015. Low-level mercury exposure and risk of asthma in school-age children. *Epidemiology*, 26(5):733-739.	Excluded, as the primary study has already been assessed in an included systematic review (Roy *et al.*, 2017)
Kim, B.M., Chen, M.H., Chen, P.C., Park, H., Ha, M., Kim, Y., Ha, E.H. *et al.* 2017. Path analysis of prenatal mercury levels and birth weights in Korean and Taiwanese birth cohorts. *Science of the Total Environment*, 605:1003-1010.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al.*, 2021)
Lee, Y.J. *&* Hwang, I.C. 2014. Relationship between serum ferritin level and blood mercury concentration using data from the Korean national health and nutrition examination survey (2010–2012). *Environmental research*, 135:271-275.	Excluded, as the primary study has already been assessed in an included systematic review (Roy *et al.*, 2017 and Xu *et al.*, 2021)

TABLE A5.5 **PRIMARY STUDIES EXCLUDED AS THEY HAD ALREADY BEEN ASSESSED IN ONE OF THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH "TOXIC EFFECT OF MeHg" (cont.)**

Primary studies assessed (n = 44)	Primary study assessed in systematic review
Llop, S., Ballester, F., Murcia, M., Forns, J., Tardon, A., Andiarena, A., Lopez-Espinosa, M.J. *et al.* 2017. Prenatal exposure to mercury and neuropsychological development in young children: the role of fish consumption. *International Journal of Epidemiology*, 46(3):827-838.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Llop, S., Tran, V., Ballester, F., Barbone, F., Sofianou-Katsoulis, A., Sunyer, J., Broberg, K. *et al.* 2017. CYP3A genes and the association between prenatal methylmercury exposure and neurodevelopment. *Environment international*, 105:34-42.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Marques, R.C. Bernardi, J.V. Dórea, J.G. Brandão, K.G. Bueno, L. Leão, R.S. *&* Malm, O. 2013. Fish consumption during pregnancy, mercury transfer, and birth weight along the Madeira River Basin in Amazonia. *International journal of environmental research and public health*, 10(6):2150-2163.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al.*, 2021)
McKean, S.J., Bartell, S.M., Hansen, R.L., Barfod, G.H., Green, P.G. *&* Hertz-Picciotto, I. 2015. Prenatal mercury exposure, autism, and developmental delay, using pharmacokinetic combination of newborn blood concentrations and questionnaire data: a case control study. *Environmental Health*, 14(1):1-12.	Excluded, as the primary study has already been assessed in an included systematic review (Jafari *et al.*, 2017)
Mozaffarian, D., Shi, P., Morris, J.S., Spiegelman, D., Grandjean, P., Siscovick, DS. *&* Rimm, E.B. 2011. Mercury exposure and risk of cardiovascular disease in two US cohorts. *New England Journal of Medicine*, 364(12):1116-1125.	Excluded, as the primary study has already been assessed in an included systematic review (Chowdhury *et al.* 2019, Gallego-Vinas *et al.* 2018 and Hu *et al.*, 2018)
Mozaffarian, D., Shi, P., Morris, J.S., Grandjean, P., Siscovick, D.S., Spiegelman, D., Forman, J.P. 2012. Mercury exposure and risk of hypertension in US men and women in 2 prospective cohorts. *Hypertension*, 60(3):645-652.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018)
Mozaffarian, D., Shi, P., Morris, J.S., Grandjean, P., Siscovick, D.S., Spiegelman, D. *&* Hu, F.B. 2013. Methylmercury exposure and incident diabetes in US men and women in two prospective cohorts. *Diabetes Care*, 36(11):3578-3584.	Excluded, as the primary study has already been assessed in an included systematic review (Roy *et al.*, 2017)
Nielsen, A.B.S., Davidsen, M. *&* Bjerregaard, P. 2012. The association between blood pressure and whole blood methylmercury in a cross-sectional study among Inuit in Greenland. *Environmental Health*, 11(1):1-10.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018)
Park, S.K., Lee, S., Basu, N. *&* Franzblau, A. 2013. Associations of blood and urinary mercury with hypertension in US adults: the NHANES 2003–2006. *Environmental research*, 123:25-32.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.* 2018)
Rajaee, M., Sánchez, B.N., Renne, E.P. *&* Basu, N. 2015. An investigation of organic and inorganic mercury exposure and blood pressure in a small-scale gold mining community in Ghana. *International journal of environmental research and public health*, 12(8):10020-10038.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018)
Suzuki, K., Nakai, K., Sugawara, T., Nakamura, T., Ohba, T., Shimada, M., Satoh, H. *et al.* 2010. Neurobehavioral effects of prenatal exposure to methylmercury and PCBs, and seafood intake: neonatal behavioral assessment scale results of Tohoku study of child development. *Environmental research*, 110(7):699-704.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Valent, F., Mariuz, M., Bin, M., Mazej, D., Tognin, V., Tratnik, J., Barbone, F. *et al.* 2013. Associations of prenatal mercury exposure from maternal fish consumption and polyunsaturated fatty acids with child neurodevelopment: a prospective cohort study in Italy. *Journal of epidemiology*, 23(5):360-370.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Valera, B., Dewailly, É., Poirier, P., Counil, E. *&* Suhas, E. 2011. Influence of mercury exposure on blood pressure, resting heart rate and heart rate variability in French Polynesians: a cross-sectional study. *Environmental Health*, 10, 1-10.	Excluded, as the primary study has already been assessed in an included systematic review (Gallego-Vinas *et al.*, 2019)
Valera, B., Dewailly, E. *&* Poirier, P. 2011. Impact of mercury exposure on blood pressure and cardiac autonomic activity among Cree adults (James Bay, Quebec, Canada). *Environmental research*, 111(8):1265-1270.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018)
Valera, B., Dewailly, É. *&* Poirier, P. 2013. Association between methylmercury and cardiovascular risk factors in a native population of Quebec (Canada): a retrospective evaluation. *Environmental research*, 120, 102-108.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018)
van Wijngaarden, E., Harrington, D., Kobrosly, R., Thurston, S.W., O'Hara, T., McSorley, E.M., Davidson, P.W. *et al.* 2014. Prenatal exposure to methylmercury and LCPUFA in relation to birth weight. *Annals of epidemiology*, 24(4):273-278.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al.*, 2021)
Vejrup, K., Brandlistuen, R.E., Brantsæter, A.L., Knutsen, H.K., Caspersen, I.H., Alexander, J., Haugen, M. *et al.* 2018. Prenatal mercury exposure, maternal seafood consumption and associations with child language at five years. *Environment International*, 110, 71-79.	Excluded, as the primary study has already been assessed in an included systematic review (Hibbeln *et al.*, 2019)
Virtanen, J.K., Nyantika, A.N., Kauhanen, J., Voutilainen, S. *&* Tuomainen, T.P. 2012. Serum long-chain n-3 polyunsaturated fatty acids, methylmercury and blood pressure in an older population. *Hypertension Research*, 35(10):1000-1004.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al.*, 2018 and Hu *et al.*, 2021)

TABLE A5.5 **PRIMARY STUDIES EXCLUDED AS THEY HAD ALREADY BEEN ASSESSED IN ONE OF THE SYSTEMATIC REVIEWS FROM THE LITERATURE SEARCH "TOXIC EFFECT OF MeHg" (cont.)**

Primary studies assessed (n = 44)	Primary study assessed in systematic review
Wells, E.M., Herbstman, J.B., Lin, Y.H., Jarrett, J., Verdon, C.P., Ward, C., Goldman, L.R. *et al.* 2016. Cord blood methylmercury and fetal growth outcomes in Baltimore newborns: potential confounding and effect modification by omega-3 fatty acids, selenium, and sex. *Environmental health perspectives*, 124(3):373-379.	Excluded, as the primary study has already been assessed in an included systematic review (Dack *et al*., 2021)
Wells, E.M., Herbstman, J.B., Lin, Y.H., Hibbeln, J.R., Halden, R.U., Witter, F.R. *&* Goldman, L.R. 2017. Methyl mercury, but not inorganic mercury, associated with higher blood pressure during pregnancy. *Environmental research*, 154, 247-252.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al*., 2018)
Wennberg, M., Bergdahl, I.A., Hallmans, G., Norberg, M., Lundh, T., Skerfving, S., Jansson, J.H. *et al.* 2011. Fish consumption and myocardial infarction: a second prospective biomarker study from northern Sweden. *The American journal of clinical nutrition*, 93(1):27-36.	Excluded, as the primary study has already been assessed in an included systematic review (Chowdhury *et al*., 2018)
Wennberg, M., Strömberg, U., Bergdahl, I.A., Jansson, J.H., Kauhanen, J., Norberg, M., Virtanen, J.K. *et al.* 2012. Myocardial infarction in relation to mercury and fatty acids from fish: a risk-benefit analysis based on pooled Finnish and Swedish data in men. *The American journal of clinical nutrition*, 96(4):706-713.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al*., 2018 and Hu *et al*., 2021)
Yorifuji, T., Tsuda, T., Kashima, S., Takao, S. *&* Harada, M. 2010. Long-term exposure to methylmercury and its effects on hypertension in Minamata. *Environmental Research*, 110(1):40-46.	Excluded, as the primary study has already been assessed in an included systematic review (Hu *et al*., 2018)
Yorifuji, T., Debes, F., Weihe, P. *&* Grandjean, P. 2011. Prenatal exposure to lead and cognitive deficit in 7-and 14-year-old children in the presence of concomitant exposure to similar molar concentration of methylmercury. *Neurotoxicology and teratology*, 33(2):205-211.	Excluded, as the primary study has already been assessed in an included systematic review (Karita *et al*., 2018)
Yorifuji, T., Tsuda, T., Inoue, S., Takao, S. *&* Harada, M. 2011. Long-term exposure to methylmercury and psychiatric symptoms in residents of Minamata, Japan. *Environment international*, 37(5):907-913.	Excluded, as the primary study has already been assessed in an included systematic review (Puty *et al*., 2019)

QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES

TABLE A5.6 QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS FROM FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg", USING THE QUALITY ASSESSMENT TOOL AMSTAR 2

Study (*n* = 34)	AMSTAR 2 grading
	High (n = 4)
Hibbeln, Joseph R. *et al.* 2019. Relationships between seafood consumption during pregnancy and childhood and neurocognitive development: Two systematic reviews. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 151:14-36.	High
Hu, Q., Han, X., Dong, G., Yan, W., Wang, X., Bigambo, F.M., Wang, X. *et al.* 2021. Association between mercury exposure and thyroid hormones levels: A meta-analysis. *Environmental Research*, 196:110928.	High
Hu, X.F., Lowe, M. *&* Chan, H.M. 2021. Mercury exposure, cardiovascular disease, and mortality: A systematic review and dose-response meta-analysis. *Environmental research*, 193:110538.	High
Sarihi, S., Niknam, M., Mahjour, S., Hosseini-Bensenjan, M., Moazzen, F., Soltanabadi, S. *&* Akbari, H. 2021. Toxic heavy metal concentrations in multiple sclerosis patients: A systematic review and meta-analysis. *EXCLI journal*, 20:1571.	High
	Moderate (n = 12)
Chowdhury, R., Ramond, A., O'Keeffe, L.M., Shahzad, S., Kunutsor, S.K., Muka, T., Di Angelantonio, E. *et al.* 2018. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ*, 29:362.	Moderate
Dack, K., Fell, M., Taylor, C.M., Havdahl, A. *&* Lewis, S.J. 2021. Mercury and prenatal growth: a systematic review. International Journal of *Environmental Research and Public Health*, 18(13):7140.	Moderate
Gallego-Vinas, G., Ballester, F., *&* Llop, S. 2019. Chronic mercury exposure and blood pressure in children and adolescents: a systematic review. *Environmental Science and Pollution Research*, 26:2238-2252.	Moderate
Hu, X.F., Singh, K,. *&* Chan, H.M. 2018. Mercury exposure, blood pressure, and hypertension: A systematic review and dose–response meta-analysis. *Environmental health perspectives*, 126(07):076002.	Moderate
Jafari, T., Rostampour, N., Fallah, A.A. *&* Hesami, A. 2017. The association between mercury levels and autism spectrum disorders: a systematic review and meta-analysis. *Journal of Trace Elements in Medicine and Biology*, 44:289-297.	Moderate
Puty, B., Leão, L.K.R., Crespo-Lopez, M.E., Carvalho, A.P.C.P.S., Fagundes, N.C.F., Maia, L.C. *&* Lima, R.R. 2019. Association between methylmercury environmental exposure and neurological disorders: a systematic review. *Journal of Trace Elements in Medicine and Biology*, 52:100-110.	Moderate
Roy, C., Tremblay, P.Y. *&* Ayotte, P. 2017. Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature. *Environmental research*, 156:747-760.	Moderate
Saghazadeh, A. *&* Rezaei, N. 2017. Systematic review and meta-analysis links autism and toxic metals and highlights the impact of country development status: Higher blood and erythrocyte levels for mercury and lead, and higher hair antimony, cadmium, lead, and mercury. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 79:340-368.	Moderate
Sirohi, D., Al Ramadhani, R. *&* Knibbs, L.D. 2021. Environmental exposures to endocrine disrupting chemicals (EDCs) and their role in endometriosis: A systematic literature review. *Reviews on Environmental Health*, 36(1):101-115.	Moderate
Xu, P., Liu, A., Li, F., Tinkov, A.A., Liu, L. *&* Zhou, J.C. 2021. Associations between metabolic syndrome and four heavy metals: a systematic review and meta-analysis. *Environmental Pollution*, 273:116480.	Moderate
Yoshimasu, K., Kiyohara, C., Takemura, S. *&* Nakai, K. 2014. A meta-analysis of the evidence on the impact of prenatal and early infancy exposures to mercury on autism and attention deficit/hyperactivity disorder in the childhood. *Neurotoxicology*, 44:121-131.	Moderate
Zhang, J., Li, X., Shen, L., Khan, N.U., Zhang, X., Chen, L., Luo, P. *et al.* 2021. Trace elements in children with autism spectrum disorder: a meta-analysis based on case-control studies. *Journal of Trace Elements in Medicine and Biology*, 67:126782.	Moderate
	Low (n = 13)
Amadi, C.N., Orish, C.N., Frazzoli, C. *&* Orisakwe, O.E. 2022. Association of autism with toxic metals: a systematic review of case-control studies. *Pharmacology Biochemistry and Behavior*, 212:173313.	Low
Bauer, J.A., Fruh, V., Howe, C.G., White, R.F. *&* Claus Henn, B. 2020. Associations of metals and neurodevelopment: a review of recent evidence on susceptibility factors. *Current epidemiology reports*, 7:237-262.	Low
De Palma, G., Catalani, S., Franco, A., Brighenti, M. *&* Apostoli, P. 2012. Lack of correlation between metallic elements analyzed in hair by ICP-MS and autism. *Journal of autism and developmental disorders*, 42:342-353.	Low
Asmus, C.I.F., Camara, V.M., Landrigan, P.J. *&* Claudio, L. 2016. A systematic review of children's environmental health in Brazil. *Annals of global health*, 82(1):132-148.	Low
Gribble, M.O., Cheng, A., Berger, R.D., Rosman, L. *&* Guallar, E. 2015. Mercury exposure and heart rate variability: a systematic review. *Current environmental health reports*, 2:304-314.	Low
Henriques, M.C., Loureiro, S., Fardilha, M. *&* Herdeiro, M.T. 2019. Exposure to mercury and human reproductive health: A systematic review. *Reproductive toxicology*, 85:93-103.	Low
Jafari Mohammadabadi, H., Rahmatian, A., Sayehmiri, F. *&* Rafiei, M. 2020. The relationship between the level of copper, lead, mercury and autism disorders: a meta-analysis. *Pediatric Health, Medicine and Therapeutics*, 11: 369-378.	Low
Kuo, C.C., Moon, K., Thayer, K.A. *&* Navas-Acien, A. 2013. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. *Current diabetes reports*, 13:831-849.	Low
Ledda, C., Cannizzaro, E., Lovreglio, P., Vitale, E., Stufano, A., Montana, A., Rapisarda, V. *et al.* 2019. Exposure to toxic heavy metals can influence homocysteine metabolism?. *Antioxidants*, 9(1):30.	Low

TABLE A5.6 **QUALITY ASSESSMENT (RISK OF BIAS) OF SYSTEMATIC REVIEWS FROM FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg", USING THE QUALITY ASSESSMENT TOOL AMSTAR 2**

Study (*n* = 34)	AMSTAR 2 grading
Miller, S., Pallan, S., Gangji, A.S., Lukic, D. *&* Clase, C.M. 2013. Mercury-associated nephrotic syndrome: a case report and systematic review of the literature. American *Journal of Kidney Diseases*, 62(1):135-138.	Low
Rossignol, D.A., Genuis, S.J., *&* Frye, R.E. 2014. Environmental toxicants and autism spectrum disorders: a systematic review. *Translational psychiatry*, 4(2):e360-e360.	Low
Saavedra, S., Fernández-Recamales, Á., Sayago, A., Cervera-Barajas, A., González-Domínguez, R. *&* Gonzalez-Sanz, J.D. 2022. Impact of dietary mercury intake during pregnancy on the health of neonates and children: a systematic review. *Nutrition Reviews*, 80(2):317-328.	Low
Yu, V., Juhász, M. Chiang, A. *&* Mesinkovska, N.A. 2018. Alopecia and associated toxic agents: a systematic review. *Skin Appendage Disorders*, 4(4):245-260.	Low
	Very low (n = 5)
Bellinger, D.C., O'Leary, K., Rainis, H. *&* Gibb, H.J. 2016. Country-specific estimates of the incidence of intellectual disability associated with prenatal exposure to methylmercury. *Environmental research*, 147:159-163.	Very low
Kadawathagedara, M., de Lauzon-Guillain, B. *&* Botton, J. 2018. Environmental contaminants and child's growth. *Journal of Developmental Origins of Health and Disease*, 9(6):632-641.	Very low
Karita, K., Iwata, T., Maeda, E., Sakamoto, M. *&* Murata, K. 2018. Assessment of cardiac autonomic function in relation to methylmercury neurotoxicity. *Toxics*, 6(3):38.	Very low
Kern, J.K., Geier, D.A., Homme, K.G., King, P.G., Bjørklund, G., Chirumbolo, S. *&* Geier, M.R. 2017. Developmental neurotoxicants and the vulnerable male brain: a systematic review of suspected neurotoxicants that disproportionally affect males. *Acta Neurobiol Exp (Wars)*, 77(4):269-296.	Very low
Sánchez-Alarcón, J., Miliβ, M., Bustamante-Montes, L.P., Isaac-Olivé, K., Valencia-Quintana, R. *&* Ramírez-Durán, N. 2021. Genotoxicity of Mercury and Its Derivatives Demonstrated In Vitro and In Vivo in Human Populations Studies. Systematic Review. *Toxics*, 9(12):326.	Very low

TABLE A5.7 **QUALITY ASSESSMENT (RISK OF BIAS) OF PRIMARY STUDIES FROM FULL-TEXT SCREENING FOR THE THEME "TOXIC EFFECTS OF MeHg", USING THE QUALITY ASSESSMENT TOOL OF THE OFFICE OF HEALTH ASSESSMENT AND TRANSLATION**

Study (n = 10)	Risk-of-bias assessment
Andrew, A.S., Chen, C.Y., Caller, T.A., Tandan, R., Henegan, P.L., Jackson, B.P, Stommel, E.W. *et al.* 2018. Toenail mercury Levels are associated with amyotrophic lateral sclerosis risk. *Muscle & nerve*, 58(1):36-41.	Tier 2
Basta, P.C..,, Viana, P.V.D.S., Vasconcellos, A.C.S.D., Périssé, A.R.S., Hofer, C.B., Paiva, N.S., Hacon, S.D.S. *et al.* 2021. Mercury exposure in Munduruku indigenous communities from Brazilian Amazon: Methodological background and an overview of the principal results. *International journal of environmental research and public health*, 18(17):9222.	Tier 2
Benefice, E., Luna-Monrroy, S. *&* Lopez-Rodriguez, R. 2010. Fishing activity, health characteristics and mercury exposure of Amerindian women living alongside the Beni River (Amazonian Bolivia). *International Journal of Hygiene and Environmental Health*, 213(6):458-464.	Tier 2
Creed, J.H., Peeri, N.C., Anic, G.M., Thompson, R.C., Olson, J.J., LaRocca, R.V., Egan, K.M. *et al.* 2019. Methylmercury exposure, genetic variation in metabolic enzymes, and the risk of glioma. *Scientific reports*, 9(1):1-7.	Tier 2
Karatela, S., Paterson, J. *&* Ward, N.I. 2017. Domain specific effects of postnatal toenail methylmercury exposure on child behaviour. *Journal of trace elements in medicine and biology*, 41:10-15.	Tier 2
Kishi, R., Araki, A., Minatoya, M., Hanaoka, T., Miyashita, C., Itoh, S., Goudarzi, H. *et al.* 2017. The Hokkaido birth cohort study on environment and children's health: cohort profile—updated 2017. *Environmental health and preventive medicine*, 22(1):1-16.	Tier 2
Oliveira, R.A.A.D., Pinto, B.D., Rebouças, B.H., Ciampi de Andrade, D., Vasconcellos, A.C.S.D. *&* Basta, P.C. 2021. Neurological impacts of chronic methylmercury exposure in Munduruku indigenous adults: somatosensory, motor, and cognitive abnormalities. *International journal of environmental research and public health*, 18(19):10270.	Tier 2
Peplow, D. *&* Augustine, S. 2014. Neurological abnormalities in a mercury exposed population among indigenous Wayana in Southeast Suriname. *Environmental Science: Processes & Impacts*, 16(10):2415-2422.	Tier 2
Turunen, A.W., Jula, A., Suominen, A.L., Männistö, S., Marniemi, J., Kiviranta, H., Verkasalo, P.K. *et al.* 2013. Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis. *Environmental research*, 120:43-54.	Tier 2
Zareba, W., Thurston, S.W., Zareba, G., Couderc, J.P., Evans, K., Xia, J. *et al. et al.* 2019. Prenatal and recent methylmercury exposure and heart rate variability in young adults: the Seychelles Child Development Study. *Neurotoxicology and teratology*, 74:106810.	Tier 2

APPENDIX 6
Se AND MeHg

LITERATURE SEARCH STRATEGY

TABLE A6.1 **LITERATURE SEARCH STRATEGY FOR THE REVIEW "Se AND MeHg"**

Database: Web of Science			
Date of search: 7 January 2022			
Literature search string		Search field	Hits
#1	*selen* OR HgSe	TS	125 791
#2	methylmercury OR MeHg or methylHg OR methyl-Hg or CH3Hg	TS	13 428
#3	mammal* OR human* OR human OR rat OR rats OR mice OR mouse OR rodent* OR ''guinea pig'' OR ''guinea pigs'' OR dogs OR dog OR monkey* OR men OR man OR women OR woman OR patient* OR child* OR toddler* OR infant* OR fetus	TS	16 212 122
#4	health* OR benefit* OR effect* OR toxi* OR intervention* OR cohor* OR uptake OR accumulation OR excretion OR clearance OR response* OR stress* OR exposure OR cocktail* OR interaction*	TS	22 328 589
#5	#1 AND #2	TS	1 302
#6	#3 AND #4	TS	8 559 078
#7	#5 AND #6	TS	715
#8	selen* OR HgSe OR methylselen*	ALL fields	122 719
#9	methylmercury OR MeHg or methylHg OR methyl-Hg or CH3Hg	ALL fields	13 442
#10	mammal* OR human* OR human OR rat OR rats OR mice OR mouse OR rodent* OR ''guinea pig'' OR ''guinea pigs'' OR dogs OR dog OR monkey* OR men OR man OR women OR woman OR patient* OR child* OR toddler* OR infant* OR fetus	ALL fields	18 794 267
#11	health* OR benefit* OR effect* OR toxi* OR intervention* OR cohor* OR uptake OR accumulation OR excretion OR clearance OR response* OR stress* OR exposure OR cocktail* OR interaction*	ALL fields	24 538 170
#12	#8 AND #9	ALL fields	1 282
#13	#10 AND #11	ALL fields	11 148 862
#14	#12 AND #13	ALL fields	771
#15	#1 AND #9 AND #13	TS + ALL fields hybrid	792
Database: PubMed			
Date of search: 7 January 2022			
Literature search string		Search field	Hits
#1	selen* OR HgSe	All fields	52 139
#2	methylmercury OR MeHg or methylHg OR methyl-Hg or CH3Hg	All fields	8 400
#3	mammal* OR human* OR human OR rat OR rats OR mice OR mouse OR rodent* OR ''guinea pig'' OR ''guinea pigs'' OR dogs OR dog OR monkey* OR men OR man OR women OR woman OR patient* OR child* OR toddler* OR infant* OR fetus	All fields	23 699 237
#4	health* OR benefit* OR effect* OR toxi* OR intervention* OR cohor* OR uptake OR accumulation OR excretion OR clearance OR response* OR stress* OR exposure OR cocktail* OR interaction*	All fields	17 949 060
#5	#1 AND #2		656
#6	#3 AND #4		13 421 491
#7	#5 AND #6		362

RECORDS EXCLUDED DURING FULL-TEXT SCREENING

TABLE A6.2 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA

Studies (n = 68)	Reason for exclusion
Achouba, A., Dumas, P., Ouellet, N., Little, M., Lemire, M. & Ayotte, P. 2019. Selenoneine is a major selenium species in beluga skin and red blood cells of Inuit from Nunavik. *Chemosphere*, 229: 549-558. https://doi.org/10.1016/j.chemosphere.2019.04.191	No health outcome measured.
Afonso, C., Bernardo, I., Bandarra, N.M., Martins, L.L. & Cardoso, C. 2019. The implications of following dietary advice regarding fish consumption frequency and meal size for the benefit (EPA + DHA and Se) versus risk (MeHg) assessment. *Int J Food Sci Nutr*, 70(5): 623-637. https://doi.org/10.1080/09637486.2018.1551334	No health outcome measured.
Alves, A.C., Monteiro, M.S., Machado, A.L., Oliveira, M., Bóia, A., Correia, A., Oliveira, N., Soares, A. & Loureiro, S. 2017. Mercury levels in parturient and newborns from Aveiro region, Portugal. *J Toxicol Environ Health A*, 80(13-15): 697-709. https://doi.org/10.1080/15287394.2017.1286926	No health outcome measured.
Ask, K., Akesson, A., Berglund, M. & Vahter, M. 2002. Inorganic mercury and methylmercury in placentas of Swedish women. *Environmental Health Perspectives*, 110(5): 523-526. https://doi.org/10.1289/ehp.02110523	No health outcome measured.
Ballesteros, M.T.L., Barrado, B.G., Serrano, I.N., Alvarez, S.I., Anaya, M.D.G. & Munoz, M.J.G. 2020. Evaluation of blood mercury and serum selenium levels in the pregnant population of the Community of Madrid, Spain. *Journal of Trace Elements in Medicine and Biology*, 57: 60-67. https://doi.org/10.1016/j.jtemb.2019.09.008	No health outcome measured.
Barany, E., Bergdahl, I.A., Bratteby, L.E., Lundh, T., Samuelson, G., Skerfving, S. & Oskarsson, A. 2003. Mercury and selenium in whole blood and serum in relation to fish consumption and amalgam fillings in adolescents. *Journal of Trace Elements in Medicine and Biology*, 17(3): 165-170. https://doi.org/10.1016/s0946-672x(03)80021-4	No health outcome measured.
Bates, C.J., Prentice, A., Birch, M.C. & Delves, H.T. 2007. Dependence of blood indices of selenium and mercury on estimated fish intake in a national survey of British adults. *Public Health Nutrition*, 10(5): 508-517. https://doi.org/10.1017/s1368980007246683	No health outcome measured.
Bates, C.J., Prentice, A., Birch, M.C., Delves, H.T. & Sinclair, K.A. 2006. Blood indices of selenium and mercury, and their correlations with fish intake, in young people living in Britain. *British Journal of Nutrition*, 96(3): 523-531. https://doi.org/10.1079/bjn20061847	No health outcome measured.
Binnington, M.J., Curren, M.S., Chan, H.M. & Wania, F. 2016. Balancing the benefits and costs of traditional food substitution by indigenous Arctic women of childbearing age: Impacts on persistent organic pollutant, mercury, and nutrient intakes. *Environment International*, 94: 554-566. https://doi.org/10.1016/j.envint.2016.06.016	No access to full-text paper.
Bjornberg, K.A., Vahter, M., Petersson-Grawe, K., Glynn, A., Cnattingius, S., Darnerud, P.O., Atuma, S., Aune, M., Becker, W. & Berglund, M. 2003. Methyl mercury and inorganic mercury in Swedish pregnant women and in cord blood: Influence of fish consumption. *Environmental Health* Perspectives, 111(4): 637-641. https://doi.org/10.1289/ehp.111-1241457	No health outcome measured.
Björnberg, K.A., Vahter, M., Grawé, K.P. & Berglund, M. 2005. Methyl mercury exposure in Swedish women with high fish consumption. *Sci Total Environ*, 341(1-3): 45-52. https://doi.org/10.1016/j.scitotenv.2004.09.033	No health outcome measured.
Bridges, K.N., Furin, C.G. & Gerlach, R.F. 2020. Subsistence fish consumption in rural Alaska: Using regional monitoring data to evaluate risk and bioavailability of dietary methylmercury. *Sci Total Environ*, 736: 139676. https://doi.org/10.1016/j.scitotenv.2020.139676	No health outcome measured.
Brumatti, L.V., Rosolen, V., Mariuz, M., Piscianz, E., Valencic, E., Bin, M., Athanasakis, E. *et al.* 2021. Impact of Methylmercury and Other Heavy Metals Exposure on Neurocognitive Function in Children Aged 7 Years: Study Protocol of the Follow-up. *Journal of Epidemiology*, 31(2): 157-163. https://doi.org/10.2188/jea.JE20190284	Study protocol and does not include primary data.
Cardoso, C., Bernardo, I., Bandarra, N.M., Martins, L.L. & Afonso, C. 2018. Portuguese preschool children: Benefit (EPA plus DHA and Se) and risk (MeHg) assessment through the consumption of selected fish species. *Food and Chemical Toxicology*, 115: 306-314. https://doi.org/10.1016/j.fct.2018.03.022	Health outcome not measured
Carneiro, M.F., Grotto, D. & Barbosa, F., Jr. 2014. Inorganic and methylmercury levels in plasma are differentially associated with age, gender, and oxidative stress markers in a population exposed to mercury through fish consumption. *J Toxicol Environ Health A*, 77(1-3): 69-79. https://doi.org/10.1080/15287394.2014.865584	Health outcome not measured
Dewailly, E., Suhas, E., Mou, Y., Dallaire, R., Chateau-Degat, L. & Chansin, R. 2008. High fish consumption in French Polynesia and prenatal exposure to metals and nutrients. *Asia Pacific Journal of Clinical Nutrition*, 17(3): 461-470. <Go to ISI>://WOS:000260195600015	Health outcome not measured
Dewailly, E., Chateau-Degat, L. & Suhas, E. 2008. Fish consumption and health in French Polynesia. *Asia Pacific Journal of Clinical Nutrition*, 17(1): 86-93. <Go to ISI>://WOS:000254880400015	Health outcome not measured
Gilman, C.L., Soon, R., Sauvage, L., Ralston, N.V.C. & Berry, M.J. 2015. Umbilical cord blood and placental mercury, selenium and selenoprotein expression in relation to maternal fish consumption. *Journal of Trace Elements in Medicine and Biology*, 30: 17-24. https://doi.org/10.1016/j.jtemb.2015.01.006	Health outcome not measured
Grandjean, P., Weihe, P., Needham, L.L., Burse, V.W., Patterson, D.G., Sampson, E.J., Jorgensen, P.J. & Vahter, M. 1995. Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. *Environmental Research*, 71(1): 29-38. https://doi.org/10.1006/enrs.1995.1064	Health outcome not measured
Gundacker, C., Komarnicki, G., Zodl, B., Forster, C., Schuster, E. & Wittmann, K. 2006. Whole blood mercury and selenium concentrations in a selected Austrian population: Does gender matter? *Science of the Total Environment*, 372(1): 76-86. https://doi.org/10.1016/j.scitotenv.2006.08.006	Health outcome not measured
Hayat, L. 1996. Cations in malignant and benign brain tumors. *Journal of Environmental Science and Health Part a-Environmental Science and Engineering & Toxic and Hazardous Substance Control*, 31(8): 1831-1840. https://doi.org/10.1080/10934529609376459	Health outcome not measured
Hoang, V.A.T., Do, H.T.T., Agusa, T., Koriyama, C., Akiba, S., Ishibashi, Y., Sakamoto, M. & Yamamoto, M. 2017. Hair mercury levels in relation to fish consumption among Vietnamese in Hanoi. *J Toxicol Sci*, 42(5): 651-662. https://doi.org/10.2131/jts.42.651	Health outcome not measured
Iwai-Shimada, M., Kameo, S., Nakai, K., Yaginuma-Sakurai, K., Tatsuta, N., Kurokawa, N., Nakayama, S.F. & Satoh, H. 2019. Exposure profile of mercury, lead, cadmium, arsenic, antimony, copper, selenium and zinc in maternal blood, cord blood and placenta: the Tohoku Study of Child Development in Japan. *Environ Health Prev Med*, 24(1): 35. https://doi.org/10.1186/s12199-019-0783-y	Health outcome not measured

TABLE A6.2 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Studies (n = 68)	Reason for exclusion
Johansen, P., Mulvad, G., Pedersen, H.S., Hansen, J.C. & Riget, F. 2007. Human accumulation of mercury in Greenland. *Sci Total Environ*, 377(2-3): 173-8. https://doi.org/10.1016/j.scitotenv.2007.02.004	No health outcome measured.
Karimi, R., Fisher, N.S. & Meliker, J.R. 2014. Mercury-nutrient signatures in seafood and in the blood of avid seafood consumers. *Sci Total Environ*, 496: 636-643. https://doi.org/10.1016/j.scitotenv.2014.04.049	No health outcome measured.
Karita, K. & Suzuki, T. 2002. Fish eating and variations in selenium and mercury levels in plasma and erythrocytes in free-living healthy Japanese men. *Biological Trace Element Research*, 90(1-3): 71-81. https://doi.org/10.1385/bter:90:1-3:71	No health outcome measured.
Kim, B.M., Choi, A.L., Ha, E.H., Pedersen, L., Nielsen, F., Weihe, P., Hong, Y.C., Budtz-Jørgensen, E. & Grandjean, P. 2014. Effect of hemoglobin adjustment on the precision of mercury concentrations in maternal and cord blood. *Environ Res*, 132: 407-12. https://doi.org/10.1016/j.envres.2014.04.030	Methodical but not related directly to health.
Korbas, M., O'Donoghue, J.L., Watson, G.E., Pickering, I.J., Singh, S.P., Myers, G.J., Clarkson, T.W. & George, G.N. 2010. The chemical nature of mercury in human brain following poisoning or environmental exposure. *ACS Chem Neurosci*, 1(12): 810-8. https://doi.org/10.1021/cn1000765	Exposure to MeHg after poisoning.
Kosatsky, T., Przybysz, R. & Armstrong, B. 2000. Mercury exposure in Montrealers who eat St. Lawrence River sportfish. *Environmental Research*, 84(1): 36-43. https://doi.org/10.1006/enrs.2000.4073	No health outcome measured and only Se in blood
Lemire, M., Kwan, M., Laouan-Sidi, A.E., Muckle, G., Pirlde, C., Ayotte, P. & Dewailly, E. 2015. Local country food sources of methylmercury, selenium and omega-3 fatty acids in Nunavik, Northern Quebec. *Science of the Total Environment*, 509: 248-259. https://doi.org/10.1016/j.scitotenv.2014.07.102	No health outcome measured.
Lemire, M., Philibert, A., Fillion, M., Passos, C.J.S., Guimaraes, J.R.D., Barbosa, F. & Mergler, D. 2012. No evidence of selenosis from a selenium-rich diet in the Brazilian Amazon. *Environment International*, 40: 128-136. https://doi.org/10.1016/j.envint.2011.07.005	Only selenium measured (not mercury)
Lemire, M., Mergler, D., Fillion, M., Sousa Passos, C.J., Guimaraes, J.R.D., Davidson, R. & Lucotte, M. 2006. Elevated blood selenium levels in the Brazilian Amazon. *Science of the Total Environment*, 366(1): 101-111. https://doi.org/10.1016/j.scitotenv.2005.08.057	No health outcome measured.
Li, Y.F., Chen, C.Y., Li, B., Wang, Q., Wang, J.X., Gao, Y.X., Zhao, Y.L. & Chai, Z.F. 2007. Simultaneous speciation of selenium and mercury in human urine samples from long-term mercury-exposed populations with supplementation of selenium-enriched yeast by HPLC-ICP-MS. *Journal of Analytical Atomic Spectrometry*, 22(8): 925-930. https://doi.org/10.1039/b703310a	Method development and specification
Lindberg, A., Björnberg, K.A., Vahter, M. & Berglund, M. 2004. Exposure to methylmercury in non-fish-eating people in Sweden. *Environ Res*, 96(1): 28-33. https://doi.org/10.1016/j.envres.2003.09.005	No health outcome measured
Little, M., Achouba, A., Dumas, P., Ouellet, N., Ayotte, P. & Lemire, M. 2019. Determinants of selenoneine concentration in red blood cells of Inuit from Nunavik (Northern Quebec, Canada). *Environment International*, 127: 243-252. https://doi.org/10.1016/j.envint.2018.11.077	No health outcome measured
Lubick, N. 2010. A balanced diet? Selenium may offset the effects of methylmercury on cataract development. *Environ Health Perspect*, 118(11): A491. https://doi.org/10.1289/ehp.118-a491b	News article
Marumoto, M., Sakamoto, M., Marumoto, K., Tsuruta, S. & Komohara, Y. 2020. Mercury and Selenium Localization in the Cerebrum, Cerebellum, Liver, and Kidney of a Minamata Disease Case. *Acta Histochem Cytochem*, 53(6): 147-155. https://doi.org/10.1267/ahc.20-00009	A single toxicology case
Miklavčič, A., Casetta, A., Snoj Tratnik, J., Mazej, D., Krsnik, M., Mariuz, M., Sofianou, K., Spirić, Z., Barbone, F. & Horvat, M. 2013. Mercury, arsenic and selenium exposure levels in relation to fish consumption in the Mediterranean area. *Environ Res*, 120: 7-17. https://doi.org/10.1016/j.envres.2012.08.010	No health outcome measured
Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W. & Jacobson, J.L. 2001. Determinants of polychlorinated biphenyls and methylmercury exposure in inuit women of childbearing age. *Environ Health Perspect*, 109(9): 957-63. https://doi.org/10.1289/ehp.01109957	No health outcome measured
Muckle, G., Ayotte, P., Dewailly, E.E., Jacobson, S.W. & Jacobson, J.L. 2001. Prenatal exposure of the northern Québec Inuit infants to environmental contaminants. *Environ Health Perspect*, 109(12): 1291-9. https://doi.org/10.1289/ehp.011091291	No health outcome measured
Nakayama, S.F., Iwai-Shimada, M., Oguri, T., Isobe, T., Takeuchi, A., Kobayashi, Y., Michikawa, T. *et al.* 2019. Blood mercury, lead, cadmium, manganese and selenium levels in pregnant women and their determinants: the Japan Environment and Children's Study (JECS). *Journal of Exposure Science and Environmental Epidemiology*, 29(5): 633-647. https://doi.org/10.1038/s41370-019-0139-0	No health outcome measured
Niane, B., Guedron, S., Moritz, R., Cosio, C., Ngom, P.M., Deverajan, N., Pfeifer, H.R. & Pote, J. 2015. Human exposure to mercury in artisanal small-scale gold mining areas of Kedougou region, Senegal, as a function of occupational activity and fish consumption. *Environmental Science and Pollution Research*, 22(9): 7101-7111. https://doi.org/10.1007/s11356-014-3913-5	No health outcome measured
Parajuli, R.P., Goodrich, J.M., Chan, H.M., Lemire, M., Ayotte, P., Hegele, R.A. & Basu, N. 2021. Variation in biomarker levels of metals, persistent organic pollutants, and omega-3 fatty acids in association with genetic polymorphisms among Inuit in Nunavik, Canada. *Environmental Research*, 200. https://doi.org/10.1016/j.envres.2021.111393	No health outcome measured
Pinheiro, M.C.N., Muller, R.C.S., Sarkis, J.E., Vieira, J.L.F., Oikawa, T., Gomes, M.S.V., Guimaraes, G.A., do Nascimento, J.L.M. & Silveira, L.C.L. 2005. Mercury and selenium concentrations in hair samples of women in fertile age from Amazon riverside communities. *Science of the Total Environment*, 349(1-3): 284-288. https://doi.org/10.1016/j.scitotenv.2005.06.026	No health outcome measured
Sakamoto, M., Haraguchi, K., Tatsuta, N., Nakai, K., Nakamura, M. & Murata, K. 2021. Plasma and red blood cells distribution of total mercury, inorganic mercury, and selenium in maternal and cord blood from a group of Japanese women. *Environ Res*, 196: 110896. https://doi.org/10.1016/j.envres.2021.110896	No health outcome measured
Sakamoto, M., Chan, H.M., Domingo, J.L., Koriyama, C. & Murata, K. 2018. Placental transfer and levels of mercury, selenium, vitamin E, and docosahexaenoic acid in maternal and umbilical cord blood. *Environ Int*, 111: 309-315. https://doi.org/10.1016/j.envint.2017.11.001	No health outcome measured
Sakamoto, M., Chan, H.M., Domingo, J.L., Kubota, M. & Murata, K. 2012. Changes in body burden of mercury, lead, arsenic, cadmium and selenium in infants during early lactation in comparison with placental transfer. Ecotoxicol *Environ Saf*, 84: 179-84. https://doi.org/10.1016/j.ecoenv.2012.07.014	No health outcome measured

TABLE A6.2 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)

Studies (n = 68)	Reason for exclusion
Sakamotoa, M., Kubota, M., Murata, K., Nakai, K., Sonoda, I. & Satoh, H. 2008. Changes in mercury concentrations of segmental maternal hair during gestation and their correlations with other biomarkers of fetal exposure to methylmercury in the Japanese population. *Environmental Research*, 106(2): 270-276. https://doi.org/10.1016/j.envres.2007.10.002	No health outcome measured
Sekovanic, A., Piasek, M., Orct, T., Grgec, A.S., Saric, M.M., Stasenko, S. & Jurasovic, J. 2020. Mercury Exposure Assessment in Mother-Infant Pairs from Continental and Coastal Croatia. Biomolecules, 10(6). https://doi.org/10.3390/biom10060821	No health outcome measured
Ser, P.H., Omi, S., Shimizu-Furusawa, H., Yasutake, A., Sakamoto, M., Hachiya, N., Konishi, S., Nakamura, M. & Watanabe, C. 2017. Differences in the responses of three plasma selenium-containing proteins in relation to methylmercury-exposure through consumption of fish/whales. *Toxicol Lett*, 267: 53-58. https://doi.org/10.1016/j.toxlet.2016.12.001	No health outcome measured
Suzuki, T., Hongo, T., Yoshinaga, J., Imai, H., Nakazawa, M., Matsuo, N. & Akagi, H. 1993. The hair-organ relationship in mercury concentration in contemporary Japanese. *Arch Environ Health*, 48(4): 221-9. https://doi.org/10.1080/00039896.1993.9940363	No health outcome measured
Svensson, B.G., Nilsson, A., Jonsson, E., Schütz, A., Akesson, B. & Hagmar, L. 1995. Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. *Scand J Work Environ Health*, 21(2): 96-105. https://doi.org/10.5271/sjweh.16	No health outcome measured
Svensson, B.G., Schütz, A., Nilsson, A., Akesson, I., Akesson, B. & Skerfving, S. 1992. Fish as a source of exposure to mercury and selenium. *Sci Total Environ*, 126(1-2): 61-74. https://doi.org/10.1016/0048-9697(92)90484-a	No health outcome measured
Trdin, A., Snoj Tratnik, J., Stajnko, A., Marc, J., Mazej, D., Sešek Briški, A., Kastelec, D. *et al.* 2020. Trace elements and APOE polymorphisms in pregnant women and their new-borns. *Environ Int*, 143: 105626. https://doi.org/10.1016/j.envint.2020.105626	No use of Se data
Trdin, A., Snoj Tratnik, J., Mazej, D., Fajon, V., Krsnik, M., Osredkar, J., Prpić, I. *et al.* 2019. Mercury speciation in prenatal exposure in Slovenian and Croatian population - PHIME study. *Environ Res*, 177: 108627. https://doi.org/10.1016/j.envres.2019.108627	No health outcome measured
Valent, F., Pisa, F., Mariuz, M., Horvat, M., Gibicar, D., Fajon, V., Mazej, D., Daris, F. & Barbone, F. 2011. Fetal and perinatal exposure to mercury and selenium: baseline evaluation of a cohort of children in Friuli Venezia Giulia, Italy. *Epidemiol Prev*, 35(1): 33-42.	Article in Italian
Valera, B., Muckle, G., Poirier, P., Jacobson, S.W., Jacobson, J.L. & Dewailly, E. 2012. Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. *Neurotoxicology*, 33(5): 1067-1074. https://doi.org/10.1016/j.neuro.2012.05.005	Selenium not measured
Vecchi Brumatti, L., Rosolen, V., Mariuz, M., Piscianz, E., Valencic, E., Bin, M., Athanasakis, E. *et al.* 2021. Impact of Methylmercury and Other Heavy Metals Exposure on Neurocognitive Function in Children Aged 7 Years: Study Protocol of the Follow-up. *J Epidemiol*, 31(2): 157-163. https://doi.org/10.2188/jea.JE20190284	Study protocol only
Walker, J.B., Houseman, J., Seddon, L., McMullen, E., Tofflemire, K., Mills, C., Corriveau, A. *et al.* 2006. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. *Environmental Research*, 100(3): 295-318. https://doi.org/10.1016/j.envres.2005.05.006	No health outcome measured
Wells, E.M., Herbstman, J.B., Lin, Y.H., Hibbeln, J.R., Halden, R.U., Witter, F.R. & Goldman, L.R. 2017. Methyl mercury, but not inorganic mercury, associated with higher blood pressure during pregnancy. *Environ Res*, 154: 247-252. https://doi.org/10.1016/j.envres.2017.01.013	Selenium as a covariate in a multi model
Wilhelm, M., Wittsiepe, J., Schrey, P., Lajoie-Junge, L. & Busch, V. 2003. Dietary intake of arsenic, mercury and selenium by children from a German North Sea island using duplicate portion sampling. *Journal of Trace Elements in Medicine and Biology*, 17(2): 123-132. https://doi.org/10.1016/s0946-672x(03)80008-1	No health outcome measured
Yalcin, S.S., Yurdakok, K., Yalcin, S., Engur-Karasimav, D. & Coskun, T. 2010. Maternal and environmental determinants of breast-milk mercury concentrations. *Turkish Journal of Pediatrics*, 52(1): 1-9. <Go to ISI>://WOS:000276572900001	No health outcome measured
Yamashita, M., Yamashita, Y., Ando, T., Wakamiya, J. & Akiba, S. 2013. Identification and determination of selenoneine, 2-selenyl-N α , N α , N α -trimethyl-L-histidine, as the major organic selenium in blood cells in a fish-eating population on remote Japanese Islands. *Biol Trace Elem Res*, 156(1-3): 36-44. https://doi.org/10.1007/s12011-013-9846-x	No health outcome measured
Yoo, Y.C., Lee, S.K., Yang, J.Y., Kim, K.W., Lee, S.Y., Oh, S.M. & Chung, K.H. 2002. Interrelationship between the concentration of toxic and essential elements in Korean tissues. *Journal of Health Science*, 48(2): 195-200. <Go to ISI>://WOS:000174717400015	No health outcome measured
Yoshinaga, J., Matsuo, N., Imai, H., Nakazawa, M., Suzuki, T., Morita, M. & Akagi, H. 1990. Interrelationship between the concentrations of some elements in the organs of Japanese with special reference to selenium-heavy metal relationships. *Sci Total Environ*, 91: 127-40. https://doi.org/10.1016/0048-9697(90)90294-5	No health outcome measured
Zhang, M.Y., Buckley, J.P., Liang, L.M., Hong, X.M., Wang, G.Y., Wang, M.C., Wills-Karp, M., Wang, X.B. & Mueller, N.T. 2022. A metabolome-wide association study of in utero metal and trace element exposures with cord blood metabolome profile: Findings from the Boston Birth Cohort. *Environment International*, 158. https://doi.org/10.1016/j.envint.2021.106976	Effect of selenium on Hg toxicity not measured
Zhang, M.Y., Liu, T.G., Wang, G.Y., Buckley, J.P., Guallar, E., Hong, X.M., Wang, M.C., Wills-Karp, M., Wang, X.B. & Mueller, N.T. 2021. In Utero Exposure to Heavy Metals and Trace Elements and Childhood Blood Pressure in a US Urban, Low-Income, Minority Birth Cohort. *Environmental Health Perspectives*, 129(6). https://doi.org/10.1289/ehp8325	No health outcome measured
Studies (n = 68)	**Reason for exclusion**
Gilman, C. L., Soon, R., Sauvage, L., Ralston, N. V., & Berry, M. J. 2015. Umbilical cord blood and placental mercury, selenium and selenoprotein expression in relation to maternal fish consumption. *Journal of Trace Elements in Medicine and Biology*, 30, 17-24.	No health outcome measured
Achouba, A., Dumas, P., Ouellet, N., Little, M., Lemire, M. & Ayotte, P. 2019. Selenoneine is a major selenium species in beluga skin and red blood cells of Inuit from Nunavik. *Chemosphere*, 229: 549-558. https://doi.org/10.1016/j.chemosphere.2019.04.191	No health outcome measured
Afonso, C., Bernardo, I., Bandarra, N.M., Martins, L.L. & Cardoso, C. 2019. The implications of following dietary advice regarding fish consumption frequency and meal size for the benefit (EPA + DHA and Se) versus risk (MeHg) assessment. *Int J Food Sci Nutr*, 70(5): 623-637. https://doi.org/10.1080/09637486.2018.1551334	No health outcome measured
Alves, A.C., Monteiro, M.S., Machado, A.L., Oliveira, M., Bóia, A., Correia, A., Oliveira, N., Soares, A. & Loureiro, S. 2017. Mercury levels in parturient and newborns from Aveiro region, Portugal. *J Toxicol Environ Health A*, 80(13-15): 697-709. https://doi.org/10.1080/15287394.2017.1286926	No health outcome measured

TABLE A6.2 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Studies (n = 68)	Reason for exclusion
Ask, K., Akesson, A., Berglund, M. & Vahter, M. 2002. Inorganic mercury and methylmercury in placentas of Swedish women. *Environmental Health Perspectives*, 110(5): 523-526. https://doi.org/10.1289/ehp.02110523	No health outcome measured
Ballesteros, M.T.L., Barrado, B.G., Serrano, I.N., Alvarez, S.I., Anaya, M.D.G. & Munoz, M.J.G. 2020. Evaluation of blood mercury and serum selenium levels in the pregnant population of the Community of Madrid, Spain. *Journal of Trace Elements in Medicine and Biology*, 57: 60-67. https://doi.org/10.1016/j.jtemb.2019.09.008	No health outcome measured
Barany, E., Bergdahl, I.A., Bratteby, L.E., Lundh, T., Samuelson, G., Skerfving, S. & Oskarsson, A. 2003. Mercury and selenium in whole blood and serum in relation to fish consumption and amalgam fillings in adolescents. *Journal of Trace Elements in Medicine and Biology*, 17(3): 165-170. https://doi.org/10.1016/s0946-672x(03)80021-4	No health outcome measured
Bates, C.J., Prentice, A., Birch, M.C. & Delves, H.T. 2007. Dependence of blood indices of selenium and mercury on estimated fish intake in a national survey of British adults. *Public Health Nutrition*, 10(5): 508-517. https://doi.org/10.1017/s1368980007246683	No health outcome measured.
Bates, C.J., Prentice, A., Birch, M.C., Delves, H.T. & Sinclair, K.A. 2006. Blood indices of selenium and mercury, and their correlations with fish intake, in young people living in Britain. *British Journal of Nutrition*, 96(3): 523-531. https://doi.org/10.1079/bjn20061847	No health outcome measured.
Binnington, M.J., Curren, M.S., Chan, H.M. & Wania, F. 2016. Balancing the benefits and costs of traditional food substitution by indigenous Arctic women of childbearing age: Impacts on persistent organic pollutant, mercury, and nutrient intakes. *Environment International*, 94: 554-566. https://doi.org/10.1016/j.envint.2016.06.016	No access to full-text paper.
Bjornberg, K.A., Vahter, M., Petersson-Grawe, K., Glynn, A., Cnattingius, S., Darnerud, P.O., Atuma, S., Aune, M., Becker, W. & Berglund, M. 2003. Methyl mercury and inorganic mercury in Swedish pregnant women and in cord blood: Influence of fish consumption. *Environmental Health Perspectives*, 111(4): 637-641. https://doi.org/10.1289/ehp.111-1241457	No health outcome measured.
Björnberg, K.A., Vahter, M., Grawé, K.P. & Berglund, M. 2005. Methyl mercury exposure in Swedish women with high fish consumption. *Sci Total Environ*, 341(1-3): 45-52. https://doi.org/10.1016/j.scitotenv.2004.09.033	No health outcome measured.
Bridges, K.N., Furin, C.G. & Gerlach, R.F. 2020. Subsistence fish consumption in rural Alaska: Using regional monitoring data to evaluate risk and bioavailability of dietary methylmercury. *Sci Total Environ*, 736: 139676. https://doi.org/10.1016/j.scitotenv.2020.139676	No health outcome measured.
Brumatti, L.V., Rosolen, V., Mariuz, M., Piscianz, E., Valencic, E., Bin, M., Athanasakis, E. *et al.* 2021. Impact of Methylmercury and Other Heavy Metals Exposure on Neurocognitive Function in Children Aged 7 Years: Study Protocol of the Follow-up. *Journal of Epidemiology*, 31(2): 157-163. https://doi.org/10.2188/jea.JE20190284	Study protocol and does not include primary data.
Walker, J.B., Houseman, J., Seddon, L., McMullen, E., Tofflemire, K., Mills, C., Corriveau, A. *et al.* 2006. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. *Environmental Research*, 100(3): 295-318. https://doi.org/10.1016/j.envres.2005.05.006	Health outcome not measured.
Cardoso, C., Bernardo, I., Bandarra, N.M., Martins, L.L. & Afonso, C. 2018. Portuguese preschool children: Benefit (EPA plus DHA and Se) and risk (MeHg) assessment through the consumption of selected fish species. *Food and Chemical Toxicology*, 115: 306-314. https://doi.org/10.1016/j.fct.2018.03.022	Health outcome not measured.
Carneiro, M.F., Grotto, D. & Barbosa, F., Jr. 2014. Inorganic and methylmercury levels in plasma are differentially associated with age, gender, and oxidative stress markers in a population exposed to mercury through fish consumption. *J Toxicol Environ Health A*, 77(1-3): 69-79. https://doi.org/10.1080/15287394.2014.865584	Health outcome not measured.
Dewailly, E., Chateau-Degat, L. & Suhas, E. 2008. Fish consumption and health in French Polynesia. *Asia Pacific Journal of Clinical Nutrition*, 17(1): 86-93.	Health outcome not measured.
Dewailly, E., Suhas, E., Mou, Y., Dallaire, R., Chateau-Degat, L. & Chansin, R. 2008. High fish consumption in French Polynesia and prenatal exposure to metals and nutrients. *Asia Pacific Journal of Clinical Nutrition*, 17(3): 461-470.	Health outcome not measured.
Grandjean, P., Weihe, P., Needham, L.L., Burse, V.W., Patterson, D.G., Sampson, E.J., Jorgensen, P.J. & Vahter, M. 1995. Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. *Environmental Research*, 71(1): 29-38. https://doi.org/10.1006/enrs.1995.1064	Health outcome not measured.
Gundacker, C., Komarnicki, G., Zodl, B., Forster, C., Schuster, E. & Wittmann, K. 2006. Whole blood mercury and selenium concentrations in a selected Austrian population: Does gender matter? *Science of the Total Environment*, 372(1): 76-86. https://doi.org/10.1016/j.scitotenv.2006.08.006	Health outcome not measured.
Hayat, L. 1996. Cations in malignant and benign brain tumors. *Journal of Environmental Science and Health Part a-Environmental Science and Engineering & Toxic and Hazardous Substance Control*, 31(8): 1831-1840. https://doi.org/10.1080/10934529609376459	Health outcome not measured.
Hoang, V.A.T., Do, H.T.T., Agusa, T., Koriyama, C., Akiba, S., Ishibashi, Y., Sakamoto, M. & Yamamoto, M. 2017. Hair mercury levels in relation to fish consumption among Vietnamese in Hanoi. *J Toxicol Sci*, 42(5): 651-662. https://doi.org/10.2131/jts.42.651	No health outcome measured in relation to toxicity of MeHg.
Iwai-Shimada, M., Kameo, S., Nakai, K., Yaginuma-Sakurai, K., Tatsuta, N., Kurokawa, N., Nakayama, S.F. & Satoh, H. 2019. Exposure profile of mercury, lead, cadmium, arsenic, antimony, copper, selenium and zinc in maternal blood, cord blood and placenta: the Tohoku Study of Child Development in Japan. *Environ Health Prev Med*, 24(1): 35. https://doi.org/10.1186/s12199-019-0783-y	No health outcome measured.
Johansen, P., Mulvad, G., Pedersen, H.S., Hansen, J.C. & Riget, F. 2007. Human accumulation of mercury in Greenland. *Sci Total Environ*, 377(2-3): 173-8. https://doi.org/10.1016/j.scitotenv.2007.02.004	No health outcome measured.
Karimi, R., Fisher, N.S. & Meliker, J.R. 2014. Mercury-nutrient signatures in seafood and in the blood of avid seafood consumers. *Sci Total Environ*, 496: 636-643. https://doi.org/10.1016/j.scitotenv.2014.04.049	No health outcome measured.
Karita, K. & Suzuki, T. 2002. Fish eating and variations in selenium and mercury levels in plasma and erythrocytes in free-living healthy Japanese men. *Biological Trace Element Research*, 90(1-3): 71-81. https://doi.org/10.1385/bter:90:1-3:71	No health outcome measured.
Kim, B.M., Choi, A.L., Ha, E.H., Pedersen, L., Nielsen, F., Weihe, P., Hong, Y.C., Budtz-Jørgensen, E. & Grandjean, P. 2014. Effect of hemoglobin adjustment on the precision of mercury concentrations in maternal and cord blood. *Environ Res*, 132: 407-12. https://doi.org/10.1016/j.envres.2014.04.030	Methodical, but not related directly to health.

TABLE A6.2 PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)

Studies (n = 68)	Reason for exclusion
Korbas, M., O'Donoghue, J.L., Watson, G.E., Pickering, I.J., Singh, S.P., Myers, G.J., Clarkson, T.W. & George, G.N. 2010. The chemical nature of mercury in human brain following poisoning or environmental exposure. *ACS Chem Neurosci*, 1(12): 810-8. https://doi.org/10.1021/cn1000765	Exposure to MeHg after poisoning.
Kosatsky, T., Przybysz, R. & Armstrong, B. 2000. Mercury exposure in Montrealers who eat St. Lawrence River sportfish. *Environmental Research*, 84(1): 36-43. https://doi.org/10.1006/enrs.2000.4073	No health outcome measured and only Se in blood
Lemire, M., Kwan, M., Laouan-Sidi, A.E., Muckle, G., Pirlde, C., Ayotte, P. & Dewailly, E. 2015. Local country food sources of methylmercury, selenium and omega-3 fatty acids in Nunavik, Northern Quebec. *Science of the Total Environment*, 509: 248-259. https://doi.org/10.1016/j.scitotenv.2014.07.102	No health outcome measured.
Lemire, M., Mergler, D., Fillion, M., Sousa Passos, C.J., Guimaraes, J.R.D., Davidson, R. & Lucotte, M. 2006. Elevated blood selenium levels in the Brazilian Amazon. *Science of the Total Environment*, 366(1): 101-111. https://doi.org/10.1016/j.scitotenv.2005.08.057	No health outcome measured.
Lemire, M., Philibert, A., Fillion, M., Passos, C.J.S., Guimaraes, J.R.D., Barbosa, F. & Mergler, D. 2012. No evidence of selenosis from a selenium-rich diet in the Brazilian Amazon. *Environment International*, 40: 128-136. https://doi.org/10.1016/j.envint.2011.07.005	Only selenium measured (not mercury)
Li, Y.F., Chen, C.Y., Li, B., Wang, Q., Wang, J.X., Gao, Y.X., Zhao, Y.L. & Chai, Z.F. 2007. Simultaneous speciation of selenium and mercury in human urine samples from long-term mercury-exposed populations with supplementation of selenium-enriched yeast by HPLC-ICP-MS. *Journal of Analytical Atomic Spectrometry*, 22(8): 925-930. https://doi.org/10.1039/b703310a	Method development and specification
Lindberg, A., Björnberg, K.A., Vahter, M. & Berglund, M. 2004. Exposure to methylmercury in non-fish-eating people in Sweden. *Environ Res*, 96(1): 28-33. https://doi.org/10.1016/j.envres.2003.09.005	No health outcome measured
Little, M., Achouba, A., Dumas, P., Ouellet, N., Ayotte, P. & Lemire, M. 2019. Determinants of selenoneine concentration in red blood cells of Inuit from Nunavik (Northern Quebec, Canada). *Environment International*, 127: 243-252. https://doi.org/10.1016/j.envint.2018.11.077	No health outcome measured
Lubick, N. 2010. A balanced diet? Selenium may offset the effects of methylmercury on cataract development. *Environ Health Perspect*, 118(11): A491. https://doi.org/10.1289/ehp.118-a491b	News article
Marumoto, M., Sakamoto, M., Marumoto, K., Tsuruta, S. & Komohara, Y. 2020. Mercury and Selenium Localization in the Cerebrum, Cerebellum, Liver, and Kidney of a Minamata Disease Case. *Acta Histochem Cytochem*, 53(6): 147-155. https://doi.org/10.1267/ahc.20-00009	A single toxicology case
Miklavčič, A., Casetta, A., Snoj Tratnik, J., Mazej, D., Krsnik, M., Mariuz, M., Sofianou, K., Spirić, Z., Barbone, F. & Horvat, M. 2013. Mercury, arsenic and selenium exposure levels in relation to fish consumption in the Mediterranean area. *Environ Res*, 120: 7-17. https://doi.org/10.1016/j.envres.2012.08.010	No health outcome measured
Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S.W. & Jacobson, J.L. 2001. Determinants of polychlorinated biphenyls and methylmercury exposure in inuit women of childbearing age. *Environ Health Perspect*, 109(9): 957-63. https://doi.org/10.1289/ehp.01109957	No health outcome measured
Muckle, G., Ayotte, P., Dewailly, E.E., Jacobson, S.W. & Jacobson, J.L. 2001. Prenatal exposure of the northern Québec Inuit infants to environmental contaminants. *Environ Health Perspect*, 109(12): 1291-9. https://doi.org/10.1289/ehp.011091291	No health outcome measured
Nakayama, S.F., Iwai-Shimada, M., Oguri, T., Isobe, T., Takeuchi, A., Kobayashi, Y., Michikawa, T. *et al.* 2019. Blood mercury, lead, cadmium, manganese and selenium levels in pregnant women and their determinants: the Japan Environment and Children's Study (JECS). *Journal of Exposure Science and Environmental Epidemiology*, 29(5): 633-647. https://doi.org/10.1038/s41370-019-0139-0	No health outcome measured
Niane, B., Guedron, S., Moritz, R., Cosio, C., Ngom, P.M., Deverajan, N., Pfeifer, H.R. & Pote, J. 2015. Human exposure to mercury in artisanal small-scale gold mining areas of Kedougou region, Senegal, as a function of occupational activity and fish consumption. *Environmental Science and Pollution Research*, 22(9): 7101-7111. https://doi.org/10.1007/s11356-014-3913-5	No health outcome measured
Parajuli, R.P., Goodrich, J.M., Chan, H.M., Lemire, M., Ayotte, P., Hegele, R.A. & Basu, N. 2021. Variation in biomarker levels of metals, persistent organic pollutants, and omega-3 fatty acids in association with genetic polymorphisms among Inuit in Nunavik, Canada. *Environmental Research*, 200. https://doi.org/10.1016/j.envres.2021.111393	No health outcome measured
Pinheiro, M.C.N., Muller, R.C.S., Sarkis, J.E., Vieira, J.L.F., Oikawa, T., Gomes, M.S.V., Guimaraes, G.A., do Nascimento, J.L.M. & Silveira, L.C.L. 2005. Mercury and selenium concentrations in hair samples of women in fertile age from Amazon riverside communities. *Science of the Total Environment*, 349(1-3): 284-288. https://doi.org/10.1016/j.scitotenv.2005.06.026	No health outcome measured
Sakamoto, M., Chan, H.M., Domingo, J.L., Koriyama, C. & Murata, K. 2018. Placental transfer and levels of mercury, selenium, vitamin E, and docosahexaenoic acid in maternal and umbilical cord blood. *Environ Int*, 111: 309-315. https://doi.org/10.1016/j.envint.2017.11.001	No health outcome measured
Sakamoto, M., Chan, H.M., Domingo, J.L., Kubota, M. & Murata, K. 2012. Changes in body burden of mercury, lead, arsenic, cadmium and selenium in infants during early lactation in comparison with placental transfer. *Ecotoxicol Environ Saf*, 84: 179-84. https://doi.org/10.1016/j.ecoenv.2012.07.014	No health outcome measured
Sakamoto, M., Haraguchi, K., Tatsuta, N., Nakai, K., Nakamura, M. & Murata, K. 2021. Plasma and red blood cells distribution of total mercury, inorganic mercury, and selenium in maternal and cord blood from a group of Japanese women. *Environ Res*, 196: 110896. https://doi.org/10.1016/j.envres.2021.110896	No health outcome measured
Sakamoto, M., Murata, K., Kubota, M., Nakai, K. & Satoh, H. 2010. Mercury and heavy metal profiles of maternal and umbilical cord RBCs in Japanese population. *Ecotoxicol Environ Saf*, 73(1): 1-6. https://doi.org/10.1016/j.ecoenv.2009.09.010	No health outcome measured
Sekovanic, A., Piasek, M., Orct, T., Grgec, A.S., Saric, M.M., Stasenko, S. & Jurasovic, J. 2020. Mercury Exposure Assessment in Mother-Infant Pairs from Continental and Coastal Croatia. *Biomolecules*, 10(6). https://doi.org/10.3390/biom10060821	No health outcome measured
Ser, P.H., Omi, S., Shimizu-Furusawa, H., Yasutake, A., Sakamoto, M., Hachiya, N., Konishi, S., Nakamura, M. & Watanabe, C. 2017. Differences in the responses of three plasma selenium-containing proteins in relation to methylmercury-exposure through consumption of fish/whales. *Toxicol Lett*, 267: 53-58. https://doi.org/10.1016/j.toxlet.2016.12.001	No health outcome measured
Suzuki, T., Hongo, T., Yoshinaga, J., Imai, H., Nakazawa, M., Matsuo, N. & Akagi, H. 1993. The hair-organ relationship in mercury concentration in contemporary Japanese. *Arch Environ Health*, 48(4): 221-9. https://doi.org/10.1080/00039896.1993.9940363	No health outcome measured

TABLE A6.2 **PRIMARY STUDIES EXCLUDED DURING FULL-TEXT SCREENING OF HUMAN STUDIES FOR THE REVIEW "Se AND MeHg", BASED ON INCLUSION AND EXCLUSION CRITERIA (cont.)**

Studies (n = 68)	Reason for exclusion
Svensson, B.G., Nilsson, A., Jonsson, E., Schütz, A., Akesson, B. & Hagmar, L. 1995. Fish consumption and exposure to persistent organochlorine compounds, mercury, selenium and methylamines among Swedish fishermen. *Scand J Work Environ Health*, 21(2): 96-105. https://doi.org/10.5271/sjweh.16	No health outcome measured
Svensson, B.G., Schütz, A., Nilsson, A., Akesson, I., Akesson, B. & Skerfving, S. 1992. Fish as a source of exposure to mercury and selenium. *Sci Total Environ*, 126(1-2): 61-74. https://doi.org/10.1016/0048-9697(92)90484-a	No health outcome measured
Trdin, A., Snoj Tratnik, J., Mazej, D., Fajon, V., Krsnik, M., Osredkar, J., Prpić, I. *et al.* 2019. Mercury speciation in prenatal exposure in Slovenian and Croatian population - PHIME study. *Environ Res*, 177: 108627. https://doi.org/10.1016/j.envres.2019.108627	No use of Se data
Trdin, A., Snoj Tratnik, J., Stajnko, A., Marc, J., Mazej, D., Sešek Briški, A., Kastelec, D. *et al.* 2020. Trace elements and APOE polymorphisms in pregnant women and their new-borns. *Environ Int*, 143: 105626. https://doi.org/10.1016/j.envint.2020.105626	No health outcome measured
Valent, F., Pisa, F., Mariuz, M., Horvat, M., Gibicar, D., Fajon, V., Mazej, D., Daris, F. & Barbone, F. 2011. Fetal and perinatal exposure to mercury and selenium: baseline evaluation of a cohort of children in Friuli Venezia Giulia, Italy. *Epidemiol Prev*, 35(1): 33-42.	Article in Italian
Valera, B., Muckle, G., Poirier, P., Jacobson, S.W., Jacobson, J.L. & Dewailly, E. 2012. Cardiac autonomic activity and blood pressure among Inuit children exposed to mercury. *Neurotoxicology*, 33(5): 1067-1074. https://doi.org/10.1016/j.neuro.2012.05.005	Selenium not measured
Vecchi Brumatti, L., Rosolen, V., Mariuz, M., Piscianz, E., Valencic, E., Bin, M., Athanasakis, E. *et al.* 2021. Impact of Methylmercury and Other Heavy Metals Exposure on Neurocognitive Function in Children Aged 7 Years: Study Protocol of the Follow-up. *J Epidemiol*, 31(2): 157-163. https://doi.org/10.2188/jea.JE20190284	Study protocol only
Walker, J.B., Houseman, J., Seddon, L., McMullen, E., Tofflemire, K., Mills, C., Corriveau, A. *et al.* 2006. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. *Environmental Research*, 100(3): 295-318. https://doi.org/10.1016/j.envres.2005.05.006	No health outcome measured
Wells, E.M., Herbstman, J.B., Lin, Y.H., Hibbeln, J.R., Halden, R.U., Witter, F.R. & Goldman, L.R. 2017. Methyl mercury, but not inorganic mercury, associated with higher blood pressure during pregnancy. *Environ Res*, 154: 247-252. https://doi.org/10.1016/j.envres.2017.01.013	Selenium as a covariate in a multi model
Wilhelm, M., Wittsiepe, J., Schrey, P., Lajoie-Junge, L. & Busch, V. 2003. Dietary intake of arsenic, mercury and selenium by children from a German North Sea island using duplicate portion sampling. *Journal of Trace Elements in Medicine and Biology*, 17(2): 123-132. https://doi.org/10.1016/s0946-672x(03)80008-1	No health outcome measured
Yalcin, S.S., Yurdakok, K., Yalcin, S., Engur-Karasimav, D. & Coskun, T. 2010. Maternal and environmental determinants of breast-milk mercury concentrations. *Turkish Journal of Pediatrics*, 52(1): 1-9. <Go to ISI>://WOS:000276572900001	No health outcome measured
Yamashita, M., Yamashita, Y., Ando, T., Wakamiya, J. & Akiba, S. 2013. Identification and determination of selenoneine, 2-selenyl-N α , N α , N α -trimethyl-L-histidine, as the major organic selenium in blood cells in a fish-eating population on remote Japanese Islands. *Biol Trace Elem Res*, 156(1-3): 36-44. https://doi.org/10.1007/s12011-013-9846-x	No health outcome measured
Yoo, Y.C., Lee, S.K., Yang, J.Y., Kim, K.W., Lee, S.Y., Oh, S.M. & Chung, K.H. 2002. Interrelationship between the concentration of toxic and essential elements in Korean tissues. *Journal of Health Science*, 48(2): 195-200. <Go to ISI>://WOS:000174717400015	No health outcome measured
Yoshinaga, J., Matsuo, N., Imai, H., Nakazawa, M., Suzuki, T., Morita, M. & Akagi, H. 1990. Interrelationship between the concentrations of some elements in the organs of Japanese with special reference to selenium-heavy metal relationships. *Sci Total Environ*, 91: 127-40. https://doi.org/10.1016/0048-9697(90)90294-5	No health outcome measured
Zhang, M.Y., Buckley, J.P., Liang, L.M., Hong, X.M., Wang, G.Y., Wang, M.C., Wills-Karp, M., Wang, X.B. & Mueller, N.T. 2022. A metabolome-wide association study of in utero metal and trace element exposures with cord blood metabolome profile: Findings from the Boston Birth Cohort. *Environment International*, 158. https://doi.org/10.1016/j.envint.2021.106976	No health outcome measured
Zhang, M.Y., Liu, T.G., Wang, G.Y., Buckley, J.P., Guallar, E., Hong, X.M., Wang, M.C., Wills-Karp, M., Wang, X.B. & Mueller, N.T. 2021. In Utero Exposure to Heavy Metals and Trace Elements and Childhood Blood Pressure in a US Urban, Low-Income, Minority Birth Cohort. *Environmental Health Perspectives*, 129(6). https://doi.org/10.1289/ehp8325	Effect selenium has on Hg toxicity not measured

QUALITY ASSESSMENT (RISK OF BIAS) OF HUMAN PRIMARY STUDIES

TABLE A6.3 QUALITY ASSESSMENT (RISK OF BIAS) OF HUMAN PRIMARY STUDIES

Study (n = 45)	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Ai, C.E., Li, C.J., Tsou, M.C., Chen, J.L., Hsi, H.C. & Chien, L.C. 2019. Blood and seminal plasma mercury levels and predatory fish intake in relation to low semen quality. Environmental Science and Pollution Research, 26(19):19425-19433.	+	+	+	++	-	++	-	Tier 2
Ayotte, P., Carrier, A., Ouellet, N., Boiteau, V., Abdous, B., Sidi, E.A.L., Dewailly, É. *et al.* 2011. Relation between methylmercury exposure and plasma paraoxonase activity in inuit adults from Nunavik. Environmental health perspectives, 119(8):1077-1083.	+	+	+	++	++	++	+	Tier 1
Bélanger, M.C., Dewailly, É., Berthiaume, L., Noël, M., Bergeron, J., Mirault, M.É. & Julien, P. 2006. Dietary contaminants and oxidative stress in Inuit of Nunavik. Metabolism, 55(8):989-995.	+	+	++	+	++	++	++	Tier 1
Bélanger, M.C., Mirault, M.É., Dewailly, E., Berthiaume, L. & Julien, P. 2008. Environmental contaminants and redox status of coenzyme Q10 and vitamin E in Inuit from Nunavik. Metabolism, 57(7):927-933.	+	+	++	+	++	++	++	Tier 1
Bélanger, M.C., Mirault, M.E., Dewailly, E., Plante, M., Berthiaume, L., Noël, M. & Julien, P. 2008. Seasonal mercury exposure and oxidant-antioxidant status of James Bay sport fishermen. Metabolism, 57(5):630-636.	-	-	++	+	++	++	+	Tier 2
Boucher, O., Muckle, G., Jacobson, J.L., Carter, R.C., Kaplan-Estrin, M., Ayotte, P., Jacobson, S.W. 2014. Domain-specific effects of prenatal exposure to PCBs, mercury, and lead on infant cognition: results from the Environmental Contaminants and Child Development Study in Nunavik. Environmental health perspectives, 122(3):310-316.	++	+	++	+	+	+	++	Tier 1
Chen, C., Xun, P., McClure, L.A., Brockman, J., MacDonald, L., Cushman, M., He, K. *et al.* 2018. Serum mercury concentration and the risk of ischemic stroke: the reasons for geographic and racial differences in stroke trace element study. Environment international, 117:125-131.	+	+	++	+	+	++	+	Tier 1
Chen, Z., Myers, R., Wei, T., Bind, E., Kassim, P., Wang, G. Wang, X. *et al.* 2014. Placental transfer and concentrations of cadmium, mercury, lead, and selenium in mothers, newborns, and young children. Journal of exposure science & environmental epidemiology, 24(5):537-544.	- -	+	-	+	-	-	++	Tier 2
Choi, A.L., Budtz-Jørgensen, E., Jørgensen, P.J., Steuerwald, U., Debes, F., Weihe, P. & Grandjean, P. 2008. Selenium as a potential protective factor against mercury developmental neurotoxicity. Environmental Research, 107(1):45-52.	-	+	++	+	++	++	++	Tier 2
Emanuele, E. & Meliker, J. 2017. Seafood intake, polyunsaturated fatty acids, blood mercury, and serum C-reactive protein in US National Health and Nutrition Examination Survey (2005–2006). International Journal of Environmental Health Research, 27(2):136-143.	+	-	++	+	++	++	+	Tier 2
Engström, K.S., Wennberg, M., Strömberg, U., Bergdahl, I.A., Hallmans, G., Jansson, J.H., Broberg, K. *et al.* 2011. Evaluation of the impact of genetic polymorphisms in glutathione-related genes on the association between methylmercury or n-3 polyunsaturated long chain fatty acids and risk of myocardial infarction: a case-control study. Environmental health, 10(1):1-8.	++	++	++	++	+	++	++	Tier 1
Fillion, M., Lemire, M., Philibert, A., Frenette, B., Weiler, H.A., Deguire, J.R., *et al.* Mergler, D. 2011. Visual acuity in fish consumers of the Brazilian Amazon: risks and benefits from local diet. Public health nutrition, 14(12):2236-2244.	++	+	+	++	-	++	+	Tier 1
Fillion, M., Lemire, M., Philibert, A., Frenette, B., Weiler, H.A., Deguire, J.R., Mergler, D. *et al.* 2013. Toxic risks and nutritional benefits of traditional diet on near visual contrast sensitivity and color vision in the Brazilian Amazon. Neurotoxicology, 37:173-181.	++	+	+	++	-	++	+	Tier 1
Golding, J., Gregory, S., Emond, A., Iles-Caven, Y., Hibbeln, J., Taylor, C.M. 2016. Prenatal mercury exposure and offspring behaviour in childhood and adolescence. *Neurotoxicology*, 57:87-94.	++	+	++	++	++	+	++	Tier 1
Golding, J., Gregory, S., Iles-Caven, Y., Hibbeln, J., Emond, A., Taylor, C.M. 2016. Associations between prenatal mercury exposure and early child development in the ALSPAC study. *Neurotoxicology*, 2016;53:215-22.	++	+	++	++	++	+	++	Tier 1
Golding, J., Hibbeln, J.R., Gregory, S.M., Iles-Caven, Y., Emond, A. *&* Taylor, C.M. 2017. Maternal prenatal blood mercury is not adversely associated with offspring IQ at 8 years provided the mother eats fish: a British prebirth cohort study. *International journal of hygiene and environmental health*, 220(7):1161-1167.	++	+	++	- -	+	+	-	Tier 2
Gregory, S., Iles-Caven, Y., Hibbeln, J.R., Taylor, C.M. *&* Golding, J. 2016. Are prenatal mercury levels associated with subsequent blood pressure in childhood and adolescence? The Avon prebirth cohort study. *BMJ open*, 6(10):e012425.	++	+	++	-	++	+	++	Tier 1

TABLE A6.3 **QUALITY ASSESSMENT (RISK OF BIAS) OF HUMAN PRIMARY STUDIES (cont.)**

Study ($n = 45$)	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Gustin, K., Barman, M., Skröder, H., Jacobsson, B., Sandin, A., Sandberg, A.S., Kippler, M. *et al.* 2021. Thyroid hormones in relation to toxic metal exposure in pregnancy, and potential interactions with iodine and selenium. *Environment International*, 157:106869.	++	+	++	++	++	++	++	Tier 1
Hu, X.F., Eccles, K.M. *&* Chan, H.M. 2017. High selenium exposure lowers the odds ratios for hypertension, stroke, and myocardial infarction associated with mercury exposure among Inuit in Canada. *Environment International*, 102:200-206.	+	+	-	++	+	-	+	Tier 2
Hui, L.L., Chan, M.H.M., Lam, H.S., Chan, P.H.Y., Kwok, K.M., Chan, I.H.S, Fok, T.F. *et al*. 2016. Impact of fetal and childhood mercury exposure on immune status in children. *Environmental research*, 144:66-72.	++	-	+	+	-	+	+	Tier 2
Karimi, R., Vacchi-Suzzi, C. *&* Meliker, J.R. 2016. Mercury exposure and a shift toward oxidative stress in avid seafood consumers. *Environmental research*, 146:100-107.	+	+	+	+	+	+	+	Tier 1
Kobayashi, S., Kishi, R., Saijo, Y., Ito, Y., Oba, K., Araki, A., Children's Study Group *et al*.. 2019. Association of blood mercury levels during pregnancy with infant birth size by blood selenium levels in the Japan Environment and Children's Study: A prospective birth cohort. *Environment international*, 125:418-429.	++	++	+	+	+	++	-	Tier 1
Kuras, R., Kozlowska, L., Reszka, E., Wieczorek, E., Jablonska, E., Gromadzinska, J., Wasowicz, W. *et al.* 2019. Environmental mercury exposure and selenium-associated biomarkers of antioxidant status at molecular and biochemical level. A short-term intervention study. *Food and Chemical Toxicology*, 130:187-198.	+	++	+	++	+	+	+	Tier 1
Kuras, R., Reszka, E., Wieczorek, E., Jablonska, E., Gromadzinska, J., Malachowska, B., Wasowicz, W. *et al.* 2018. Biomarkers of selenium status and antioxidant effect in workers occupationally exposed to mercury. *Journal of Trace Elements in Medicine and Biology*, 49:43-50.	++	+	-	++	+	++	+	Tier 2
Lei, H.L., Wei, H.J., Chen, P.H., Hsi, H.C. *&* Chien, L.C. 2015. Preliminary study of blood methylmercury effects on reproductive hormones and relevant factors among infertile and pregnant women in Taiwan. *Chemosphere*, 135:411-417.	- -	++	+	- -	+	+	-	Tier 2
Lemire, M., Fillion, M., Frenette, B., Mayer, A., Philibert, A., Passos, C.J.S., Mergler, D. *et al.* 2010. Selenium and mercury in the Brazilian Amazon: opposing influences on age-related cataracts. *Environmental Health Perspectives*, 118(11):1584-1589.	+	++	++	+	+	+	+	Tier 1
Lemire, M., Fillion, M., Frenette, B., Passos, C.J.S., Guimarães, J.R.D., Barbosa Jr, F. *&* Mergler, D. 2011. Selenium from dietary sources and motor functions in the Brazilian Amazon. *Neurotoxicology*, 32(6):944-953.	+	++	+	+	+	-	+	Tier 1
Maeda, E., Murata, K., Kumazawa, Y., Sato, W., Shirasawa, H., Iwasawa, T., Terada, Y. 2019. Associations of environmental exposures to methylmercury and selenium with female infertility: A case–control study. *Environmental research*, 168:357-363.	-	+	++	- -	+	- -	- -	Tier 2
Mao, X., Chen, C., Xun, P., Daviglus, M., Steffen, L.M., Jacobs Jr, D.R., He, K. 2019. Effects of seafood consumption and toenail mercury and selenium levels on cognitive function among American adults: 25 y of follow up. *Nutrition*, 61:77-83.	+	-	++	+	+	+	+	Tier 1
Monastero, R.N., Karimi, R., Nyland, J.F., Harrington, J., Levine, K. *&* Meliker, J.R. 2017. Mercury exposure, serum antinuclear antibodies, and serum cytokine levels in the Long Island Study of Seafood Consumption: A cross-sectional study in NY, USA. *Environmental research*, 156:334-340.	+	+	++	+	+	++	+	Tier 1
Mozaffarian, D., Shi, P., Morris, J.S., Grandjean, P., Siscovick, D.S., Spiegelman, D., Forman, J.P. 2012. Mercury exposure and risk of hypertension in US men and women in 2 prospective cohorts. *Hypertension*, 60(3):645-652.	++	-	++	+	+	+	+	Tier 2
Mozaffarian, D., Shi, P., Morris, J.S., Spiegelman, D., Grandjean, P., Siscovick, D.S., Rimm, E.B. 2011. Mercury exposure and risk of cardiovascular disease in two US cohorts. *New England Journal of Medicine*, 364(12):1116-1125.	++	-	+	+	+	+	+	Tier 2
Nakamura, M., Hachiya, N., Murata, K.Y., Nakanishi, I., Kondo, T., Yasutake, A., Sakamoto, M. *et al*. 2014. Methylmercury exposure and neurological outcomes in Taiji residents accustomed to consuming whale meat. *Environment international*, 68:25-32.	+	-	++	-	-	+	-	Tier 2
Nyland, J.F., Fillion, M., Barbosa Jr, F., Shirley, D.L., Chine, C., Lemire, M., Silbergeld, E.K. *et al.* 2011. Biomarkers of methylmercury exposure immunotoxicity among fish consumers in Amazonian Brazil. *Environmental health perspectives*, 119(12):1733-1738.	+	++	+	+	-	++	+	Tier 2
Oken, E., Rifas-Shiman, S.L., Amarasiriwardena, C., Jayawardene, I., Bellinger, D.C., Hibbeln, J.R., Gillman, M.W. *et al.* 2016. Maternal prenatal fish consumption and cognition in mid childhood: mercury, fatty acids, and selenium. *Neurotoxicology and teratology*, 57:71-78.	+	+	+	+	-	++	+	Tier 1
Park, K. *&* Seo, E. 2016. Association between toenail mercury and metabolic syndrome is modified by selenium. *Nutrients*, 8(7):424.	+	+	+	+	+	++	+	Tier 1

TABLE A6.3 **QUALITY ASSESSMENT (RISK OF BIAS) OF HUMAN PRIMARY STUDIES (cont.)**

Study (n = 45)	KQ1 (Confounding)	KQ2 (Exposure)	KQ3 (Outcome)	Q4 (Selection)	Q5 (Attrition)	Q6 (Selective reporting)	Q7 (Other bias)	Tier
Park, K. & Seo, E. 2017. Toenail mercury and dyslipidemia: Interaction with selenium. *Journal of Trace Elements in Medicine and Biology*, 39:43-49.	+	+	+	+	+	+	+	Tier 1
Park, S.K., Lee, S., Basu, N. & Franzblau, A. 2013. Associations of blood and urinary mercury with hypertension in US adults: the NHANES 2003–2006. *Environmental research*, 123:25-32.	++	+	+	+	+	+	+	Tier 1
Rocha, A.V., Cardoso, B.R., Zavarize, B., Almondes, K., Bordon, I., Hare, D.J., Cozzolino, S.M.F. *et al.* 2016. GPX1 Pro198Leu polymorphism and GSTM1 deletion do not affect selenium and mercury status in mildly exposed Amazonian women in an urban population. *Science of the Total Environment*, 571:801-808.	+	+	+	-	+	+	-	Tier 2
Saint-Amour, D., Roy, M.S., Bastien, C., Ayotte, P., Dewailly, E., Després, C., Muckle, G. *et al.* 2006. Alterations of visual evoked potentials in preschool Inuit children exposed to methylmercury and polychlorinated biphenyls from a marine diet. *Neurotoxicology*, 27(4):567-578.	+	++	+	-	+	++	+	Tier 1
Steuerwald, U., Weihe, P., Jørgensen, P.J., Bjerve, K., Brock, J., Heinzow, B. Grandjean, P. 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *The Journal of pediatrics*, 136(5):599-605.	+	++	+	+	+	+	-	Tier 1
Tatsuta, N., Murata, K., Iwai-Shimada, M., Yaginuma-Sakurai, K., Satoh, H. & Nakai, K. 2017. Psychomotor ability in children prenatally exposed to methylmercury: the 18-month follow-up of Tohoku study of child development. *The Tohoku Journal of Experimental Medicine*, 242(1):1-8.	+	+	+	+	+	+	-	Tier 1
Tratnik, J.S., Falnoga, I., Trdin, A., Mazej, D., Fajon, V., Miklavčič, A., Horvat, M. *et al.* 2017. Prenatal mercury exposure, neurodevelopment and apolipoprotein E genetic polymorphism. *Environmental research*, 152:375-385.	+	++	+	+	-	+	+	Tier 1
Walker, E.V., Girgis, S., Yuan, Y. & Goodman, K.J. 2021. Community-driven research in the Canadian arctic: dietary exposure to methylmercury and gastric health outcomes. International *Journal of Circumpolar Health*, 80(1):1889879.	-	- -	-	- -	+	-	-	Tier 3
Wells, E.M., Herbstman, J.B., Lin, Y.H., Jarrett, J., Verdon, C.P., Ward, C., Goldman, L.R. *et al.* 2016. Cord blood methylmercury and fetal growth outcomes in Baltimore newborns: potential confounding and effect modification by omega-3 fatty acids, selenium, and sex. *Environmental health perspectives*, 124(3):373-379.	+	-	+	-	+	+	+	Tier 2
Wennberg, M., Bergdahl, I.A., Hallmans, G., Norberg, M., Lundh, T., Skerfving, S., Jansson, J.H. *et al.* 2011. Fish consumption and myocardial infarction: a second prospective biomarker study from northern Sweden. *The American journal of clinical nutrition*, 93(1):27-36.	+	+	+	+	-	-	+	Tier 1
Zhang, J., Wang, J., Hu, J., Zhao, J., Li, J. & Cai, X. 2021. Associations of total blood mercury and blood methylmercury concentrations with diabetes in adults: an exposure-response analysis of 2005-2018 NHANES. *Journal of Trace Elements in Medicine and Biology*, 68:126845.	-	- -	-	+	+	-	-	Tier 3

EXTRACTION OF DATA FROM HUMAN PRIMARY STUDIES

TABLE A6.4 OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg"

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Ai *et al.* 2019. Taiwan May 2012–February 2013	Cross-sectional Multiple linear regression	N = 84 37 years (average) 26-52 (range) 100% Participants from Center for Reproductive Medicine and Science, Taipei Medical University, Taiwan, without sub- or infertility diagnosis, had regular sex for one year and their female partners did not get pregnant	ICP-MS Mean ±SD, range Hg, µg/L Blood (N = 84) 9 ±5.9 0.3-31.3 Low quality semen group 9.3 ±5.9 High quality semen group 8.9 ±5.9 Seminal plasma (N = 39) 1.12±0.56 0.2-2.48 Low quality semen group 1.26 ±0.61 High quality semen group 1.05 ±0.52	ICP-MS Mean ±SD, range Se, µg/L Blood (N = 84) 205 ±58 112-39 Low quality semen group 206±60.9 High quality semen group 205±57.8 Seminal plasma (N = 39) 82.3±24.0 27.6-152 Low quality semen group 73.5±22.3 High quality semen group 87.3±23.9	Sperm quality according to WHO reference values was used to divide into high (N = 27) and low (N = 57) semen quality groups. Measurement of Hg and Se levels in blood and sperm plasma. Fish consumption by questionnaire. Categorization of Hg levels into high, medium and low.	Dose-dependent correlation between blood Hg and normal sperm count. No significant difference between high and low quality semen for Se. Weekly fresh fish intake in low-semen-quality group 1.9 ±0.5 meals per week not significantly different from high-semen-quality group, 2.3±1.2 meals/week. High predatory fish intake had lower percentage of normal morphology in sperm, highest percentage with no predatory fish intake. Same trend for sperm plasma Hg levels, but not significant.	Tier 2	No effect of Se on Hg effect on semen quality. Study group small.
Ayotte *et al.* 2011. None Inuit with high seafood diet of Nunavik (Québec, Canada). 2004	Cross-sectional, community-stratified random sampling of households. Multivariate analyses/ multiple regression adjusted for age, HDL cholesterol levels, omega-3 fatty acid content of erythrocyte membranes and PON1 variants.	N = 896 Mean 36.5 years N= 405 male and N= 896 female	Blood Hg ICP MS Geometric mean: 53.2 nmol/L (0.4-720 nmol/L)	Blood Se ICP-MS Geometric mean: 3.8 µmol/L (1.5-23 µmol/L)	Coronary heart disease (CHD) protective marker paraoxonase 1 (PON1) activity, has been shown to be inhibited by MeHg	Associated with PON1 activities was inverse for blood Hg concentrations, whereas positive for blood Se concentrations.	Tier 1	MeHg exposure seems to exert an inhibitory effect on PON1 activity, which seems to be offset by Se intake.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Bélanger *et al.* 2006. None Canadian Northern Inuit village of Salluit (Nunavik, Northern Quebec) No information	Cross-sectional Randomly selected from the municipal list. Pairwise correlations with log transformed data combined with multivariate analysis using stepwise models for each dependent variable Time point	N = 99 Mean ±sem 43 ±1 year 71f/28m 28% calculated	Blood Hg Cold vapor atomic absorption technique Mean ±SEM 106.2 ±9.8 nmol/L	Blood Se ICP MS Mean ±SEM 635.5 ±38.7 µg/L	Effects on molecules sensitive to oxidative stress: plasma oxidized low-density lipoproteins (OxLDLs), plasma homocysteine (Hcy), blood glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione (GSH).	Concentration of plasma homocysteine (Hcy) was negatively predicted by Se, suggesting a possible beneficial effect of Se. Dietary MeHg showed no association.	Tier 1	In adult Inuit, MeHg from traditional diet seems to have no direct oxidative effects on molecules involved in oxidative stress known to be involved in the pathogenesis of atherosclerosis. Concentration of plasma homocysteine was negatively predicted by Se, suggesting a possible beneficial effect of Se as it can activate pathogenic mechanisms leading to oxidative stress including a decrease in vascular reactivity and cardiovascular morbidity and mortality.
Bélanger *et al.* 2008. None Canadian Northern Inuit village of Salluit (Nunavik, Northern Quebec) No information	Cohort Randomly selected from the municipal list. Multivariate analyses. Time point	N = 99 Mean ±SD 45 ±13 years 71/28 28% calculated	Blood Hg Cold vapor atomic absorption technique Mean ±SEM 106.2 ±9.8 nmol/L	Blood Se ICP MS Mean ±SEM 635.5 ±38.7 µg/L	Assess oxidative stress by measuring plasma concentrations and redox states of alfa-tocopherol and coenzyme Q10 (CoQ10), two sensitive biomarkers of oxidative stress	Ubiquinol-10 (beta= .23, P=.007) and Co10 total (beta= .27, P=.009) were predicted by blood Se. No evidence for MeHg associated oxidative stress.	Tier 1	Low susceptibility of Inuit to LDL oxidation may be partly explained by high blood Se status that might reduce the deleterious effects of MeHg on cardiovascular health.
Bélanger *et al.* 2008. None Healthy sport fisherman working at James Bay (Northern Québec) as white-collar employees of Hydro-Québec. No information	Healthy sport fishermen Matched pair tests Six months	N = 31 22-61 years Mean ±SEM 46.7 ±1.3 100%	Cold vapor atomic absorption technique Hair Hg Mean ±SEM 1.4 ±0.3 µg/g 2.8 ±0.4 µg/g Blood Hg Mean ±SEM 21.9 ±3.7 nmol/L 35.6 ±5.2 nmol/l	Blood ICP-MS Blood Se Mean ±SEM 242.9 ±6.2 µg/L 247.7 ±5.6 µg/L	Assess effects of seasonal exposure to Hg through lipoprotein cholesterol and fatty acid profiles, LDL oxidation, and blood oxidant-antioxidant balance. Within subject longitudinal seasonal variations in hair and blood mercury, plasma oxidized LDL, lipophilic antioxidants, homocysteine, blood Se, glutathione peroxidase and reductase activities before and after fishing season.	Homocysteine did not change. No association between Hg and any of the biomarkers investigated. Strong predictors of cardiovascular risk such as HDL cholesterol, oxidized LDL and glutathione peroxidase improved during fishing season.	Tier 2	Seasonal fishing activity/ fish consumption had beneficial effects on cardiovascular health, and may suppress detrimental effects of moderate MeHg exposure.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Boucher *et al.* 2014. None Pregnant women from Inuit villages in Hudson Bay coast	Repeated measures, multiple regression November 1995 to March 2001 (follow-up time: 4.5 months)	94 infants 6.5 months 11 months 63.8%	Umbilical cord blood (Method in Muckle *et al.*, 2001) Hg Mean ±SD 22.5 ±16.6 µg/L 2.4-97.3	Umbilical cord blood (Method in Muckle et al 2001) Se Mean ±SD 296.4 ±122.8 µg/L 67.9-915.9	Hg, Se, Fagan Test of Infant Intelligence (FTII), A-not-B test and Bayley Scales of Infant Development – 2nd Edition (BSID-II)	Hg moderately correlated with Se. Small correlation (A not B test – negative correlation with perseverative errors with Se) Pearson coefficient=0.21, p<0.1. Otherwise, no significant association.	Tier 1	No association of Se with most intelligence parameters negatively associated with Hg: A-not B, which depends on working memory and is believed to be a precursor of executive function, with the exception of perseverative errors.
Chen *et al.* 2018. Reasons for Geographic and Racial Differences in Stroke cohort Residents of the US "stroke belt" and blacks oversampled. 2003-2007	Case-cohort study, multivariate-adjusted hazard ratios (HRs) and confidence intervals using the Barlow-weighting method for the Cox proportional hazards regression model Time point Mean ±SD 6 years ±2.4	662 stroke incidents randomly selected in 2 494 participants sub-cohort ≥45 45%	Serum Hg Nippon MA-3000 direct mercury analyser Median 0.03 µg/dl (inter-quartile range= 0.02-0.06 µg/dl)	Serum Se Instrumental neutron activation analysis with standard reference material. Median 13.1 µg/dl	Association of serum Hg levels with ischemic stroke, Se modified by demographic and geographic factors	No statistically significant association between serum Hg and the incidence of ischemic stroke. Serum Se associated with serum Hg. Higher serum Hg associated with less likely to have history of myocardial infarction. Inverse association of serum Hg with ischemic stroke in women, not men, which was not modified by Se.	Tier 1	This study does not support an association between Hg and the incidence of stroke within a population with low-to-moderate Hg exposure. Neither does serum Se modify this, presumably due to the relatively high level of Se in this population.
Chen *et al.* 2014. Boston Birth cohort (BBC) African-American	Paired maternal umbilical cord (N = 17) and postnatal blood samples 24-72 hour (N = 39) after delivery, infant blood at 12.5 months (mean) 6-39 months (range)	50 mother-infant pairs	ICP-MS Red blood cell Hg µg/L geometric mean, range: Maternal blood: 2.5 (1.9-3.25) Umbilical cord venous blood: 3.83 (2.93-5.04) Infant venous blood: 2.17 (1.74-2.70)	ICP-MS Red blood cell Se µg/L geometric mean, range: Maternal blood: 277.81 (255.51-302.05) Umbilical cord venous blood: 311.10 (286.48-337.84) Infant venous blood: 286.82 (272.93-301.45)	Premature birth and birthweight.	Red blood cells are better than plasma or whole blood in reflecting the free transplacental transfer of Hg and Se. No strong correlation between Se and Hg. No effect of Se on premature birth or birthweight.	Tier 2	Mother–child transfer of MeHg and Se are best measured in red blood cells. No effect of Se on premature birth or birthweight.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Choi *et al.* 2008. National Hospital Torshavn, Faroe Islands Faroe islands 1994-1995	Singleton birthed 1986-1987, high pilot whale diet 7 years	1 022+182= 1 104 recruited 880+142 = 1022 measured for Se 917 completed evaluation at age 7	Cord whole Blood Hg Cold vapor atomic absorption spectrometry µg/L nml/l geometric mean IQR Cohort 1 22.9 13.4-41.3 114.3 67-206.5 Cohort 2 20.9 12.5-40 102.7 62.4-200	Cord whole blood Se Electrothermal atomic absorption µg/L nml/l geometric mean IQR Cohort 1 111.6 100.8-123.1 1412.5 1276-1558 Cohort 2 102.5 93.2-112.0 1297.2 1180-1418	Neurodevelopment within lowest, middle and highest Se distribution (25%, 50%, 25%) Motor function: Finger tapping and hand eye coordination, attention, visuospatial performance, language Hg/Se ratio Cohort 1 0.08 0.05-0.15 Cohort 2 0.08 0.05-0.14	No consistent effects of Se or significant interaction between Se and MeHg.	Tier 2	No evidence that Se was an important protective factor against MeHg neurotoxicity. Increased Se levels were not associated with decreased mercury-related neuropsychological dysfunctions.
Emanuele 2017. US National Health and Nutrition Examination Survey (NHANES) 2005-2006	Cross-sectional, sex-stratified sample weighted multiple linear regression	1 217 16-49 years Mean 34 706 male 511 non-pregnant female, fasting 58%	ICP-MS Hg, µg/L Blood within range: % male; % female <1: 48.7%; 46.1% 1-5.8: 47.6%; 50.5% >5.8: 3.7%; 3.4%	Mcg from dietary interview Se µg/L 143 18-578 (male) 97 3-406 (female)	Seafood consumption, Hg, Se, polyunsaturated fatty acids and vitamin D concentrations in relation to C-reactive protein (mg/dl), an indicator of inflammation and predictor of cardiovascular disease.	No associations of Hg, Se or fish intake with serum C-reactive protein in sex-stratified sample weighted multiple linear regression. When all variables included in one model, fish intake was associated with lower levels of CRP in females. When controlling for seafood intake, no association for CRP with Se was found.	Tier 2	Suggested confounding in models that do not mutually adjust for seafood contaminants and nutrients. Effect of Se on Hg toxicity not investigated.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Engström *et al.* 2011. The Västerbotn Intervention Program (VIP), the WHO's Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Study in northern Sweden, and the Mammography Screening Project (MSP) Västerbotn, Northern Sweden 1987-1999 (medical history)	Logistic regression in prospective health surveillance cohort Time point	1 027 (458 cases of myocardial infarction and 569 matched controls) Age and sex distribution not given	Erythrocyte Hg In acid-digested samples using cold vapor atomic fluorescence spectrometry µg/L Mean ±SD 4.9 ±5.1/ 5.4 ±5.7 (controls/carriers of GCLM TT) 0.01-87	Erythrocyte-Se ICPMS µg/L Mean ±SD 130 ±37/ 130 ±22 (controls/carriers of GCLM TT) 72-710	To elucidate whether genetic polymorphisms in glutathione-related genes modify the association between eicosapentaenoic and docosahexaenoic acid or MeHg and risk of first myocardial infarction.	No associations of polymorphisms with myocardial infarction, but study not large enough. Also no effect when Ery-Se taken into account. Ery-Hg associated with decreasing MI risk, most likely because Ery-Hg is a marker for fish intake.		No associations of polymorphisms with myocardial infarction, but study not large enough. No effect when Ery-Se taken into account. Ery-Hg associated with decreasing MI risk, most likely because Ery-Hg is a marker for fish intake.
Fillion *et al.* 2011. None Lower Tapajós River Basin (State of Pará, Brazil May to July 2006	Cross-sectional study Time point	243 adults ≥15 years Mean ±SD Median Range 35.9 ±12.3 years 35 15-66 48.1%	Hair Hg Cold vapor atomic absorption spectrometry Mean ±SD Median Range 14.4 ±15.5 µg/g 11.5 1.0-57.9 Total Blood Hg ICP-MS Mean ±SD Median Range 51.6 ±37 41.8 1.7-189.3 µg/L Plasma Hg Mean ±SD Median (Range) 8.0 ±6.5 µg/L 6.9 (0.2-30.9)	ICP MS Total blood Se Mean ±SD Median Range 313.4 ±215.5 µg/L 250.6 103.3-1500.2 Plasma Se Mean ±SD Median Range 178.8 ±120.1 µg/L 141.3 53.6-913.2	Associations between near and distal visual acuity and biomarkers of Hg and Se from the local diet.	Near visual acuity was negatively associated with hair Hg, ≥40 years of age. Age did not influence blood Se status. Blood Se was significantly lower in the group excluded for age-related cataracts. Log-blood Se did not show any association with the outcome of acuity. Few people with Se deficiency were in the investigated population and normal Se levels may be sufficient to maintain visual function.	Tier 1	Hg may affect visual acuity in older persons. Blood Se was not significantly associated with this outcome.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Fillion *et al.* 2013. None Lower Tapajós River Basin (State of Pará, Brazil May to July 2006	Cross-sectional study Time point	228 participants ≥15 years Mean ±SD Median Range 35.3 ±12.5 years 33 15-66 49.6%	Hair Hg Cold vapor atomic absorption spectrometry Mean ±SD Median Range 14.4 ±10.6 µg/g 11.5 1-57.9	ICP MS Plasma Se Mean ±SD Median Range 182.3 ±124.9 µg/L 144.5 53.6-913.2	Near visual contrast sensitivity and colour vision.	Reduced contrast sensitivity associated with hair Hg. No association was observed for near visual contrast sensitivity for plasma Se. Mean colour confusion index tended to be negatively associated with plasma Se. A positive association was observed between plasma Se and near visual contrast at 12 cpd. Intermediate spatial frequency of contrast sensitivity (12 cycles/degree) positively associated with plasma Se. Acquired colour vision loss increased with hair Hg and decreased with plasma Se. Hair Hg was positively correlated to plasma Se.	Tier 1	Acquired colour vision loss increased with hair Hg and decreased with plasma Se. Associated effect of less colour confusion and near visual contrast might counteract colour vision loss associated with Hg.
Golding *et al.* 2016. Avon Longitudinal Study of Parents and Children (ALSPAC) (Avon, UK) 1991-1992	Cohort At 4 years and 16-17 years	Prenatal Hg measurements and offspring behaviour results were available for 2 776 (at 47 months) and 1 599 (at 16-17 years). Not specified in this article. Data available at <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/ http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>. 0%	Maternal blood Hg (measured in first half of pregnancy). Whole blood Hg analysed with ICP-DRC-MS Maternal Hg (µg/L): Median: 1.86 Range: 0.17-12.76	Maternal blood Se (measured in first half of pregnancy). Whole blood Se analysed with ICP-DRC-MS. Maternal Se (µg/L): Median: 108 Range: 17-324	Offspring behavioural assessment: Strengths and Difficulties Questionnaire, compared with Hg and Se levels and fish/no fish consumption of mothers	No significant differences between the associations with Hg found among the offspring of women who ate fish in pregnancy and those who did not, nor did adjustment for Se make a difference.	Tier 1	There were no adverse effects of maternal prenatal mercury levels on the behaviour of the offspring, also not when analyses were confined to those offspring whose mothers had eaten fish in pregnancy and no consistent differences were found between fish and non-fish eaters. Their findings were not influenced by the association between Hg and blood Se.
Golding *et al.* 2016. ALSPAC study (Avon, UK) 1991-1992	Cohort Pregnancy cohort (first half of pregnancy) and follow-up of children at ages 6, 18, 30 and 42 months.	N = 2 875–3 264 (depending on outcome) Mean 28 years 0%	Maternal blood Hg levels (measured in first half of pregnancy). Whole blood Hg analysed with ICP-DRC-MS. Maternal Hg (µg/L): Median: 1.86 Range: 0.17-12.76	Maternal blood Se levels (measured in first half of pregnancy). Whole blood Se analysed with ICP-DRC-MS. Maternal Se (µg/L): Median: 108 Range: 17-324	Child neurodevelopment measured from questions in the Denver Developmental Screening Test. Included a total developmental score, and different subcategories (social, fine motor, gross motor, language)	Positive association between Hg levels and child developmental outcomes. Se concentrations made little difference to the size of the positive associations between Hg and the developmental outcomes.	Tier 1	Se did not ameliorate any deleterious effects of Hg on child development between 6 and 42 months of age.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Golding *et al.* 2017. ALSPAC study (Avon, UK) 1991-1992	Cohort Multiple and logistic regression analyses. Stratification considered children of fish eaters separately. Pregnancy cohort Follow-up at age 8	2 062 offspring Mean age not provided; data available in database. 0% (of mothers)	Maternal blood Hg levels (measured in first half of pregnancy). Whole blood Hg analysed with ICP-DRC-MS. Maternal Hg (µg/L): Median: 1.86 Range: 0.17-12.76 Children: Range <1.28 - >3.39 µg/L	Maternal blood Se levels (measured in first half of pregnancy). Whole blood Se analysed with ICP-DRC-MS. Maternal Se (µg/L): Median: 108 Range: 17-324 /L	Verbal, performance and total intelligence quotient (IQ)	Positive association of Hg with intelligence. Level of the mother's blood Se did not change the effect sizes.	Tier 2	Se did not influence positive effect of fish consumption on intelligence, despite correlation of fish consumption with Hg.
Gregory *et al.* 2016. ALSPAC study Avon, the United Kingdom 1991-1992,	Cohort Pregnancy cohort 1991-1992. with follow up after 7, 9, 11, 13,15 & 17 years	N = 4 484 for blood sampling and then from 2 207 down to 1 268 for child measurements after 7 to 17 years	Maternal (whole) blood Hg levels (measured in first half of pregnancy). Whole blood Hg analysed with ICP-DRC-MS. Maternal Hg (µg/L): Median: 1.86 Range: 0.17-12.76	Maternal (whole) blood Se levels (measured in first half of pregnancy). Whole blood Se analysed with ICP-DRC-MS. Maternal Se (µg/L): Median: 108 Range: 17-324	Child blood pressure measured (systolic and diastolic)	Little evidence that blood pressure in children was affected by the mother's blood mercury blood levels or fish intake.	Tier 1	Since there was little or no effect from maternal prenatal blood Hg on the resting blood pressure and heart rates, there was also little effect of Se. Hg and Se blood values were closely correlated.
Gustin *et al.* 2021. NICE cohort (Sweeden) 2015-2018	Cohort Pregnancy cohort, only mothers	N = 655 included but after exclusions 542 were analysed 30 years, mean	Blood levels measured in RBC (µg/L): was 0.29 to 4.2 with a median of 1.5.	Blood levels measured in plasma (µg/L): 46–93 median 67	Free and total T3 and T4 as health outcomes, together with TSH.	Erythrocyte Hg was non-linearly associated with fT3, TT3 and fT3:fT4 ratio. No or very slight effect of Se was reported.	Tier 1	Authors conclude that Hg can interfere with thyroid hormones, but that Se does not affect this interference.
Hu *et al.* 2017. The International Polar Year Inuit Health Study (IHS) Nunavut ++ Northern Canada 2007–2008	Cohort Inuits aged 18 + years	N = 2 595 agreed to participate and 2 169 completed individual questionnaire and had valid blood samples	Blood levels of Hg ranged from 0.3 to 70 with a median of 7.8 µg/L	Blood levels of Se ranged from 150 to 1500 with a median of 280 µg/L The authors divided the participants in 4 groups depending on values higher or lower of median value of Hg and Se	The health outcome was "self-reported physician-diagnosed condition of myocardial infarction, stroke, and high blood pressure measured." No time for the reporting was given.	High Se and low Hg had the lowest prevalence of cardiovascular outcomes (except stroke) and thereby provide evidence that Se may exhibit a protective effect against Hg on vascular disease.	Tier 2	This study indicates that exposure to Se in the absence of Hg is associated with cardiovascular risk, while high exposure to Hg in absence of Se is associated with increased cardiovascular risk.
Hui *et al.* 2016. The Chinese mercury birth cohort Children born July 2000 to December 2001 Follow-up after 6–9 years	Cross-sectional Follow-up after 6–9 years	N = 1 057 in the original birth cohort. N = 608 met for follow-up examination, 407 got all parameters measured. 0, mean age of follow up was 8.3 years. 54%	Cord blood nmol/L, median (inter-quantile) : 46.1 (33.1-65.1) Blood follow-up 13.0 (8.63-18.69)	Blood follow-up Se: nmol/L, median (inter-quantile) 1.17 (1.02-1.26) This figure is obviously wrong and can be used only as relative values. On molar basis Se is always higher that Hg. Probably was µml/L	Cytokines and TNF-alpha as measurements of immune system function.	Authors conclude that there is a small but significant association between mercury and IL-10 concentration. The association was more pronounced when selenium and cord blood mercury were low. The clinical significance is unclear.	Tier 2	In this study, Se seems to alleviate Hg toxicity. Although the clinical significance is unclear. The study has some shortcomings, which the review process should have detected.

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Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Karimi *et al.* 2016. Long Island, NY, the United States. (2010-2014) Not clearly provided	Cross-sectional Recruited avid seafood eaters from Long Island	N = 268 for blood samples. 290 were recruited. 47.88 (mean) ±18.24 (SD) 42%	Hg whole blood 7.71 ±8,12 (IQR: 2.46, 10.50)	Se whole blood 293.54 ±101.99(IQR: 65.79; 277.95)	GSH and GSH:GSSG as health outcomes and indicative for oxidative stress. Also reported omega-3 index.	Association of high Hg from fish consumption and GSH:GSSG. This was slightly less pronounced in those with highest Se in blood.	Tier 1	Association between elevated Hg from seafood and a shift in redox-status towards oxidative stress. This is, however, shifting in a much quicker time frame than the mercury. Authors rather vague on the effect of Se.
Kobayashi *et al.* 2019 Japanese Environment and Children Study Recruitment January 2011 to March 2014	Cohort study These mothers were only followed to delivery in this study	N that gave blood samples were 96 095 Then 20 000 were selected for blood measurement. After withdrawals etc. 17 998 gave blood samples. Further exclusions reduced the data set to 15 444 samples with the right meta data included. Mean age of mothers 30.9 ± 4.9 years Child sex 51.7m / 48.3f	Blood Hg 4.21 mean (IQR 2.59; 5.18) Range 0.334 to 30.1 and median 3.66.	Blood Se at 171.4 (mean; (IQR158.0; 183.0) Range 99.9 to 371.0)	Birth weight and "small for gestational age" as outcomes. Also birth head circumference was measured.	No effect on birth weight and "small for gestational age" as outcomes, but a weak correlation with head circumference and blood Hg.	Tier 1	Interestingly high levels of blood Hg in the Japanese pregnant women. The only possible negative effect was on head circumference, where authors claim that the higher Se did not give a high enough protective effect.
Kuras *et al.* 2018. Polish men from Lodz Both groups sampled from May to June 2015	Comparative case-control cohort study. Comparing work-exposed men with non-exposed men.	N = 131 Hg exposed 41 (31-51) years Median (IQR) N = 67 non-exposed 37 (30-54) y Median (IQR) (The latter group same as next paper.)	Median (IQR) Exposed group Hg blood 6.06 (4.01-8.94) Hg Urine 11.84 (7.55-21.04) Non-exposed Hg blood: 0.52 (0.35-0.73) Hg Urine 0.16 (0.12-0.24)	Median (IQR) Exposed group: Se-Plasma: 82.85 (72.03-90.28) Se-U: 13.44 (11.53-16.65) Non-exposed: Se-Plasma: 72.74 (66.25-80.14) Se-U: 11.89 (9.89-14.94)	Antioxidant systems activity and gene expression of central proteins in antioxidant system.	Authors conclude that there is upregulation of central genes in antioxidant defence in exposed workers. Also, some correlation of Hg with selenoprotein-P and antioxidants in blood was detected.	Tier 2	This work shows several interesting correlations between Hg and Se. High Hg in exposed workers can draw functional Se out of the system.
Kuras *et al.* 2019. Polish men from Lodz Cohort with intervention from June 2015 to August 2015	Cohort study Men with different nutritional status eating fish daily during two weeks and then back to normal diet for 4 weeks	N = 67 Healthy, non-exposed to Hg Mean 41.0 ± 12.7 years	Blood levels before exposure: W=0 0.623 ±0.412 W=1(E): 0.902 ±0.463 W=2(E): 1.282 ±0.487 W=6; 0.782 ±0.599 Hair levels before exposure: 0.237 ±0.164 W=6 0.288 ±0.150 Urine levels of Hg : W=0; 0.23 ±0.22 W=1; 0.23 ±0.19 W=2; 0.16 ±0.17	Plasma levels of Se: W=0; 73.3 ±11.6 W=1 (E); 81.6 ±10.2 W=2 (E); 80.8 ±12.3 W=6; 79.6 ±11.7 …..... Urine levels of Se: W=0; 13.1 ±3.6 W=2 (E); 17.0 ±4.1 W=6; 10.4 ±2.8	Biomarkers of pro- and antioxidant effects TBARS, TAA, GSH-Px Gene expression	Authors claim that their study confirms the existence of a biological relationship between Hg and Se. They report an increase in TBARS as an effect of fish intake but there is little evidence for direct action of Se into GSH-Px.	Tier 1	The paper shows that both Hg and Se increase in an intervention with high fish intake. There is interaction between Hg and Se but no direct evidence for a protective effect of Se.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Lei *et al.* 2015. Infertile women from Taiwan enrolled August 2008 to March 2010	Cohort study Comparing infertile women with pregnant women including food frequency questionnaire	N = 310 infertile women compared with 57 fertile (pregnant) women Mean ±SD Age infertile 35.2 ±3.9 years Age fertile 34.8 ±4.1 years In the infertile group women were divided into two groups based on Hg Blood level of 5.8 µg/L	Infertile women – Blood MeHg: Median ±SD ±5.21 Pregnant – 5.13 ±2.75	Blood Se In infertile women with Hg > 5.8; 242 ±42.2 In infertile women with Hg < 5.8; 240 ±36.9	Measured outcomes: Fertility and reproductive hormones correlated to mercury	Authors found slightly lower prolactin in the highest mercury group and higher MeHg in infertile group compared with pregnant women.	Tier 2	No effect of Se on Hg found, as also very small effect of Hg was found. The authors discuss a possible link with fish consumption, but this is not really found.
Lemire *et al.* 2010. Adults from rural area in Tapajos River Basin, State of Para, Brazil Human samples May to July 2006.	Cross-sectional. Have followed this population since mid-1990s.	448 agreed to participate, but due to different problems only about 220 were sampled and further exclusions criteria reduced the final number to 211. 96 women and 115 men all over 40 years divided into groups age 40 to 65 (171) and 65 to 87 (40). Mean age 50 years (40–64) in first group and 73 years (65–87) in second group.	Blood Hg: Median (range)-(µg/L) 44 (4.3-298) Plasma Hg Median (range)-(µg/L) 6.4 (0.2-40)	Blood Se: Median (range)-(µg/L) 222 (124-1500) Plasma Se Median (range)-(µg/L) 133 (57-913)	The measured outcome was cataract formation graded in 4 levels of seriousness	Authors found that cataracts were most prevalent in persons with high B-Hg and Low P–Se. This was mostly so in lower range of P-Se. Authors are not sure if this weak effect is caused by the effect of Se as an antioxidant or as an effect by counteracting the negative effect of Hg on cataract formation.	Tier 1	As this study is performed in a population with some of the world's highest Hg exposures, it is interesting to observe the correlation of blood Hg and cataracts. Se seems to have an effect, but mechanism is not clear. This may be caused by the effect of Se as an antioxidant.
Lemire *et al.* 2011. Adults from rural area in Tapajos River Basin, State of Para, Brazil Human samples May to July 2006.	Cross- sectional. Have followed this population since mid-1990s.	448 agreed to participate, and a total 407 were included in tests and analyses Several more were excluded because of problems with creatinine analyses. As such, for urine samples only 319 participated. Mean age was 41.5 years, (range 15–87) 50/50 female/male (n = 204/ n= 203)	Blood Hg Mean/Median (range): 51.0 / 42.5 (1.7-289) µg/L	Blood Mean/Median (range): 288/ 228 (103-1500) µg/L Plasma Se Mean/Med. (range): 163 / 135 (54-913) Hair Se Mean/Med.(range): 0.84 / 0.69 (0.38-3.81) Urine Se (µg/g cr) 57.0 /33.6 (2.3-1375)	The outcome measurements were different motor functions (dexterity) Tests: BAMT Santa Ana Dynamometer Grooved Pegboard	Authors' conclusion is mainly that there is a positive correlation between High P-Se and motor outcomes, more when including Hg as a counteracting confounder. This population has extremely high Hg exposure.	Tier 1	Authors indicate that there is some correlation between high P-Se and motor function outcomes. Extremely high Hg concentration in this population.

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Maeda *et al.* 2019 Japan 2016-2017	Case-control study Case is females attended at Akita hospital because lack of pregnancy. Control is other women from same in their 30s	The case included 98 female patients aged 35.2 ±4.1 (mean ±SD) The control group were recruited from 169 participants, 49 consented and further 6 were excluded. Control then included 43 women with mean age 33.6 ± 2.5 years, meaning that the control group was significantly younger than the case group	Blood Hg in case group µg/L (median, (5^{th}-95^{th} percentiles) ; 5.3 (2.2-14.5) In control group: 5.0 (1.8-10.0) (Not significant difference)	Blood Se in case group µg/L (mean ± SD) ; 189± 25 In control group: 200 ± 25 (Significant difference)	The outcome measured in this study is infertility and reproductive hormones	Authors indicate that low Se levels in blood were lower in the infertile group. They also claim that mercury is higher in the infertile group adjusted to age and Se and indicate a toxic effect of these rather low levels of Hg and that Se can mitigate the effect	Tier 2	The difference in Se blood levels is not very strong and not existing for mercury, based on unadjusted figures. The authors indicate a toxic effect of these rather low levels of Hg and that Se can mitigate the effect.
Mao *et al.* 2019. Analysing data from the CARDIA study. the United States of America Sampling from 1985 and still ongoing.	Cross- sectional Followed since 1985 and still ongoing.	N = 5 115 were recruited in 1985 to 1986, Then at 18–30 years. Sampling year 2, 5, 7, 10, 15, 20, 25, 30 and ongoing. 43.6	Toenail Hg (µg/g - ppm) 0.32 ± 0.37 I quintiles based on omega-3 intake 0.22-0.26-0.30-0.37-0.43 Measured Y2	Toenail Se (µg/g - ppm) 0.86 ± 0.15 I quintiles based on omega-3 intake 0.88-0.87-0.86-0.85-0.84 Measured Y2	Three cognitive tests: RAVLT (words) DSST (symbols) Strop test All after 25 Y	Authors find that higher omega-3 fatty acid intake and non-fried fish improves outcome of the DSST test. Neither Hg nor Se interfered with the main conclusion, but these statistics are based on very old Se and Hg data.	Tier 1 (Rated too positi-vely?)	Unfortunately, the exposure data in terms of toenail Hg and toenail Se at Y 2 might not be relevant, since mercury follows the omega-3 data there is no really negative effect to improve.
Monastero *et al.* 2017 Long Island, the United States of America; avid seafood consumers 2011–2012	Cohort study Food frequency questionnaire and health question and then one single sampling.	996 were interested, 746 were eligible (based on food frequency survey) and 290 chose to enrol. 287 had blood samples drawn. Mean (SD); 48 years (18.2) 41.1% males	Blood Hg measured by ICP-MS and the cohort divided into lower than 4.58 (µg/L) and higher than 4.58 µg/L. Upper decile (19.8 – 51.0)	Blood Se (ng/mL) Mean (SD) 294.3 (101.5) 295.3 (99.3) for the low Hg group 291.4 (106.9) for the high Hg group	Cytokines and ANA titres used as measurements of immune system function	Authors did not find any effect of high Hg on the cytokines measured nor at ANA titres. Se did not vary between high Hg and low Hg groups.	Tier 1 (Rated too positi-vely?)	This experiment, which is the same as reported by Karimi *et al.*, showed no difference in outcome with mercury and no effects on or difference in blood Se concentration.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Mozaffarian *et al.* 2011 (Cardiovascular disease) Health Professional Follow Up Study (HPFS) (Male US health professionals) and Nurses Health Study (NHS) 1986 and 1976	Nested case-control (based on two cohorts) Conditional logistic regression HPFS was only men, toenail clippings from 68% of participants in 1987, and 52% of NHS in 1982-83	HPFS enrolled 51 529 males in 1986 aged 40 to 75 years mean ±SD 61.1 ±9.0 NHS enrolled 120 700 females in 1976 aged 30 to 55 years mean ±SD 53.8 ±6.1 Of these cardiovascular disease (coronary heart disease and stroke) was prospectively identified in 3 427 participants and matched to risk-set-sampled controls; dentists were excluded.	Toenail Hg measured by neutron activation analysis. Median, Interdecile range Case: 0.23 µg/g, 0.06-0.94 Control: 0.25 µg/g, 0.07-0.97 Males/Female Median, Interdecile range Case: 0.30 µg/g, 0.07-1.26/ 0.21 µg/g 0.06-0.77 Control: 0.31 µg/g, 0.07-1.31/0.23 µg/g 0.07-0.76	Toenail Se measured by neutron activation analysis. Males/Female Mean ±SD Case: 0.92 ±0.61 µg/g/ 0.78 ±0.22 µg/g Control: 0.92 ±0.6 µg/g, /0.78 ±0.25 µg/g	CVD	First and fifth quintile comparison relative risks: Coronary heart disease 0.85 (CI 0.69-1.04; P=0.1 for trend); stroke 0.84 (CI 0.62-1.14; P=0.27 for trend); total cardiovascular disease 0.85 (CI 0.72-1.01; P 0.006 for trend). Similar in analysis of participants with low Se concentration or low overall fish consumption.	Tier 2	No evidence of clinically relevant adverse effects of mercury exposure on coronary heart disease, stroke or total cardiovascular disease in US adults at the exposure levels investigated. This was also true when a subgroup with low Se concentrations (<0.7 µg/g) was analysed or in analysis stratified according to fish consumption. As the authors did not find any negative effects of the Hg exposure through fish, they also could not conclude on beneficial effects of seafood intake or Se.
Mozaffarian *et al.* 2012. (Hypertension Health Professional Follow Up Study (HPFS) US Men Nurses Health Study (NHS) US Women	Nested case-control (based on two cohorts) HPFS was only men, toenail clippings from 68% of participants in 1987, and 52% of NHS in 1982-83	HPFS enrolled 51 529 males in 1986 aged 40 to 75 years NHS enrolled 120 700 females in 1976 aged 30 to 55 years 6 045 were included for analyses after exclusion of 3 263 with hypertension at baseline.	Toenail Hg µg/g measured by neutron activation analysis. Mean (5^{th}, 95^{th} percentile) 0.30 (0.07, 1.31) in men 0.21 (0.07, 0.76) in women	Toenail Se measured by neutron activation analysis. Mean ±SD 0.92 ±0.63 in men and 0.79 ±0.20 in women	Outcome was physician-diagnosed hypertension, biannually. The validity was confirmed in validation studies based on review of medical charts and direct BP measurements.	Authors did not find clinically apparent adverse effects of chronic methylmercury exposure at usual exposure levels seen in these men and women on hypertension.	Tier 2	As the authors did not find any negative effects of the mercury exposure through fish, they also could not conclude on beneficial effects of omega-3-fatty acids or Se.
Nakamura *et al.* 2014. Taiji, coastal Japan 2010–2011	Multivariate analysis and another non-linear model	194 Taiji (traditional whaling town) residents (117 males, 77 females, 20–85 years) 60.3%	Measured in 23 subjects Oxygen combustion-gold amalgamation method Hair: Male/female/ total Geometric mean 17.2/12.1/14.9 µg/g Median 18.7, 15.1/17.8 min max 1.1-101.9, 2.1-73.1/1.1-101.9; 25/75 percentile 11.1, 32.7/5.9-24.3/7.9, 28.7 of which 10/2/12 above 50 µg/g (NOAEL by WHO) Blood	Measured in 23 subjects ICP-MS Only correlation found, not values.	Neurological and dietary surveys. Audiometry, MRI, electromyography: cranial nerve affection, muscular weakness, tremor, rigidity, coordinated movements, one foot standing, gait, touch sensation, pain sensation, position sense, vibratory sensation, two-point discrimination, graphesthesia, stereognosis	Hair mercury levels significantly correlated with whale meat intake. In another nonlinear model, significant increase was observed in the odds ratio for sensorineural hearing loss and simple gait disturbance with mercury levels >50 µg/g, but were assigned to other neurological causes than Hg exposure at closer examination.	Tier 2	No significant correlations between hair mercury levels and neurological outcomes in multivariate analysis. Positive correlation between whole blood Hg and Se, which might be one cause of absence of adverse effects of MeHg in this study.

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Nyland *et al.* 2011. Part of study described in Lemire *et al.* 2006. Adults living along the Tapajós River (affected by MeHg – gold extraction), Brazil 2006	Cross-sectional epidemiological study	232 of 448 in parent study. 15–87 years 112 males, 120 females 48.28%	Hg ICP-MS for fluid, cold vapor atomic absorption spectrometry for hair Median (range) Geometric mean Hair 14.1 µg/g (1.1-62.4) Blood 53.5 µg/L (4.3-288.9) 42.5 µg/L Plasma 8.8 µg/L (0.2-40) Urine 3.0 µg/L (0.2-16.1)	Se ICP-MS	To test the hypothesis that MeHg exposures affect levels of serum biomarkers and to examine interactions between Hg and Se in terms of these responses. Antinuclear (ANA) and antinucleolar (ANoA) autoantibody levels and eight cytokines in serum samples	Elevated titers of ANA were positively associated with Hg exposure for blood and plasma, unadjusted and adjusted for sex and age. Proinflammatory ([interleukin (IL)-6 and interferon (IFN)-γ], anti-inflammatory (IL-4), and IL-17 cytokine levels were increased with MeHg exposure. Although Se status was associated with MeHg level (correlation coefficient = 0.86; 95% CI: 0.29, 1.43), Se status was not associated with any changes in ANA and did not modify associations between Hg and ANA titers. Food frequency questionnaire.	Tier 2	No association of Se with any changes in ANA and did not modify associations between Hg and ANA titers. Positive correlation between blood Hg and Se.
Oken *et al.* 2016. Project Viva cohort Women attending prenatal care at Atrius Harvard Vanguard Medical Associates, Massachusetts, the United States of America 1999-2002	Prospective longitudinal study Multivariable linear regression adjusted for characteristics including home environment and maternal intelligence Mid-childhood (median 7.7 years) follow up	1 068 pairs (872 with blood) 7.7 years for cognitive tests. Maternal 32.2 years ±5.3 (mean ±SD), 15.3–44.9 Children: 50%	Erythrocyte Hg Mean ±SD Min max 4.0 ng/g ±3.6 0-38.2	Erythrocyte Se Mean ±SD Min max 205.6 ng/ml ±34.6 44.3-380.3	Child neurodevelopment cognitive tests: Kauffman Brief Intelligence Test (KBIT) Food questionnaires at median 27.9 weeks gestation	Child verbal and nonverbal scores and tests of memory and visual motor abilities were not related to any exposures. Mutual adjustments of each of the exposure measures did not substantially change estimates.	Tier 1 (Half the partic-ipan-ts with-drew)	In this population with an average fish consumption of 1.5 servings per week, authors did not find evidence for an association of maternal prenatal fish intake or Hg or Se status with verbal- or non-verbal intelligence, visual motor function, or visual memory at median 7.7 years of age.
Park, K. & Seo, E. 2016. The Trace Element Study of Korean Adults in the Yeungnam area (SELEN) Korean area Yeungnam area 2012–2013	Prospective cohort Multivariable linear regression analysis	232 male +269 female = 501 >35 years, 44.8 ±0.24 (mean ± se) 46.31%	Toenail mercury Neutron activation analysis Mean 0.4 µg/g	Toenail selenium Neutron activation analysis Median 0.985 µg/g Mean 0.69 µg/g	Metabolic syndrome (MetS) (combination of diabetes, high blood pressure [hypertension] and obesity)	Positive association between toenail mercury and metabolic syndrome, which was stronger at lower selenium and weaker at higher selenium. Half the participants were overweight.	Tier 1	Selenium modifies association between toenail mercury and metabolic syndrome. Association non-significant for above-median levels of toenail selenium.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Park, K. & Seo, E. 2017. The Trace Element Study of Korean Adults in the Yeungnam area (SELEN) Korean area Yeungnam area 2012-2013	Prospective cohort Multivariable linear regression analysis	232 male +269 female = 501 >35 years, 44.8 ±0.24 (mean ± se) 46.31%	Toenail mercury Neutron activation analysis Mean 0.4 µg/g Men: 0.47 µg/g Women: 0.34 µg/g	Toenail selenium Neutron activation analysis Median 0.985 µg/g Mean 0.69 µg/g	Hypercholesterolemia, hyper-LDL-cholesterolemia, hypo-HDL-cholesterolemia, hypertriglyceridemia, and dyslipidemia	Participants in the highest tertile of toenail mercury levels had 4.08 (95% CI 1.09–15.32, p for trend = 0.02) times higher risk of hyper-LDL-cholesterolemia, and 2.24 (95% CI 1.15–4.37, p for trend = 0.004) times higher risk of dyslipidaemia than those in the lowest tertile. These associations became weak and non-significant, showing OR 0.98 and 95% CI 0.25-3.80 for hypercholesterolemia and OR 1.99 and 95% CI 0.73–5.45 for dyslipidemia at toenail selenium levels >0.685 µg/g.	Tier 1	High toenail mercury associated with higher risk of hyper-LDL-cholesterolemia, and dyslipidemia. These associations were non-significant, at toenail selenium levels >0.685 µg/g.
Park *et al.* 2013. National Health and Nutrition Examination Survey (NHANES) the United States of America 2003-2006	Cross-sectional associations	2 117 for selenium data >40 years for selenium data (weighted mean ± se) 46.6 ±0.5 48.6	ICP MS geometric means (95% confidence intervals) Blood Hg ICP MS 1.03 (0.95, 1.11) mg/L Urine Hg Cold vapor atomic absorption or ICP-DRC-MS 0.51 (0.47, 0.54) mg/L	Serum ICP-DRC-MS 137.2 ±1.39 µg/L		The weighted prevalence of hypertension was 32.2%. The geometric means (95% confidence intervals) of blood total and urinary mercury were 1.03 (0.95, 1.11) mg/L and 0.51 (0.47, 0.54) mg/L, respectively. The adjusted odds ratios for a doubling increase in blood Hg and urinary Hg were 0.94 (0.87 to 1.01) and 0.87 (0.78 to 0.99), respectively, after adjusting for potential confounders. The associations remained similar, even after adjusting for either omega-3 fatty acids or Se or both.	Tier 1	Association between blood Hg (both MeHg and inorganic Hg) and urinary Hg (mainly inorganic) was not modified by Se. No association of hypertension with blood Hg, but a suggestive inverse association with urinary Hg.
Rocha *et al.* 2016. Young women from the relatively large city of Porto Velho Western Amazonas, Brazil	Cohort study Young women, premenopausal Mean 26.6 years (range 18-48)	Because of the genetic dimension, they enrolled 200 participants but 51 were excluded due to incomplete sampling, and 149 women were in the study. The aim was to differentiate the response to mercury and selenium exposure due to genotyping selenium containing enzymes known to affect mercury and selenium metabolism.	The food survey showed surprisingly low fish intake. Hair Hg µg/g (Mean ±SD) 0.60 ±0.74, which is rather low for this area.	Plasma Se µg/L 49.76 ±19.34 (5.85-109.37) Mean ±SD (range) which shows Se deficiency. Estimated mean (SD) selenium intake was 48.84 ±20.37 µg/day	Outcome measured was activity of Se containing enzymes (GSH-Px) and biomarkers of oxidative stress (ORAC & MDA) Differentiated due to genetic profiling.	No effect was found. Further, there was no difference in outcomes between the different genetic isoforms of antioxidant defence.	Tier 1	This study had very low exposure of mercury and no effect of mercury or modification of that effect of Se was found.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Saint-Amour *et al.* 2006.	Cohort study of children from Nunavik Arctic Canada Mothers recruited in 1993 to 1996 and children recruited 5 to 6 years after delivery.	There were 483 newborns in the original Nunavik Cord Blood Monitoring Program. Of these, 110 children were recruited 5-6 years after birth. (mean 5.4 years). 38.5%	Cord blood Hg (=µg/L calculated from nmol/L) 16.5 (13.4-20.3) Mean (95% CI) Arithmetic mean 23.9; SD 20.3, range 1.8-104. Child blood Hg (=µg/L calculated from nmol/L) 5.9 (4.5-7.7) Mean (95% CI) Arithmetic mean 9.9; SD 9.1, range 0.2-38.2.	Cord blood Se (=µg/L calculated from nmol/L) 319 (278-367) Mean (95% CI) Arithmetic mean 351; SD 164; range 164-774. Child blood Se (=µg/L calculated from nmol/L) 331 (288-382) Mean (95% CI) Arithmetic mean 429; SD 427, range 158-2566.	Visual test named. Visual evoked potentials (VEPs). Designated N75 and P100, N150.	Authors conclude that there was a negative impact on these outcomes caused by the PCB and/or MeHg. They did not find any significant interaction with nutrients. They therefore conclude that they contradict notions that Se can protect against environmental neurotoxins.	Tier 1	The study design focused on toxicological effect, and not very specific on Se effect on MeHg toxicity.
Steuerwald *et al.* 2000. The women were residents of the northwestern region and not in the capital area. Recruitment in 1994–1995	Cohort study of pregnant women from Faroe Islands Neurologic examination of newborn (only) within 14 days of delivery.	The cohort was established of 182 singleton term births born in Torshavn. 51.1%	Maternal whale meat, whale blubber and seafood intake was recorded. Cord blood Hg µg/L 20.4 (11.8-40.0; 1.90-102) Cord serum Hg µg/L 2.54 (1.65-3.66; 0.70-8.74) Hair Hg µg/g 4.08 (2.45-7.35; 0.36-16.3) geometric mean (interquartile range; total range)	Serum µg/L Mean ±SD 103.4 ±14.2	Outcomes were neurological examination of newborn infants at two weeks of age. Collected in a Neurological Optimality Score (NOS).	The authors found a significant decrease in the neonatal NOS connected to methylmercury from seafood (but not from PCB which was also high). They also conclude that there was no evidence that Se caused important protection against Hg associated decrease in NOS.	Tier 1	Very high levels of Hg in all mercury-exposure parameters. Very important part of Faroe Island study but not really designed/protocolled to test Se effects.
Tatsuta *et al.* 2017.	Prospective cohort of pregnant women in Japan, giving birth in 2003-2006 and children tested in 2004-2008.	There were 879 pregnant women who gave written informed consent, 749 mother-child pairs registered and completed data was collected for 566. The children were 285 boys and 281 girls.	Maternal seafood intake was estimated to provide Hg at 0.9 (0.1-3.8) and 0.9 (0.2-3.0) µg/kg body weight/week respectively in mothers of boys and girls. Hair mercury 2.5 µg/g (range 0.3-11.0). Cord blood Hg 16.5 (5.7-36.9) - 15.0 (4.8-39.3) for mothers of boys and girls respectively (median (5-95th percentile)	Cord plasma selenium Ng/g was 66.3 ±10.2 and 67.0 ±9.6 in mothers of boys and girls respectively.	Outcomes measured using Bayley Scales of Infant Development (BSID-II) and Kyoto Scale of Psychological Development (KSPD). Measured at 18 months of age.	Main finding was that prenatal Hg negatively affected psychomotor performance as measured in I BSID-II.	Tier 1	Good correlation between cord blood Hg and hair Hg. Small but significant negative effect of Hg on the psychomotor part of BSID-II test. No effect of Se corrected as confounder.

TABLE A6.4 **OVERVIEW OF HUMAN PRIMARY STUDIES (N = 45) FOR THE REVIEW "HEALTH EFFECTS OF MeHg" (cont.)**

Author, year Trial or study name Geography Year of sampling	Study type Study duration and follow-up time Statistical approach	Number of participants in the study (n) Age (years) at exposure assessment Sex (% males)	Measurement and levels of exposure (Hg)	Measurement and levels of exposure (Se)	Measurement of outcome	Overall results	Risk of bias (OHAT)	Overall conclusion
Tratnik *et al.* 2017. Women giving birth in Slovenia and Croatia Southern Europe	Two comparative cohorts from Ljubljana, Slovenia (large city) and Rijeka, Croatia, (coastal city) Prospective cohort Project begun in 2006, completed in 2011.	601 pregnant women were recruited in Slovenia and 243 from Croatia. But only 361 of the children had Hg in cord blood, Bayley-III assessment and Apoc genotyping, leaving in total 361 mother/child pairs in the study, 237 from Slovenia and 124 from Croatia. Children were also stratified genetically through Apolipoprotein E genotyping.	Consumption of sea fish was different in the cohorts In Slovenia 25% ate fish more than once per week, in Croatia 68.5%. Mean cord blood was 1.58 ng/g in Slovenia and 3.40 ng/g in Croatia. Maternal hair mean Hg was 273 ng/g in Slovenia and 576 ng/g in Croatia	Selenium in cord blood serum was 40.1 ng/g (range 15-70 ng/g)	Outcome measured as child neurodevelopmental outcomes using Bayley-III (cognitive, language and motor scales)	Hg-related decrease in cognitive score only in children carrying at least one Apoε4 allele, and general decrease in fine motor scores. Positive association between Se and the language score, but not in the subgroup of children carrying the Apoε4 allele. Unclear if effect of Se on Hg toxicity or just separate effects.	Tier 1	Weak effect of Se for a genetic subgroup.
Wells *et al.* 2016. Women giving birth in Baltimore, the United States of America, Nov. 2004 to March 2005	Cross-sectional	There were 597 births, of which 341 included collection of umbilical cord blood. 300 of these had enough for initial lab analysis and is called the Baltimore THREE study. 29 more were excluded due to lack of total data sets. 55.4%	Me-Hg in umbilical cord blood Inorganic Hg in blood. Hg method had rather high LOD (or more correct LOQ) which does have a negative impact on the data set. Geometric mean cord MeHg was 0.94 µg/L with 95% CI 0.8 (1.07)	Umbilical cord serum Se geometric mean 70 µg/L (95% CI 68.5; 71.4)	Outcomes measured were different birth parameters such as birth weight, birth length, gestational age, head circumference and Ponderal Index.	Ponderal index decreased with increasing MeHg. This was not influenced by Se. Hg and Se did not correlate.	Tier 2	The negative association of MeHg with birth weight and ponderal index was influenced by Se.
Wennberg *et al.* 2011 Northern Sweden Health and Disease Study (NSHDS) with three underlying studies (VIP, MONICA, MSP) 1987–1999	Case-control study based on three studies.	The total base of screened subjects was about 73 000 by 31 Dec. 1999 Number of cases with myocardial infarction (MI) was 7 337, of which Hg/Se/Fatty acid data was available for 431/431/374. These were matched with controls (499/497/434). Mean age at event 58.7 years (34.1 – 77.1), average time between baseline and event 7 years, 11 months.	Meals of fish/week Erythrocyte Hg was 3.47 (0.01-45.9) in males in cases and 3.95 (0.15-81.4) in male controls and for women 3.04 (0.43-23.4) in cases and 3.68 (0.19-16.7) in controls.	Meals of fish /week; 1.00 in cases and 1.00 in controls for men, 1.05 and 1.05 for women Erythrocyte mean (range) Se was 120 (72.5-302) µg/L in males in cases and 123 (75.5-250) in male controls and for women 126 (86-207) in cases and 132 (81.0 – 400) in controls.	Outcome measured was myocardial infarction, of which some resulted in sudden cardiac death (SCD) These are compared with a reference group.	Authors report no effect of Hg on myocardial infarction.	Tier 1	Since there were no negative effects of raised Hg concentrations caused by fish intake, it was not possible to detect protective effects of Se. There was a small increase in risk of SCD with increasing Ery-Se, but the authors indicate it could be a random effect.

APPENDIX 7
OCCURRENCE DATA OF MeHg AND DIOXINS AND dl-PCBs

LITERATURE SEARCH STRATEGY

TABLE A7.1 LITERATURE SEARCH STRATEGY FOR THE REVIEW "OCCURRENCE DATA" FOR DATA ON HG AND MeHg

Database: Web of Science		
Date of literature search: 22 November 2021		
#	Literature search string	Total hits
1	TI=(Hg OR mercury OR MeHg OR Me-Hg OR "methyl Hg" OR "methyl-Hg" OR "methylmercury" OR "methyl-mercury")	22 384
2	AB=(Hg OR mercury OR MeHg OR Me-Hg OR "methyl Hg" OR "methyl-Hg" OR "methylmercury" OR "methyl-mercury")	75 521
3	AK=(Hg OR mercury OR MeHg OR Me-Hg OR "methyl Hg" OR "methyl-Hg" OR "methylmercury" OR "methyl-mercury")	16 453
4	#1 OR #2 OR #3	79 534
5	TI=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	329 805
6	AB=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	725 705
7	AK=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	208 439
8	#5 OR #6 OR #7	803 288
9	TI=(concentration* OR level* OR measure* OR amount* OR value* OR content* OR determin*)	1 190 004
10	AB=(concentration* OR level* OR measure* OR amount* OR value* OR content* OR determin*)	10 070 218
11	AK=(concentration* OR level* OR measure* OR amount* OR value* OR content* OR determin*)	478 607
12	#9 OR #10 OR #11	10 410 632
13	#4 AND #8 AND #12	6 202
14	#4 AND #8 AND #12 and Review Articles or Proceedings Papers or Meeting Abstracts or Corrections or Editorial Materials or Letters or Retracted Publications or News Items (Exclude - Document Types)	5 884

TABLE A7.2 **LITERATURE SEARCH STRATEGY FOR THE REVIEW "OCCURRENCE DATA" FOR DATA ON DIOXINS AND dl-PCBs**

Database: Web of Science		
Date of literature search: 22 November 2021		
#	**Literature search string**	**Total hits**
1	TI=(dioxin* OR furan* OR PCDD* OR PCDF* OR "polychlorinated dibenzodioxin*" OR "polychlorinated dibenzofuran*" OR TEQ)	9 089
2	AB=(dioxin* OR furan* OR PCDD* OR PCDF* OR "polychlorinated dibenzodioxin*" OR "polychlorinated dibenzofuran*" OR TEQ)	22 298
3	AK=(dioxin* OR furan* OR PCDD* OR PCDF* OR "polychlorinated dibenzodioxin*" OR "polychlorinated dibenzofuran*" OR TEQ)	6 734
4	#1 OR #2 OR #3	24 262
5	TI=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	329 805
6	AB=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	725 705
7	AK=(Fish* OR finfish* OR crayfish* OR crawfish* or cuttlefish* OR inkfish* or milkfish* or catfish* or Pisces or seafood* or "sea food*" or sea-food* or "blue food*" or blue-food* or "aquatic food*" or aquatic-food* or anchov* or Engraulis or pollock* or tuna* or herring* or whiting* or sardin* or mackerel* or pilchard* or crab* or shrimp* or prawn* or squid* or octopus or cephalopod* or mollusc* or mussel* or shell* or scallop* or cod or "Largehead hairtail" or carp* or tilapia* or salmon* or pangasius or krill or decapod* or oyster* or scad* or Crassostrea or tagelus or clam* or cockle* or urchin* OR echinoderm* OR echinoid* or "sea cucumber*" OR holothuroid* or catla or Carassius or labeo or trout* or bream* or Cyprinid* or shark* or skate* or crustacea* or "aquatic invertebrate*" or "marine invertebrate*" or lobster* or bivalv* OR whelk* OR gastropod* or abalone* or snail* or limpet* or conch* or periwinkle* or nautilus*)	208 439
8	#5 OR #6 OR #7	803 288
9	TI=(concentration* OR level* OR measurement* OR amount* OR value* OR content* OR determinat*)	1 190 004
10	AB=(concentration* OR level* OR measurement* OR amount* OR value* OR content* OR determinat*)	10 070 218
11	AK=(concentration* OR level* OR measurement* OR amount* OR value* OR content* OR determinat*)	478 607
12	#9 OR #10 OR #11	10 410 632
13	#4 AND #8 AND #12	1 031
14	#4 AND #8 AND #12 and Review Articles or Proceedings Papers or Editorial Materials or Letters or Meeting Abstracts or Retracted Publications (Exclude – Document Types)	967

QUALITY ASSESSMENT OF ARTICLES FOR OCCURRENCE DATA

Insert Table A7.3 Quality assessment of articles for Occurrence data

OCCURRENCE DATA

Insert Table A7.4 Occurrence data from the literature

Insert Table A7.5 Occurrence data from EFSA

Insert Table A7.6 Occurrence data of Hg and MeHg from WHO-GEMS

FOOD SAFETY AND QUALITY SERIES

11. FAO. 2016. Risk based imported food control, manual.
2. FAO and WHO. 2016. Risk communication applied to food safety, handbook.
3. FAO. 2016. Enhancing early warning capabilities and capacities for food safety.
4. FAO. 2017. Food safety risk management: evidence-informed policies and decisions, considering multiple factors.
5. FAO and WHO. 2018. Technical guidance for the development of the growing area aspects of bivalve mollusc sanitation programmes.

5a. FAO and WHO. 2021. Technical guidance for the development of the growing area aspects of bivalve mollusc sanitation programmes, second edition.

6. FAO. 2019. Technical guidance principles of risk-based meat inspection and their application.
7. FAO and WHO. 2019. Food control system assessment tool.
   - > Introduction and glossary
   - > Dimension A – inputs and resources
   - > Dimension B - control functions
   - > Dimension C - interaction with stakeholders
   - > Dimension D - science/knowledge base and continuous improvement
8. FAO. 2020. Climate change: unpacking the burden on food safety.
9. FAO and WHO. 2020. Report of the expert meeting on ciguatera poisoning.
10. FAO. 2020. FAO guide to ranking food safety risks at the national level.
11. FAO and WHO. 2020. Joint FAO/WHO expert meeting on tropane alkaloids.
12. FAO. 2022. Technical guidance for the implementation of e-notification systems for food control.
13. FAO and WHO. 2022. Report of the expert meeting on food safety for seaweed - Current status and future perspectives.
14. FAO and WHO. 2022. Risk assessment of food allergens. Part 1: Review and validation of Codex Alimentarius priority allergen list through risk assessment.
15. FAO and WHO. 2022. Risk assessment of food allergens. Part 2: Review and establish threshold levels in foods for the priority allergens.

16. FAO and WHO. 2023. Risk assessment of food allergens – Part 3: Review and establish precautionary labelling in foods of the priority allergens.

17. FAO and WHO. 2024. Risk assessment of food allergens – Part 4: Establishing exemptions from mandatory declaration for priority food allergens.

18. FAO. 2022. Microplastics in food commodities – A food safety review on human exposure through dietary sources.

19. FAO. 2023. The impact of pesticide residues on the gut microbiome and human health – A food safety perspective.

20. FAO. 2023. The impact of veterinary drug residues on the gut microbiome and human health – A food safety perspective.

21. FAO. 2023. The impact of microplastics on the gut microbiome and health – A food safety perspective.

22. FAO and WHO. The impact of food additives on the gut microbiome and health - A food safety perspective. In progress.

23. FAO and WHO. 2023. Risk assessment of food allergens. Part 5: Review and establish threshold levels for specific tree nuts (Brazil nut, macadamia nut or Queensland nut, pine nut), soy, celery, lupin, mustard, buckwheat and oats.

24. FAO. 2023. Food safety implications from the use of environmental inhibitors in agrifood systems.

25. FAO. 2024. Risk assessment of 3-monochloropropane-1,2-diol, glycidol, and their fatty acid esters in lipid-based nutrient supplements and ready-to-use therapeutic food.

26. FAO. 2024. Report of the FAO Technical Meeting on the gut microbiome in food safety chemical risk assessment. In progress.

27.FAO & WHO. 2024. FAO/WHO background document on the risks and benefits of fish consumption.

28. Joint FAO/WHO Expert Consultation on risks and benefits of fish consumption. Meeting report. In progress.

29. FAO. 2024. Food Safety in a Circular Economy. In progress.


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RISK ASSESSMENT OF 3-MONOCHLOROPROPANE-1,2-DIOL, GLYCIDOL, AND THEIR FATTY ACID ESTERS IN LIPID-BASED NUTRIENT SUPPLEMENTS AND READY-TO-USE THERAPEUTIC FOOD

FOOD SAFETY IN THE CONTEXT OF LIMITED FOOD AVAILABILITY

New literature became available following the last Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption held in 2010. FAO and WHO decided to generate a background report consisting of a comprehensive literature review, followed by an expert consultation, to update the report with new scientific evidence. This background document aims to provide scientific evidence about the risks and benefits of fish consumption that were the basis for the Expert Consultation and contains the results and methodology followed to carry out five extensive literature reviews focused on: evidence of health benefits from fish consumption; toxic effects of dioxins and dioxin-like polychlorinated biphenyls (dl-PCBs); toxic effects of methylmercury (MeHg); the role of selenium (Se) with regard to the health effects of MeHg; and occurrence data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products.

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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
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