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MEETING REPORT

JOINT FAO/WHO
EXPERT CONSULTATION ON
THE RISKS AND BENEFITS OF FISH CONSUMPTION

ROME, 9–13 OCTOBER 2023

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WORLD HEALTH ORGANIZATION
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PREPARATION OF THIS DOCUMENT

Since the 2010 Food and Agriculture Organization of the United Nations (FAO)/ World Health Organization (WHO) Expert Consultation on the Risks and Benefits of Fish Consumption, new evidence has become available in this arena. As such, FAO and WHO decided, with agreement from the Codex Committee on Fish and Fishery Products, to hold another expert consultation in 2023 in order to update the conclusions and recommendations of the previous expert consultation. In order to meet the needs of this multidisciplinary exercise, experts for the 2023 consultation were selected from a global call for experts. Furthermore, a systematic literature review on the risks and benefits of fish consumption was commissioned to the Norwegian Institute of Marine Research, and the findings were published in a background document, which informed the expert consultation. Resource persons who authored the background document also supported the expert consultation. This report highlights key messages of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption held in Rome, Italy, from 9 to 13 October 2023 and provides conclusions and recommendations. The work was coordinated by Esther Garrido Gamarro, of the Secretariat, with support from Jogeir Toppe, Juliana De Oliveira Mota, Vittorio Fattori, Moez Sanaa, Markus Lipp, Molly Ahern and Angeliki Vlachou, also of the Secretariat. The document was edited by Dianne Berest. Layout was provided by Gloria Loriente.

ABSTRACT

Evolving science and debate concerning the benefits and risks of consuming fish have resulted in confusion over the years, and national and international food safety agencies have recognized the need to provide useful, clear and relevant information in this regard to consumers. In October 2023, FAO and WHO held the second Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption to analyse new scientific evidence on the matter and draw relevant conclusions and recommendations. The expert consultation was supported by the Background Document on the Risks and Benefits of Fish Consumption, containing information resulting from a systematic literature review. The overall conclusions of the exercise show that consuming fish provides energy, protein and a range of other nutrients important for health, and that there are benefits related to fish consumption during all life stages (pregnancy, childhood and adulthood). General population studies show that the benefits and individual effects of fish consumption vary depending on overall diet (for instance, selenium intake and exposure to contaminants), the characteristics of consumers (such as long-chain n-3 polyunsaturated fatty acid [n3 LCPUFA] status and individual susceptibility), and the fish that is consumed (including fish species and food preparation methods). Regarding the risks, the data on dietary exposure to dioxins and dioxin-like polychlorinated biphenyls (dl-PCBs) from different foods of animal origin, including fish, indicate that there is consistent evidence for an association between dioxin exposure and reduced semen quality. They further indicate that exposure to total dioxins and dl-PCBs has been associated with altered sex ratio and weaker tooth enamel. In children, there is also an association between dioxin and dl-PCB exposure with body mass index (BMI) z-scores, and increased thyroid stimulating hormone (TSH) with prenatal high-level exposures. In adults, there was some evidence for associations of high exposure to dioxins with cancer, cardiovascular effects and diabetes. In addition, the data analysed indicate that maternal fish consumption during pregnancy is associated with improved offspring neurological development, despite evidence from some populations showing that methylmercury (MeHg) exposure from fish consumption in early life (prenatal and early childhood) has been associated with less neurodevelopmental benefit expected from fish consumption. There is limited evidence of adverse health effects from MeHg exposure in relation to cardiovascular, neurological and other health outcomes in adulthood. There is heterogeneous evidence regarding associations of childhood MeHg exposure with neurological outcomes, possibly reflecting differences in study populations, including selenium (Se) status. Based on physiological mechanisms and evidence from animal studies, MeHg health effects will vary according to Se status and intake; however, evidence from human studies in this regard was limited.

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ABBREVIATIONS

AF	atrial fibrillation
BMI	body mass index
BRAFO	Benefit Risk Analysis of Foods Project
CHD	coronary heart disease
CVD	cardiovascular disease
DALY	disability-adjusted life year
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
JECFA	Joint FAO/WHO Expert Committee on Food Additives
n-3 LCPUFA	long-chain n-3 polyunsaturated fatty acid
MI	myocardial infarction
PAD	peripheral arterial disease
PCB	polychlorinated biphenyl
dl-PCB	dioxin-like polychlorinated biphenyl
RBA	risk-benefit assessments
RCT	randomized controlled trial
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF	toxic equivalency factor
TEQ	toxic equivalency
TSH	thyroid stimulating hormone
TWI	tolerable weekly intake
WHO	World Health Organization
VKM	Norwegian Scientific Committee for Food and Environment

DECLARATION OF INTEREST

All participants completed a declaration of interests form in advance of the expert consultation.

Five resource technical people declared interest in the topic under consideration: Amund Maage, Synnøve Næss Sleire, Bente M. Nilsen, Ole Jakob Nøstbakken and Josef Rasinger had close-related involvement in this work. It could not be ruled out that the declared interests could be perceived as potential conflicts of interest. Therefore, while these individuals were invited to participate in the expert consultation, they participated as technical resource people and were excluded from the decision-making process regarding the final recommendations. The rest of the declared interests reported were not considered by FAO and WHO to present any conflict considering the objectives of the expert consultation.

All the declarations, together with any updates, were made known and available to all the participants at the beginning of the expert consultation.

All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.

EXECUTIVE SUMMARY

BACKGROUND AND OBJECTIVES

Evolving science and debate concerning the benefits and risks of consuming fish have resulted in confusion over the years, and national and international food safety agencies have recognized the need to provide useful, clear and relevant information about this issue to consumers.

The thirty-eighth Session of the Codex Committee on Food Additives and Contaminants requested the Codex Alimentarius Commission, at its twenty-ninth session in 2006, to seek scientific advice from the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) on the risks and benefits of fish consumption. Specifically, the committee requested a comparison of the health benefits of fish consumption with the health risks associated with contaminants that may be present in fish, namely methylmercury and dioxins (defined here to include polychlorinated dibenzo-p-dioxins [PCDDs], polychlorinated dibenzofurans [PCDFs] and dioxin-like polychlorinated biphenyls [dl-PCBs]). The request of the Codex Alimentarius Commission was driven by growing public concern regarding the presence of chemical contaminants in fish, which arose alongside increasing clarity regarding the multiple nutritional benefits of fish consumption.

In response to the request, FAO and WHO held the Expert Consultation on the Risks and Benefits of Fish Consumption, from 25 to 29 January 2010, at FAO headquarters in Rome, Italy (hereafter referred to as the 2010 Expert Consultation). Participating experts reviewed data on levels of nutrients n-3 LCPUFAs, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) and on specific chemical contaminants (MeHg and dioxins) in a range of fish species, as well as scientific literature covering the risks and benefits of fish consumption. The review was used to consider risk–benefit assessments for specific endpoints, including for sensitive groups of the population. The results of the review and the conclusions and recommendations of the expert consultation were set forth in the publication, Report of the Joint Expert Consultation on the Risks and Benefits of Fish Consumption (FAO and WHO, 2011).

Since then, new evidence has become available on the risks and benefits of fish consumption and, in 2021, the thirty-fifth Session of the Codex Committee on Fish and Fishery products agreed on the added value of updating the previous report on the basis of this new evidence (FAO and WHO, 2021). Thus, in October 2023, FAO and WHO held a second Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption (hereafter referred to as the 2023 Expert Consultation) to analyse new scientific evidence and to update their conclusions and recommendations. Three main objectives guided the expert consultation to set a framework for assessing the health benefits and risks of fish consumption and to provide guidance to the Codex Alimentarius Commission in their work on managing risks: i) to examine the results of recent systematic literature reviews on the health risks and benefits of fish consumption; ii) to draw conclusions regarding the health risks and benefits associated with fish consumption; and iii) to recommend a series of steps that Member Nations can take to better assess and manage the risks and benefits of fish consumption.

For the purpose of this report, the term "fish" is defined as finfish (vertebrates) and shellfish (invertebrates), whether of marine or freshwater origin, farmed or wild. Marine mammals and algae, as well as sustainability issues and environmental impacts, although important, are considered to be outside the scope of this report.

APPROACH

In order to inform the 2023 Expert Consultation, FAO and WHO commissioned a systematic literature review on the risks and benefits of fish consumption from the Norwegian Institute of Marine Research (IMR). The results and conclusions of the review were set forth in the FAO/WHO Background Document on the Risks and Benefits of Fish Consumption (FAO & WHO, 2024) (hereafter referred to as the Background Document).

The IMR conducted five extensive literature reviews to develop the Background Document, focusing on the evidence of health benefits from fish consumption, the toxic effects of dioxins and dl-PCBs, the toxic effects of MeHg, the role of selenium (Se) regarding the health effects of MeHg, and occurrence data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products.

The experts participating in the expert consultation were selected from a global public call for experts. Twenty-one experts were selected, covering different areas of expertise, including nutrition, toxicology, epidemiology and risk–benefit assessment. The experts were supported by the resource persons who authored the Background Document. Based on the strength of the evidence provided in the Background Document and considering the 2010 Expert Consultation report, the Expert Committee examined the benefits of total, fatty and lean fish consumption for a number of human health outcomes, including allergy and immunology, birth and growth outcomes, bone health, cancer, cardiovascular disease, type 2 diabetes, mortality, neurodevelopment and neurological disorders, and overweight and obesity. Potential adverse effects of dioxins were investigated with respect to chloracne and other dermal effects, male and female reproductive effects, birth outcomes, thyroid disease and thyroid hormones, type 2 diabetes and obesity, cardiovascular effects, hepatic disorders and digestive effects, effects on the immune system, effects on the nervous system, effects on teeth and bones, and cancer. Exposure to MeHg from fish consumption was considered for neurological outcomes, cardiovascular outcomes, growth and other health outcomes. Furthermore, the role of Se with respect to MeHg effects was investigated for cardiovascular outcomes, oxidative stress, immune system, reproduction, thyroid hormones, birth outcomes, neurodevelopment and cognition, vision function and motor function.

CONCLUSIONS

The 2023 Expert Consultation agreed on the following overall conclusions regarding human health benefits from fish consumption:

> Consuming fish provides energy, protein and a range of other nutrients important for health.

> Consuming fish is part of the cultural traditions of many peoples. In some populations, fish is a major source of food, animal protein and a range of other nutrients that are important for health.

> Strong evidence exists for the benefits of total fish consumption during all life stages: pregnancy, childhood and adulthood. For example, associations are found for maternal consumption during pregnancy with improved birth outcomes and for adult consumption with reduced risks for cardiovascular and neurological diseases. This evidence for health benefits of total fish consumption reflects the overall effects of nutrients and contaminants in fish on the studied outcomes, including nutrients and contaminants not specifically considered in the evidence review.

> Benefits derived from general population studies and individual effects will vary depending on overall diet (such as Se intake and exposure to other contaminants), the characteristics of consumers (such as n-3 LCPUFA status and individual susceptibility), and the fish consumed (considering fish species and food preparation methods).

> Risk–benefit assessments at regional, national or even subnational levels are needed to refine fish consumption recommendations considering local consumption habits, fish contamination levels and nutrient content, nutritional status of the population of interest, cultural habits and demographics.

In addition, the 2023 Expert Consultation agreed on the following conclusions regarding the toxic effects of dioxins, dl-PCBs and MeHg, and the role of Se regarding the health effects of MeHg:

> Dietary exposure to dioxins and dl-PCBs comes from multiple different foods of animal origin, including fish. The contribution of fish consumption to these exposures will vary based on region of residence and on the amount, source and types of fish consumed.

> Studies are lacking regarding the effects of dioxin and dl-PCB exposure from fish consumption on human health in general populations. The current evidence base is mainly from populations highly exposed to dioxins and dl-PCBs because of occupational exposure or local contamination.

> There is consistent evidence for an association between dioxin exposure and reduced semen quality. Exposure to total dioxins and dl-PCBs has been associated with altered sex ratio and weaker tooth enamel.

- Maternal fish consumption during pregnancy is associated with improved offspring neurological development, despite evidence from some populations showing that MeHg exposure from fish consumption in early life (prenatal and early childhood) has been associated with less neurodevelopmental benefit expected from fish consumption.
- There is limited evidence of adverse health effects from MeHg exposure in relation to cardiovascular, neurological and other health outcomes in adulthood.
- There is heterogeneous evidence regarding associations of childhood MeHg exposure with neurological outcomes in childhood, possibly reflecting differences in study populations, including Se status.
- Based on physiological mechanisms and evidence from animal studies, MeHg health effects will vary according to Se status and intake; however, human studies showing these effects were limited in this assessment.

RECOMMENDATIONS

To maximize the benefits of fish consumption for the general population across all life stages, the 2023 Expert Consultation recommends that Member Nations:

- acknowledge fish as an important dietary source of energy, protein and a range of other nutrients important for health, and that fish consumption is an important part of the cultural traditions of many populations;
- emphasize the benefits of fish consumption for multiple health outcomes throughout the life course, including during pregnancy, childhood and adulthood;
- collect standardized data on fish contaminants and nutrients;
- develop, maintain and improve existing databases on levels and trends over time of specific contaminants, in particular MeHg, dioxins and dl-PCBs, as well as nutrient content, such as Se and n3 LCPUFAs, for fish consumed, by region;
- collect standardized data on dietary intake of fish, including amount, type and source, representative at regional, national or even subnational levels, for quantitative risk–benefit assessment of fish; and
- develop and evaluate riskanalysis strategies (risk assessment, risk management and risk communication) that maximize the benefits and minimize the risks from consuming fish.

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CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Fish is an integral component of a balanced diet. It is a dietary source of energy, high-quality protein and a range of other nutrients, minerals and trace elements; fat-soluble vitamins; and essential fatty acids, including long-chain n-3 polyunsaturated fatty acids (n3 LCPUFAs). However, evolving science and debate concerning the benefits and risks of consuming fish have resulted in confusion over the years, and national and international food safety agencies have recognized the need to provide consumers with useful, clear and relevant information in this regard.

The thirty-eighth Session of the Codex Committee on Food Additives and Contaminants requested that the Codex Alimentarius Commission, at its twenty-ninth session in 2006, seek scientific advice from the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) on the risks and benefits of fish consumption. Specifically, the committee requested a comparison of the health benefits of fish consumption with the health risks associated with the contaminants that may be present in fish, namely methylmercury (MeHg) and dioxins (defined here to include polychlorinated dibenzo-p-dioxins [PCDDs] and polychlorinated dibenzofurans [PCDFs] as well as dioxin-like polychlorinated biphenyls [dl-PCBs]). The request of the Codex Alimentarius Commission was driven by growing public concern in recent years regarding the presence of chemical contaminants in fish, which arose alongside increasing clarity regarding the multiple nutritional benefits of consuming fish.

In response to the request, FAO and WHO held the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption, from 25 to 29 January 2010, at FAO headquarters in Rome, Italy (hereafter referred to as the 2010 Expert Consultation). The expert consultation reviewed data on levels of nutrients (n3 LCPUFAs, EPA and DHA) and specific chemical contaminants (MeHg and dioxins) in a range of fish species, as well as scientific literature covering the health risks and benefits of fish consumption. The review was used to consider risk–benefit assessments for specific health endpoints and subpopulations, including for sensitive groups of the population. The results of the review were set forth in the Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption, published in 2011 (FAO and WHO, 2011).

Since then, new evidence has become available and, in 2021, the thirty-fifth Session of the Codex Committee on Fish and Fishery Products agreed to update the previous report on the basis of the new evidence. Thus, from 9 to 13 October 2023, FAO and WHO held the second Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption in Rome, Italy, (hereafter referred to as the 2023 Expert Consultation) to analyse new scientific evidence and update their conclusions and recommendations. The 21 experts participating in the meeting were selected from a global public call for experts, covering different areas of expertise, including nutrition, toxicology, epidemiology and risk–benefit assessment.

1.2 SCOPE AND OBJECTIVES

In order to inform the expert consultation, FAO and WHO commissioned a systematic literature review from the Norwegian Institute of Marine Research (IMR) on the risks and benefits of fish consumption. The results of the review were set forth in the FAO/WHO Background Document on the Risks and Benefits of Fish Consumption (hereafter referred to as the Background Document) (FAO & WHO, 2024), and resource persons who authored the Background Document provided support to the experts during the consultation.

The literature review included existing evidence scans, namely the report Benefit and risk assessment of fish in the Norwegian diet, published by The Norwegian Scientific Committee for Food and Environment (Andersen *et al.*, 2022); the report Diet, Nutrition, Physical Activity and Cancer: a Global Perspective, from the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR, 2018a); reports from the European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain containing expert opinion on MeHg (CONTAM *et al.*, 2012) and on dioxins (CONTAM *et al.*, 2018); and additional publications from a systematic literature search conducted to identify publications not considered in these prior evidence scans. In all, the IMR conducted five extensive literature reviews to develop the Background Document, focusing on the following topics:

1. **Evidence of health benefits from fish consumption:** To evaluate the evidence of health benefits from fish consumption, the literature consisted of the 2022 report published by the Norwegian Scientific Committee for Food and Environment (VKM) (Andersen *et al.*, 2022), in addition to systematic reviews and original primary studies identified in the systematic literature search.
2. **Toxic effects of dioxins and dl-PCBs:** To evaluate the evidence of toxic effects of dioxins and dl-PCBs (published since the 2010 Expert Consultation), the literature consisted of the 2018 EFSA report on the risks of dioxins (CONTAM *et al.*, 2018) and original primary studies included from the systematic literature search.
3. **Toxic effects of MeHg:** To evaluate the evidence of toxic effects of MeHg (published since the 2010 Expert Consultation), the literature consisted of the EFSA Statement on the benefits of fish/seafood consumption compared to the

risks of methylmercury in fish/seafood (EFSA Scientific Committee, 2015), the 2022 VKM report (Andersen *et al.,* 2022), and systematic reviews and original primary studies included from the systematic literature search.

4. **The role of selenium (Se) regarding the health effects of MeHg**: To evaluate the evidence of the role of Se regarding the health effects of MeHg, the literature consisted of original primary studies included from the systematic literature search.
5. **Occurrence data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products:** To evaluate the data for MeHg, dioxins and dl-PCBs in fishery and aquaculture products (published since the 2010 Expert Consultation), data were obtained from public databases (WHO's Global Environment Monitoring System [GEMS] database and EFSA's Chemical Monitoring database) and extracted from the systematic literature search.

The expert consultation did not consider other contaminants in fish potentially related to human health, such as non-dioxin-like PCBs, per- and polyfluorinated alkyl substances (PFAS) and polybrominated diphenyl ethers (PBDEs), considering the contaminants MeHg, dioxins and dl-PCBs as the priority for this exercise.

For the "Health Benefits of Fish Consumption" and for the "Role of Se with regard to the health effects of MeHg", a final weight of evidence using the grading classifications from the 2018 WCRF/AICR report –Continuous Update Project Expert Report 2018. Judging the evidence, was performed, grading the evidence for the different health outcomes as "convincing" (strong evidence), "probable" (strong evidence), "limited, suggestive", "limited, no conclusion", or "substantial effect on risk unlikely" (strong evidence) (WCRF/AICR, 2018b).

Based on the strength of the evidence provided in the Background Document and considering the 2010 Expert Consultation report, the 2023 Expert Consultation examined the benefits of total, fatty and lean fish consumption for several human health outcomes, including allergy and immunology, birth and growth outcomes, bone health, cancer, cardiovascular disease, type 2 diabetes, mortality, neurodevelopment and neurological disorders, and overweight and obesity. In addition, the expert consultation investigated potential adverse effects of dioxins and dl-PCBs with respect to chloracne and other dermal effects, male and female reproductive effects, birth outcomes, thyroid disease and thyroid hormones, type 2 diabetes and obesity, cardiovascular effects, hepatic disorders and digestive effects, effects on the immune system, effects on the nervous system, effects on teeth and bones, and cancer. The expert consultation also considered exposure to MeHg from fish consumption for neurological outcomes, cardiovascular outcomes, growth and other health outcomes. Furthermore, the role of Se with respect to MeHg effects was also investigated for cardiovascular outcomes, oxidative stress, immune system, reproduction, thyroid hormones, birth outcomes, neurodevelopment and cognition, vision function, and motor function. **Table 1** summarizes the health endpoints considered by the expert consultation for the benefits of fish consumption and for each of the contaminants.

TABLE 1. **HEALTH ENDPOINTS CONSIDERED BY THE EXPERT CONSULTATION**

COMPONENTS OF FISH CONSIDERED	HEALTH ENDPOINT
Benefits of total, fatty and lean fish consumption	Allergy and immunology Birth and growth outcomes Bone health Cancer Cardiovascular disease Type 2 diabetes Mortality Neurodevelopment and neurological disorders Overweight and obesity
Toxic effects of dioxins and dlPCBs	Chloracne and other dermal effects Male and female reproductive effects Birth outcomes Thyroid disease and thyroid hormones Type 2 diabetes 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
Toxic effects of methylmercury	Neurological outcomes Cardiovascular outcomes Growth Other health outcomes
The role of selenium with respect to the health effects of methylmercury	Cardiovascular outcomes Oxidative stress Immune system Reproduction Thyroid hormone Birth outcome Neurodevelopment and cognition Vision function Motor function

Note: dl-PCB: dioxin-like polychlorinated biphenyl.

Three main objectives guided the expert consultation to set a framework for assessing the health benefits and risks of fish consumption and to provide guidance to the Codex Alimentarius Commission in their work on managing risks: i) to examine the results of recent systematic literature reviews on the risks and benefits of fish consumption; ii) to draw conclusions regarding the health benefits and risks associated with fish consumption; and iii) to recommend a series of steps that Member Nations could take to better assess and manage the risks and benefits of fish consumption.

For the purposes of this report, the term “fish” is defined as finfish (vertebrates) and shellfish (invertebrates), whether of marine or freshwater origin, farmed or wild. Marine mammals and algae are outside the scope of this report.

CHAPTER 2

RISK AND BENEFIT APPROACH

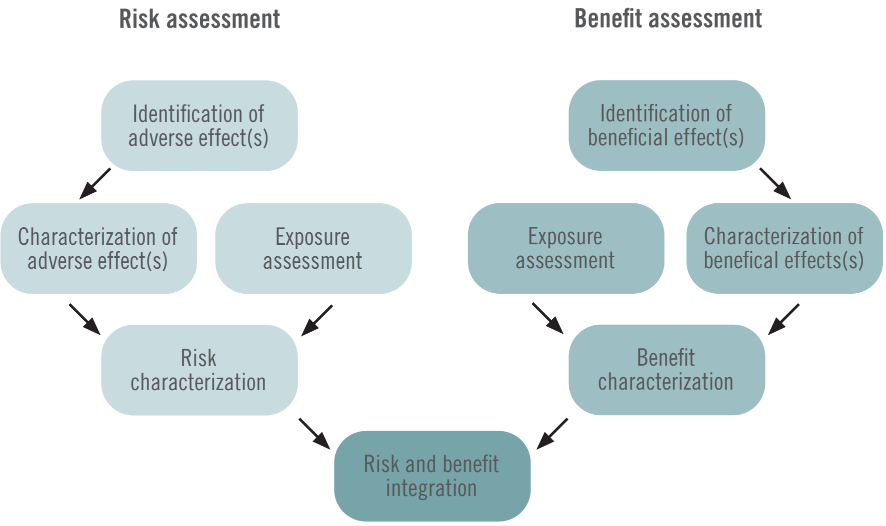
2.1 RISK–BENEFIT ASSESSMENT METHODOLOGIES

Risk–benefit assessments (RBAs) of foods have been performed for more than two decades. The first ground-breaking studies were conducted in the beginning of the millennium (Havelaar *et al.*, 2000 and Renwick *et al.*, 2004), followed by European projects such as the Benefit-Risk Analysis of Foods (BRAFO) project (Boobis *et al.*, 2013), which developed methodologies and frameworks for conducting RBAs and performed various case studies. In 2010, the EFSA Scientific Committee published the scientific opinion, Guidance on human health risk-benefit assessment of foods, and various articles have been published that promote the use of a common language and understanding of the applications and utility of RBA for decision support, including Nauta *et al.*, 2018 and Pires *et al.*, 2019.

By default, RBAs of foods are multidisciplinary and combine research within the fields of nutrition, epidemiology, toxicology and microbiology. The process of an RBA follows that of a traditional risk assessment; that is, it includes four steps: identification of adverse and beneficial health effects, characterization of adverse and beneficial health effects (dose–response characterization); exposure assessment (for chemical contaminants, microbiological hazards and nutrients or intake assessment of food); and risk and benefit characterization. RBAs, however, include a fifth step in which the characterized risks and benefits are compared or integrated (Hoekstra *et al.*, 2012; Nauta *et al.*, 2018 and Tijhuis *et al.*, 2012). The five steps of an RBA are illustrated in Figure 1. Approaches and metrics to compare risks and benefits are described in Section 2.1.1. Risk-benefit approaches and in Section 2.2. Risk–benefit assessment metrics.

The definition of a clear risk–benefit question is important before initiating an RBA. Preferably in consultation with a risk–benefit manager, the purpose, scope and limits of the assessment should be defined, including the target population(s) and intake scenarios. Usually, a reference scenario (for instance, current fish consumption, or zero consumption) is compared with one or more alternative scenarios. The alternative scenarios are usually theoretical and may be based on, for example, recommended intake levels for a given food, or a worst-case scenario, such as consumption of highly-polluted fish species (Thomsen *et al.*, 2018), or any other scenario that may be of interest to public health policymakers, consumers or other stakeholders.

FIGURE 1. **THE RISK–BENEFIT ASSESSMENT PROCESS**



Source: Thomsen *et al.*, 2022.

2.1.1 RISK–BENEFIT APPROACHES

RBAs can be qualitative or quantitative. In a qualitative RBA, the human health risks or benefits associated with a food, food component or diet are not quantified, but rather described and compared qualitatively. In a quantitative RBA, both risks and benefits are quantified, but the comparison of risks and benefits need not necessarily be quantitative. Tiered approaches for RBAs have been proposed to guide the assessment from qualitative to quantitative comparison of risks and benefits, depending on the weight of evidence available for adverse and beneficial health effects, the data available and the uncertainty associated with the estimated risks and benefits (Boobis *et al.*, 2013; EFSA, 2010). Other RBA approaches aim for the quantification of the overall health impact of dietary changes or interventions.

A tiered approach for RBAs was developed by the BRAFO project (Hoekstra *et al.*, 2012). The approach describes four tiers of increasing complexity and quantification, with separate risk and benefit assessments at the first tier, followed by a qualitative comparison of risks and benefits at the second tier, a fully quantitative integration at the third tier, and a probabilistic assessment at the fourth tier (Hoekstra *et al.*, 2012). The steps required to reach a conclusion at each tier follow the steps included in the Codex risk-assessment paradigm (FAO/WHO, 2006). The primary aim of the BRAFO tiered approach is to refine the assessment when it is necessary to reach a conclusion of whether the benefits outweigh the risks, or vice versa (Hoekstra *et al.*, 2012). The ESFA Scientific Committee also recommended a tiered approach for performing RBAs of food (EFSA, 2010). The approach is similar to the BRAFO tiered approach and encourages an additional statement of the strengths and weaknesses of the evidence base and its associated uncertainties at each tier.

Quantitative risk–benefit comparisons may be deemed necessary during a tiered approach or may be applied to answer a risk–benefit question that specifically requests a quantitative comparison. These approaches imply that the human health risks and benefits are quantified and, if possible, integrated in a common measure. Different types of models and metrics can be applied for this type of comparison. Quantitative methods may take a deterministic (point estimate) or a probabilistic (using probability distributions) approach. Whereas deterministic approaches are more easily applicable, probabilistic approaches allow for the assessment of underlying uncertainties, variability or both. Furthermore, probabilistic assessments make it possible to investigate the parameters that contribute most to the overall uncertainty of the assessment.

2.2 RISK–BENEFIT ASSESSMENT METRICS

Various metrics to quantify human health risks and benefits of food consumption exist. The choice of metric depends on the objective of the RBA, the adverse and beneficial effects considered, and the data available for the assessment.

2.2.1 COMPARISON OF EXPOSURE WITH RECOMMENDED AND SAFE-INTAKE LEVELS

Risk–benefit assessment can be done by comparing the intake of nutrients with dietary reference values (DRVs) or recommended intakes and exposure to chemical contaminants applying, for example, health-based guidance values or, alternatively, a lower confidence limit of a benchmark dose for substances showing a non-threshold effect. This approach resembles the approaches taken in traditional risk assessment in nutrition and chemical toxicology and typically results in an estimate of the probability of reaching (in the case of nutrients) or exceeding (in the case of chemical contaminants and nutrients) these thresholds (EFSA NDA Panel, 2010; EFSA Scientific Committee, 2017; Tijhuis *et al.*, 2012; World Health Organization, 2009).

2.2.2 COMMON METRICS

Common metrics usually refer to single-dimension measures of risk or benefits, such as increased or decreased incidence, prevalence and mortality of disease. Comparing incidence or prevalence of different diseases is not straightforward. As such, common metrics are most useful when risks and benefits affect the same health outcome. Mortality from different diseases is more easily compared and may be more useful for risk–benefit comparison. However, potential differences in the population groups affected should be considered. For instance, one might argue that the death of a child is more adverse than the death of an elderly person. Continuous endpoints, such as intelligence quotient (IQ), which has been used as a metric for several risk–benefit assessments of fish, are also considered a common metric (FAO and WHO, 2011; Hoekstra *et al.*, 2013; Zeilmaker *et al.*, 2013).

2.2.3 COMPOSITE METRICS

In contrast to common metrics, composite metrics are multidimensional and enable the integration of incidence/prevalence, severity, duration and mortality of disease. Consequently, composite metrics enable a direct comparison of risks and benefits affecting different health outcomes. Composite metrics include disability-adjusted life years (DALYs), which is a health-gap measure that compares a given state of health with an ideal state of health and wellbeing. One DALY is equal to one healthy year of life lost (Devleesschauwer *et al.*, 2014; Gold, Stevenson and Fryback, 2002; Murray, 1994).

2.3 EXISTING RISK–BENEFIT ASSESSMENTS OF FISH

A scoping review of risk–benefit assessments of fish and seafood published between 2000 and 2019 identified 106 studies conducted across Europe (n = 61), Asia (n = 14), North America (n = 28), Africa (n = 1); and at the global level (n = 2) (Thomsen *et al.*, 2022). Two additional studies did not consider a specific population. A clear inequity in locally relevant risk–benefit assessments of fish and seafood was found.

Although general conclusions on the risk–benefit balance of fish and seafood consumption could not be drawn, the studies reviewed showed that a diet consisting of a variety of lean and fatty fish and other seafood is recommended for the general population, and that women of childbearing age and children should limit the consumption of fish and other seafood types that have a high likelihood of contamination. The review also emphasized the importance of locally relevant risk–benefit assessments, reflecting both national or regional dietary habits and contamination, in particular in regions where evidence on the health impact of fish and seafood consumption is currently lacking (Thomsen *et al.*, 2022). This requires conducting RBAs that address risk–benefit questions relevant to the local populations and that apply population-specific fish and seafood consumption and contamination data, in addition to other data required for an RBA.

2.4 DATA REQUIREMENTS FOR QUANTITATIVE RISK–BENEFIT ASSESSMENTS OF FISH AND SEAFOOD

The data requirements for each step of an RBA vary for the different methods available (**Table 2**). Some data are required at the national or subnational level, such as food consumption, food contamination, biomonitoring data (if available) and population statistics, while others are applicable across populations and may be collected from scientific literature and international databases. When specific data types are lacking for a population, studies may consider using data from other (similar) populations and surrogate data. All data assumptions and limitations must be documented.

TABLE 2. **DATA REQUIREMENTS FOR EACH STEP OF RISK–BENEFIT ASSESSMENT STUDIES AND POSSIBLE DATA SOURCES**

DATA REQUIREMENT	DESCRIPTION	DATA SOURCES	RISK–BENEFIT ASSESSMENT METHOD
Hazard and benefit identification			
	Evidence of adverse and beneficial effects associated with food consumption, nutrient intake, or chemical exposure	Scientific literature, scientific expert reports by national or international authorities, such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA)	All
Exposure assessment			
Food consumption	Consumption levels of food categories (e.g. fish) or subcategories (e.g. fish species or products) in specific populations (in grams per day or week), preferably including demographic information. (Alternative: use of theoretical consumption amounts, e.g. zero consumption)	National: Dietary surveys International: Chronic individual food consumption database (CIFOCOss); Global Individual Food Consumption Data Tool (GIFT), and others	All
Food contamination	Concentration of chemical contaminants in food categories	National: Food monitoring databases and reports. Total diet studies (TDS) International: Global Environment Monitoring System (GEMS)/Food Contamination Monitoring and Assessment Programme	All
Nutrient profiles	Nutrient content of foods	National: Food composition databases International: Food composition databases of FAO/International Network of Food Data Systems	All
Human biomonitoring data	Measures of internal exposure to contaminants. These data may be used when background exposure from other sources is estimated.	Scientific literature, national or international databases	All
Hazard characterization			
Health-based guidance values, dietary reference values, dietary and nutrient recommendations	Thresholds of safe (chemicals, nutrients) and adequate/recommended (nutrients, whole foods) intakes	National, regional or global food and health authorities	Threshold approach
Dose–response relationship	Model describing the quantitative relationship between intake/exposure and (the probability of) a health outcome	Scientific literature, including systematic literature reviews, international reports	Incidence, mortality, composite metrics
Duration of disease	Duration of symptoms of health outcomes (days or years)	Scientific literature, health statistics	Composite metric – disability-adjusted life years (DALY)
Disability weights	Weighing factor that reflects the severity of health outcomes, ranging from 0 (perfect health) to 1 (death)	Scientific literature, including disability weights reported by the Global Burden of Disease Study.	Composite metric – DALY
Life expectancy	Life expectancy tables, at national or global level	Life Expectancy Table of the World Health Organization, Life Expectancy Table of the Institute of Health Metrics and Evaluations, national statistics	Composite metric – DALY
Population statistics	Population numbers by age and sex.	National statistics	Composite metric – DALY

It is important to highlight that this chapter introduces some of the principles that have been used for the current exercise and, thus, provides Member Nations with the information necessary to carry out RBAs.

2.5 CONCLUSIONS AND RECOMMENDATIONS

2.5.1 CONCLUSIONS

- Various methods to assess the risk–benefit balance of fish consumption patterns are available.
- Existing studies show high heterogeneity in methods and metrics applied; in the nutrients, contaminants and health outcomes included; and in the fish species and products considered.
- There are large disparities in the availability of nationally and regionally relevant RBAs of fish and seafood across the globe. Most existing studies were conducted for European and North American populations, while only few are available for other regions of the world.
- RBAs at regional, national or subnational level are needed to assess the risk–benefit balance of fish consumption levels, considering local consumption habits, fish contamination levels, nutrient content of fish, nutritional status of populations, cultural habits and demographics.

2.5.2 RECOMMENDATIONS

The 2023 Expert Consultation recommends that Member Nations:

- allocate resources to conduct national- or regional-level RBAs of fish that can account for dietary patterns, food availability, food contamination, cultural preferences and cooking practices, and relevant subpopulations;
- collect standardized data on fish and seafood contamination, nutrient content and food consumption representative at regional, national or subnational levels;
- create capacity for RBA, risk–benefit communication and knowledge translation for policymaking;
- leverage existing efforts in their regions to overcome identified data and knowledge gaps (for example, applying data from neighboring countries; involving RBA experts);
- engage stakeholders and experts from multiple disciplines across food safety and nutrition, including toxicology, microbiology, nutrition and epidemiology; and
- integrate other aspects of fish consumption, such as environmental impacts and long-term sustainability (including, for example, specific topics such as fish populations and sustainable fishing).

CHAPTER 3

EVIDENCE OF HEALTH BENEFITS FROM FISH CONSUMPTION

3.1 BACKGROUND

Fish and other seafood are a dietary source of several important nutrients, including high-quality protein, n-3 LCPUFAs, EPA and DHA, vitamin A, vitamin D, vitamin B12, iodine, iron, Se and zinc (Byrd, Thilsted and Fiorella, 2021). Globally, fish provide about 7 percent of all protein and 17 percent of animal protein consumed and contribute more than 50 percent of the animal protein consumed by populations in several countries in Africa and Asia (FAO, 2022). Besides the beneficial effects of proteins and n-3 LCPUFAs reported in some studies, in recent decades, the potential health benefits of micronutrients from fish consumption have also received attention (Golden *et al.*, 2021). The benefits of fish consumption have been related to the intake of essential micronutrients and n-3 LCPUFAs, as consuming seafood can potentially reduce micronutrient deficiencies (Golden *et al.*, 2021). Because of the nutrients in fish, consumption is associated with several health benefits, such as anti-oxidation, anti-inflammation, neuroprotection and cardioprotection (Chen *et al.*, 2022).

Concerns exist, however, about contaminants present in fish, including dioxins and MeHg, which may mitigate or negate the nutritional benefits associated with fish consumption. Therefore, it is important to consider the overall associations of fish consumption with health outcomes. The health effects of dioxins, dl-PCBs and MeHg are covered in Chapter 4 and Chapter 5 of this report.

This chapter summarizes the expert consultation's review of evidence related to the consumption of total or unspecified fish, as well as, specifically (where available) fatty fish, lean fish and shellfish, in relation to a number of health outcomes. Fewer studies of fatty fish, lean fish and shellfish were available. As such, conclusions in this regard tend to be limited based on the more limited evidence base. Note that the studies related to fish consumption as an exposure incorporate the combined health effects of nutrients and contaminants included in the fish consumed. Note also that, unlike the 2010 Expert Consultation, this expert consultation did not specifically review the health effects of n-3 LCPUFAs.

3.2 APPROACH

This chapter is based on the findings of the literature review presented in the Background Document, which were reviewed by the experts participating in the 2023 Expert Consultation, bringing to bear their diverse experience and expertise.

Chapter 3 of the Background Document, which explores evidence of health benefits from fish consumption, is based on a systematic literature review of the epidemiological evidence on fish consumption and health benefits performed by the IMR. The literature search was performed in the databases PubMed, Web of Science and Cochrane Library, from inception to December 2021, and included both systematic reviews and original primary studies.

In addition to the research identified in the literature search, the IMR incorporated several existing evidence reviews. For all outcomes except cancers, the IMR used a previous systematic literature review summarized in the report, Benefit and risk assessment of fish in the Norwegian diet, published by VKM in 2022 (Andersen *et al.*, 2022). In the preparation of the VKM report, the search for original primary studies was performed in the databases Ovid MEDLINE, Embase and PsycINFO, from inception to October 2021. The search for systematic reviews was performed in Ovid MEDLINE and Embase from 2016 to October 2021 using the same search terms as those used for primary studies. To avoid reporting duplicate publications, the systematic reviews and primary studies that were included in the VKM report were excluded for further assessment in the Background Document.

For cancer outcomes, the Background Document relied on the report – Diet, nutrition, physical activity and cancer: a global perspective (WCRF/AICR, 2018a). The VKM report also relied on this report, as the authors found it sufficiently comprehensive.

The Background Document summarized epidemiological evidence for different categories of fish consumption (total or unspecified fish, fatty fish, lean fish and shellfish only) by the following categories of health outcomes: allergy and immunology, birth and growth outcomes, bone health, cancer, cardiovascular diseases (CVDs overall and by subtype), type 2 diabetes, overweight and obesity, mortality (overall and cause-specific), and neurodevelopment and neurological disorders. The health outcomes considered reflect those for which nutrients or contaminants found in fish have an established or potential role. Consumption refers to adult consumption, unless specified as maternal consumption during pregnancy or consumption by children. Not all categories of fish could be summarized in relation to consumption in all life stages or to all health outcomes, due to the limited evidence available. A final weight of evidence using the grading criteria from the WCRF/AICR report (2018b) was performed, grading the evidence for an effect of fish consumption on the different health outcomes "convincing" (strong evidence), "probable" (strong evidence), "limited, suggestive", "limited, no conclusion", or "substantial effect on risk unlikely" (strong evidence).

The Background Document integrated all the evidence from the literature review, from the WCRF/AICR report Diet, Nutrition, Physical Activity, and Cancer: a Global Perspective. (WCRF/AICR, 2018a), and from the 2022 VKM report that met the inclusion and exclusion criteria and passed the quality assessment (risk of bias). As noted by the 2023 Expert Consultation, the evidence reflects the scientific evidence that has been published, which may underrepresent some countries and world regions due to lack of studies in these geographical areas. The Background Document does not present population characteristics, fish consumption levels, or mechanistic evidence on nutrients in fish, which eliminates the possibility of refining conclusions regarding the effect of fish consumption on the different health outcomes according to these characteristics or mechanisms.

Table 3 summarizes the evidence considered for each outcome in relation to fish consumption, as well as the weight-of-evidence conclusions from the 2022 VKM report, the Background Document, the 2010 Expert Consultation and the conclusions of this expert consultation. The summary includes the number of systematic reviews and original primary studies included from the literature search in the Background Document, in addition to the number of systematic reviews and original primary studies included in the 2022 VKM report.

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Allergy and Immunology							
Allergic rhinitis in children	Maternal total fish consumption 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	Limited, no conclusion	Not included
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	Limited, no conclusion	Not included
Allergic sensitization in children	Maternal total fish consumption 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	Limited, no conclusion	Not included
Allergic sensitization in children	Child total fish consumption	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	Limited, no conclusion	Not included
Asthma in children	Maternal total, fatty and lean consumption 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	Limited, no conclusion	Not included
Eczema in children	Maternal total fish consumption 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 (down graded from VKM 2022)	Limited, suggestive (protective)	Not included
Eczema in children	Child total fish consumption	VKM 2022 Section 4.29: Systematic reviews, n = 1; Primary studies, n = 2	Limited, suggestive (protective for consumption in the first year of life, but not later)	Systematic reviews, n = 0; Primary studies, n = 0	Limited, suggestive (protective for consumption in the first year of life, but not later)	Limited, suggestive (protective for consumption in the first year of life, but not later)	Not included
Multiple sclerosis	Total fish consumption	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)	Limited, suggestive (protective)	Not included
Rheumatoid arthritis	Total fish consumption	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 (down graded from VKM 2022)	Limited, suggestive (protective)	Not included
Birth and growth outcomes							
Preterm birth	Maternal total fish consumption 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)	Probable (protective effect at a threshold)	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Preterm birth	Maternal fatty fish consumption 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	Limited, no conclusion	Not included
Preterm birth	Maternal lean fish consumption 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	Limited, no conclusion	Not included
Small-for-gestational age	Maternal total fish consumption 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)	Limited, suggestive (protective)	Not included
Small-for-gestational age	Maternal fatty fish consumption 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	Limited, no conclusion	Not included
Small-for-gestational age	Maternal lean fish consumption 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	Limited, no conclusion	Not included
Birth weight	Maternal total, fatty and lean fish consumption 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)	Limited, suggestive (positive association)	Not included
Birth weight	Maternal fatty fish consumption 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)	Limited, suggestive (positive association)	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Birth weight	Maternal lean fish consumption 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)	Limited, suggestive (positive association)	Not included
Low birth weight	Maternal total fish consumption 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)	Probable (protective effect)	Not included
Low birth weight	Maternal fatty fish consumption 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	Limited, no conclusion	Not included
Low birth weight	Maternal lean fish consumption 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	Limited, no conclusion	Not included
High birth weight	Maternal total, fatty and lean fish consumption 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)	Limited, suggestive (increased risk)	Not included
Birth length	Maternal total, fatty and lean fish consumption 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	Limited, no conclusion	Not included
Head circumference	Maternal total, fatty and lean fish consumption 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	Limited, no conclusion	Not included
Bone health							
Hip fracture	Total fish consumption	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)	Limited, suggestive (protective effect only at high consumption)	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Cancer							
Liver cancer	Total fish consumption	WCRF 2018	Limited, suggestive (protective) (from WCRF 2018)	Systematic reviews, n = 1; Primary studies, n = 0	Limited, suggestive (protective)	Limited, suggestive (protective)	Not included
Colorectal cancer	Total fish consumption	WCRF 2018	Limited, suggestive (protective) (from WCRF 2018)	Systematic reviews, n = 0; Primary studies, n = 3	Limited, suggestive (protective)	Limited, suggestive (protective)	Not included
Nasopharyngeal cancer	Cantonese-style salted fish	WCRF 2018	Not included in VKM 2022	Systematic reviews, n = 0; Primary studies, n = 0	Convincing evidence (increased risk)	Strong evidence (increased risk)	Not included
Pancreatic cancer	Total fish consumption	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 1; Primary studies, n = 0	Limited, no conclusion	Limited, no conclusion	Not included
Breast cancer	Total fish consumption	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 1; Primary studies, n = 0	Limited, no conclusion	Limited, no conclusion	Not included
CVD*							
Total cardiovascular disease	Total fish consumption	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)	Limited, suggestive (protective effect)	Not included
Total cardiovascular disease	Fatty fish consumption	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	Limited, no conclusion	Not included
Total cardiovascular disease	Lean fish consumption	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	Limited, no conclusion	Not included
CHD	Total fish consumption	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)	Probable (protective effect)	Not included
CHD	Fatty fish consumption	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)	Limited, suggestive (protective effect)	Not included
CHD	Lean fish consumption	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)	Limited, no conclusion	Not included
CHD	Shellfish	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 0; Primary studies, n = 1	Limited, no conclusion	Limited, no conclusion	CHD in realation to shellfish alone was not included
Myocardial infarction	Total fish consumption	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)	Limited, suggestive (protective effect)	Not included
Myocardial infarction	Fatty fish consumption	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)	Limited, suggestive (protective effect)	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Myocardial infarction	Lean fish consumption	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)	Limited, no conclusion	Not included
Total stroke	Total fish consumption	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)	Probably (protective effect)	Not included
Total stroke	Fatty fish consumption	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)	Limited, suggestive (protective effect)	Not included
Total stroke	Lean fish consumption	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)	Limited, suggestive (protective effect)	Not included
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	Limited, no conclusion	Stroke in realation to shellfish alone was not included
Ischemic stroke	Total fish consumption	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)	Limited, suggestive (protective effect)	Probable evidence of benefit
Hemorrhagic stroke	Total fish consumption	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)	Limited, suggestive (protective effect)	Not included
Atrial fibrillation	Total fish consumption	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)	Limited, suggestive (adverse effect)	Emerging, possible, or probable evidence of benefit
Atrial fibrillation	Fatty fish consumption	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	Limited, no conclusion	Not included
Atrial fibrillation	Lean fish consumption	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)	Limited, suggestive (protective effect)	Not included
Heart failure	Total fish consumption	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)	Limited, suggestive (protective effect)	Emerging, possible, or probable evidence of benefit
Venous thromboembolism	Total fish consumption	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	Limited, no conclusion	Not included
Peripheral arterial disease	Total fish consumption	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 0; Primary studies, n = 1	Limited, no conclusion	Limited, no conclusion	Not included
Peripheral arterial disease	Fatty fish consumption	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 0; Primary studies, n = 1	Limited, no conclusion	Limited, no conclusion	Not included
Peripheral arterial disease	Lean fish consumption	Not included in VKM 2022	Not included in VKM 2022	Systematic reviews, n = 0; Primary studies, n = 1	Limited, no conclusion	Limited, no conclusion	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Type 2 diabetes							
Type 2 diabetes	Total fish consumption	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	Limited, no conclusion	Not included
Type 2 diabetes	Fatty fish consumption	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	Limited, no conclusion	Not included
Type 2 diabetes	Lean fish consumption	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)	Limited, no conclusion	Not included
Mortality							
Alzheimer's disease mortality	Total fish consumption	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	Limited, no conclusion	Not included
**CVD mortality	Total fish consumption	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)	Probable (protective) cleare dose-response with the new evidence from 1-3 times/month to 5 times/week. n increase in fish consumption by 20 g/day was associated with a 4%	Not included
Total heart disease mortality	Total fish consumption	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 consumption	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)	Probable (protective) , reduction in CHD mortality and a suggested threshold with no further risk reduction above 60 g/day fish consumption	There is convincing evidence - from extensive prospective cohort studies and randomized trials in humans, together with supportive retrospective, ecological, metabolic and experimental animal studies, - that fish consumption reduces the risk of death from coronary heart disease
CHD mortality	Total fatty fish consumption	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		Not included
CHD mortality	Total lean fish consumption	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		Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Myocardial infarction (MI) mortality	Total fish consumption	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)	Probable (protective)	Not included
Stroke mortality	Total fish consumption	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)	Probable (protective)	Not included
Ischemic stroke mortality	Total fish consumption	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)		Not included
Hemorrhagic stroke mortality	Total fish consumption	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)		Not included
Type 2 diabetes mortality	Total fish consumption	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	Limited, no conclusion	Not included
Colorectal cancer mortality	Total fish consumption	Not included in VKM Report	Not included in VKM Report	Systematic reviews, n = 1; Primary studies, n = 0	Limited, no conclusion	Limited, no conclusion	Not included
Prostate cancer-specific mortality	Total fish consumption	Not included in VKM Report	Not included in VKM Report	Systematic reviews, n = 1; Primary studies, n = 0	Limited, no conclusion	Limited, no conclusion	Not included
All-cause mortality	Total fish consumption	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)	Probable (protective)	Not included
All-cause mortality	Fatty fish fish consumption	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	Limited, no conclusion	Not included
All-cause mortality	Fatty lean fish consumption	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	Limited, no conclusion	Not included
Neurodevelopment and neurological diseases							
Neurodevelopment in children	Maternal total fish consumption 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)	Limited, suggestive (protective)	Coviencing evidence
Neurodevelopment in children	Maternal fatty fish consumption 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	Limited, no conclusion	Not included
Neurodevelopment in children	Maternal lean fish consumption 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	Limited, no conclusion	Not included
Neurodevelopment in children	Child total fish consumption	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)	Limited, suggestive (protective)	Not included
Neurodevelopment in children	Child fatty fish consumption	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)	Limited, suggestive (protective)	Not included

TABLE 3. **EVIDENCE CONSIDERED BY THE EXPERT CONSULTATION FOR EACH OUTCOME IN RELATION TO FISH CONSUMPTION (continued)**

HEALTH OUTCOME	FISH CONSUMPTION	LITERAURE INCLUDED IN 2022 VKM REPORT FROM THE SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE 2022 VKM REPORT	UPDATED SYSTEMATIC LITERATURE SEARCH (NUMBER OF SYSTEMATIC REVIEWS AND PRIMARY STUDIES)	CONCLUSION WEIGHT OF EVIDENCE FOR 2022 VKM REPORT AND UPDATED LITERATURE SEARCH	FAO/WHO 2023 EXPERT CONSULTATION 2023 COMMENT (CRITICAL EVALUATION OF THE BACKGROUND DOCUMENT)	FAO/WHO 2010 EXPERT CONSULTATION
Neurodevelopment in children	Child lean fish consumption	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	Limited, no conclusion	Not included
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Total fish consumption	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)	Probable (protective effect)	Emerging, possible, or probable evidence of benefit
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Fatty fish consumption	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	Limited, no conclusion	Not included
Neurocognitive and psychiatric endpoints in adults (dementia, Alzheimer's disease, and cognitive decline)	Lean fish consumption	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	Limited, no conclusion	Not included
Depression and post-partum depression	Total fish consumption	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	Limited, suggestive	Possible (depression only not postpartum)
Depression and post-partum depression	Fatty fish consumption	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	Limited, no conclusion	Not included
Depression and post-partum depression	Lean fish consumption	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	Limited, no conclusion	Not included
Obesity in adults							
Obesity in adults	Total fish consumption	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	Limited, no conclusion	Not included

** Overview of the body of evidence for the risk of CVD mortality.

3.3 SUMMARY OF THE BENEFITS OF FISH CONSUMPTION

3.3.1 ALLERGY AND IMMUNOLOGY

The Background Document included evidence from the VKM report and from five systematic reviews that met the inclusion and exclusion criteria and passed the risk-of-bias assessment. (No additional primary studies were included for this outcome.) Specific associations assessed included: allergic rhinitis in children (related to maternal fish consumption during pregnancy and early fish introduction in infancy), allergic sensitization in children (related to maternal fish consumption during pregnancy), asthma in children (related to maternal fish consumption during pregnancy), eczema in children (related to maternal fish consumption during pregnancy and fish consumption in infancy), multiple sclerosis, and rheumatoid arthritis. Note that food-protein-induced enterocolitis, an atopic condition on the rise among children in recent decades for which fish has been identified as a trigger in some populations (Agyemang and Nowak-Wegrzyn, 2019), was not evaluated as an outcome.

Considering the body of evidence reviewed, the expert consultation made the final conclusions for the associations of fish consumption with allergy and immunology outcomes, as summarized in **Table 4**.

TABLE 4. **CONCLUSION OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH ALLERGY AND IMMUNOLOGY OUTCOMES**

ALLERGY AND IMMUNOLOGY	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Children						
Allergic rhinitis					Total fish (maternal consumption and early introduction)	
Allergic sensitization					Total fish (maternal consumption and child consumption)	
Asthma					Total, fatty and lean fish (maternal consumption in pregnancy)	
Eczema			Total fish (maternal consumption and child consumption in the first year of life, but not later)			
Adults						
Multiple sclerosis			Total fish consumption			
Rheumatoid arthritis			Total fish consumption			

These conclusions align with the conclusions of the VKM report and those of the Background Document, except for: 1) the association of maternal fish consumption during pregnancy with offspring eczema, and 2) the association of total fish consumption with rheumatoid arthritis.

For the association of maternal fish consumption during pregnancy with the risk of child eczema (atopic dermatitis), the VKM report graded the evidence that fish consumption during pregnancy reduces the risk of offspring eczema as "limited, suggestive", based on nine cohort studies and two independent meta-analyses of eight or ten studies. Previous meta-analyses found associations on the protective side (high–low or meta dose–response analysis), but these did not reach statistical significance, despite a relatively large number of studies. VKM found a significant association based, however, on fewer studies than the previous most recent meta-analysis. Some potentially eligible studies were not identified by VKM. Heterogeneity analysis suggests some potential methodological limitations, and there was no significant association found among studies with the largest sample size or highest study quality. Malmir, Larijani and Esmaillzadeh (2022) performed a meta dose–response analysis (with a consumption range of 0–200 grams per week) and found a protective association, with significant departure from linearity. Risk began to decrease at 50 g/week. However, the confidence limits of the curve were too wide to conclude that the relationship was statistically significant. This dose–response relationship was not found to be an upgrading factor.

The Background Document included two additional systematic reviews (Netting, Middleton and Makrides, 2014 and Venter *et al.*, 2020) that were not included in the VKM report and, with this additional information, downgraded their conclusion to "limited, no conclusion." The expert consultation reviewed these two additional reviews. Netting *et al*. identified nine publications evaluating maternal prenatal fish consumption with offspring eczema. Five of them showed protective associations. They concluded that, overall, there were no clear patterns, but that emerging trends suggest that higher consumption of fish during pregnancy may reduce allergy risk in some populations. Venter *et al.* (2020) summarized significant associations from observational studies between various components of maternal diet, including total fish, fatty fish and shellfish, during pregnancy and offspring eczema. Consumption of fatty fish and shellfish were positively associated with offspring risk of eczema. Maternal consumption of total fish was associated with a reduced risk of developing eczema. Due to heterogeneity between studies, these data were not pooled for meta-analysis and no general conclusion was made based on a lack of consistent evidence.

The VKM report graded the evidence that total fish consumption reduces the risk of rheumatoid arthritis as "limited, suggestive." The Background Document included two additional reviews on the topic and, based on the final weight of evidence, graded the evidence "limited, no conclusion". Although both reviews identified some areas of concern with the evidence base, such as heterogeneity of study designs, both identified a decreased risk of developing rheumatoid arthritis with higher fish consumption. Therefore, the expert consultation opted to retain the final weight of evidence as “limited, suggestive”, as in the VKM report.

The VKM report graded the evidence that fish consumption in infants reduces the risk of eczema as “limited, suggestive”, based on one previous meta-analysis of three studies and two additional primary studies showing protective associations for fish consumption around age 1 year, but not at older ages. Associations with eczema at 8 years 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. No conclusions could be drawn for the effects of fatty fish or lean fish due to limited evidence.

The evidence base for multiple sclerosis was graded “limited, suggestive” due to uncertain mechanism and the evidence base consisting of case-control studies only.

The 2023 Expert Consultation concluded that there is “limited, suggestive” evidence for protection of eczema in children for both maternal and early childhood fish consumption, as well as “limited, suggestive” evidence of protection for multiple sclerosis and rheumatoid arthritis in adults. Due to lack of evidence, no conclusion can be made for allergic rhinitis, sensitization or asthma.

3.3.2 BIRTH AND GROWTH OUTCOMES

For this outcome, the Background Document included two primary studies as well as the VKM risk–benefits assessment. The specific outcomes considered included preterm birth, small for gestational age, birth weight, birth length, birth head circumference and low and high birth weight. **Table 5** provides the grading, based on the final weight of evidence, as concluded by the expert consultation for the association between maternal total fish consumption in pregnancy and these birth and growth outcomes.

TABLE 5. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH BIRTH AND GROWTH OUTCOMES**

BIRTH AND GROWTH OUTCOMES	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Preterm birth		Total fish (maternal consumption in pregnancy)			Fatty or lean fish (maternal consumption in pregnancy)	
Small for gestational age			Total fish (maternal consumption in pregnancy)		Fatty or lean fish (maternal consumption in pregnancy)	
Birth weight			Total, fatty and lean fish (maternal consumption in pregnancy)			
Low birth weight		Total fish (maternal consumption in pregnancy)			Fatty or lean fish (maternal consumption in pregnancy)	
High birth weight				Total, fatty and lean fish (maternal consumption in pregnancy)		
Birth length					Total, fatty and lean fish (maternal consumption in pregnancy)	
Head circumference					Total, fatty and lean fish (maternal consumption in pregnancy)	

These conclusions align with the conclusions of the VKM report and the Background Document. Associations of maternal fish consumption with birth outcomes were not evaluated by the 2010 Expert Consultation.

The expert consultation noted some additional considerations for the probable associations of maternal fish consumption during pregnancy with preterm birth and low birth weight. In the VKM evidence summary for preterm birth, there was evidence from two studies of a biological gradient with a potential threshold. However, the VKM summary of the evidence did not reflect a stronger association with fatty fish than with lean fish, although, notably, the evidence base was more limited than for total fish and seafood. VKM's summary relative risks for the highest versus lowest consumption of lean fish and fatty fish were not statistically significant, but were in the protective direction for risk of preterm birth. An increment of 30 g/day of fatty fish has an effect on preterm birth, with a J-shape relationship. This is equivalent to the fish consumption recommendation in many guidelines (Zhao *et al.*, 2021). Consumption of >1 but <3 times/week in the mother's diet lowers the risk of preterm birth, but no further benefit is documented with higher consumption (Leventakou *et al.*, 2014). Additionally, an increment of 45 g/day decreases the risk of low birth weight. These results can differ by geographical location – the protective effect is seen more in European cohorts.

VKM's summary relative risk for primary studies with low birth weight was not statistically significant but suggested a lower risk of low birth weight for the highest versus the lowest consumption of total fish, which was supported by an independent dose–response meta-analysis (seven cohort studies) with low heterogeneity. The main effect seems to be through reduced preterm birth, because associations with low birth weight are close to null when gestational age is adjusted for and preterm births are excluded.

The 2023 Expert Consultation concluded that there is strong evidence that total fish consumption during pregnancy reduces the risk of preterm birth and low birth weight. The strength of the evidence was graded "probable (protective effect)". Evidence is "limited, suggestive" for protection against small-for-gestational-age evidence with maternal total fish consumption.

3.3.3 BONE HEALTH

For bone health, the Background Document included results from the 2022 VKM report and from four original primary studies identified in the literature search. No additional systematic reviews were included. Of the four primary studies, two were randomized controlled trials and two were prospective cohort studies. The weight of evidence was considered only for the outcome "hip fracture", since that is the only outcome that was evaluated by VKM, and the other outcomes included only involved one study, which was considered too little to grade the weight of evidence.

The 2023 Expert Consultation concluded that there is limited evidence suggesting a protective effect of fish intake for hip fracture, which aligns with the conclusions of the VKM report and the Background Document. Bone outcomes were not considered by the 2010 Expert Consultation.

3.3.4 CANCER

For cancer-related outcomes, the Background Document includes results from the WCRF/AICR report – Diet, nutrition, physical activity and cancer: a global perspective (2018a), as well as three systematic reviews and ten original primary studies originating from the literature search. The systematic reviews evaluated site-specific cancer risk, pancreatic cancer and breast cancer. The primary studies evaluated colorectal cancer, hepatocellular carcinoma, upper gastrointestinal cancer, bladder cancer, lung cancer, cancer of unknown primary, biliary tract cancer and prostate cancer.

The weight of evidence for the association between dietary fish consumption and cancer was based on the WCRF/AICR (2018a) report as well as primary studies and systematic reviews included in the evaluation. The WCRF/AICR (2018a) report concluded that there was "strong evidence" for a probable increased risk of nasopharyngeal cancer from increased consumption of Cantonese-style salted and fermented fish, and "limited, suggestive" evidence for a decreased risk of liver and colorectal cancer from increased total fish consumption. For other cancer outcomes, no conclusion could be made. **Table 6** provides a summary of the expert consultation's grading of the overall weight of evidence of total fish consumption associated with cancer.

TABLE 6. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH CANCERS**

CANCER	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	STRONG EVIDENCE FOR INCREASED RISK
Liver cancer			Total fish			
Colorectal cancer			Total fish			
Nasopharyngeal cancer						Cantonese-style salted fish
Pancreatic cancer					Total fish	
Breast cancer					Total fish	

The expert consultation's recommendations align with the conclusions of the Background Document.

The 2010 Expert Consultation did not provide an overall assessment of the association of fish consumption with cancer risk, but did review the 2008 WCRF report on food, nutrition, physical activity and cancer prevention (Wiseman, 2008), which examined the relationships between fish consumption and cancers at 13 sites. The report concluded that fish consumption was associated in a protective manner with colorectal and pancreatic cancer ("limited suggestive" evidence). In addition, nutrients commonly found in fish were identified as protective for some cancer sites: Se ("probable" for prostate cancer, "limited suggestive" for stomach), and vitamin E ("limited suggestive" for esophageal cancer). The 2008 WCRF report did not identify fish consumption as being associated with higher risk for any of the 13 major diet-related cancers assessed.

3.3.5 CARDIOVASCULAR DISEASE OUTCOMES

For cardiovascular disease (CVD) outcomes, the review conducted for the Background Document included the 2022 VKM report and additional studies (two systematic reviews and ten primary studies). The CVD outcomes summarized were total CVD and major atherosclerotic CVDs: coronary heart disease (CHD), myocardial infarction (MI), ischemic stroke and peripheral arterial disease (PAD), as well as total stroke, hemorrhagic stroke, atrial fibrillation (AF), heart failure and venous thromboembolism. For a summary of CVD mortality outcomes, see Section 3.3.7 Mortality outcomes.

The 2023 Expert Consultation weight-of-evidence conclusions on the relationship between consumption of fish (total, fatty, lean and shellfish) and the different CVD outcomes are shown in **Table 7**. The relationships of total fish consumption with the risk of CHD and total stroke were graded "probable" for a protective effect, which is considered strong evidence that justifies recommendations designed to reduce the disease risk (WCRF/AICR, 2018a).

The grading of evidence is consistent with the proposed grading in the Background Document for all CVD outcomes, except for the relationships between lean fish consumption and the risk of CHD and MI, which are both downgraded from "limited, suggestive" of no effect, to "limited, no conclusion" due to limited evidence (**Table 7**). The 2023 Expert Consultation interpreted the WCRF criteria as indicating that evidence should be graded "limited, no conclusion" until there is sufficient evidence to judge "limited, suggestive" of a *direction* of effect or "substantial effect on risk unlikely".

In the report of the 2010 Expert Consultation, the CVD outcomes considered were ischemic stroke, AF and heart failure. These outcomes were considered only in relation to total fish consumption (**Table 3**). (For CVD mortality outcomes, see Section 3.3.7). The weight-of-evidence conclusions of the 2023 Expert Consultation for all three relationships differ from those of the 2010 Expert Consultation.

TABLE 7. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH CARDIOVASCULAR DISEASE OUTCOMES**

CVD OUTCOME	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Total CVD			Total fish		Fatty fish or lean fish	
Atherosclerotic CVDs						
CHD		Total fish	Fatty fish		Lean fish or shellfish	
MI			Total fish Fatty fish		Lean fish	
Ischemic stroke			Total fish			
PAD					Total fish, fatty fish or lean fish	
Total stroke		Total fish	Fatty fish Lean fish		Shellfish	
Hemorrhagic stroke			Total fish			
Other CVDs						
AF			Lean fish	Total fish	Fatty fish	
Heart failure			Total fish			
Venous thrombo- embolism					Total fish	

Notes: CVD: cardiovascular disease, CHD: coronary heart disease, MI: myocardial infarction, PAD: peripheral arterial disease, AF: atrial fibrillation.

For ischemic stroke, the 2023 Expert Consultation concluded that “limited, suggestive (protective)” evidence exists, while the 2010 Expert Consultation concluded that there was “probable evidence of benefit” (**Table 3**). For AF, the 2023 conclusion was for a “limited, suggestive (adverse)” association, compared with the 2010 conclusion of “emerging, possible, or probable evidence of benefit” (**Table 3**). For heart failure, the 2023 conclusion was “limited, suggestive (protective)” compared with the 2010 conclusion of “emerging, possible, or probable evidence of benefit” (**Table 3**). For heart failure, the conclusions in 2010 and 2023 are considered similar and are not discussed further.

The 2023 Expert Consultation examined the evidence for ischemic stroke and AF in more detail. For total fish consumption and the risk of ischemic stroke, the 2023 Expert Consultation restated the evidence, grading it “limited suggestive” of a protective effect in both the Background Document and the 2022 VKM report. The grading by the 2023 Expert Consultation is based on the VKM report and on one primary study that was identified in the review conducted for the Background Document (Venø *et al.*, 2018). The primary study was a prospective cohort study investigating the relationship between fish in place of red meat or poultry and ischemic stroke. The study found that the relative risks of ischemic stroke were close to unity, regardless of substitution. The 2023 Expert Consultation did not emphasize the primary study by Tong *et al.* (2019), which was identified in the Background Document (for exclusion reason, see Studies in the Background Document excluded by the 2023 Expert Consultation). The grading of evidence of an association between total fish consumption and the risk of ischemic stroke in the 2010 Expert Consultation report was based on a dose–response meta-analysis by Bouzan *et al.* (2005) on *total* stroke. The grading of evidence of ischemic stroke was derived qualitatively under the assumption that most strokes are ischemic, which may explain the discrepancy in grading. For total fish and total stroke, the grading of evidence in 2023 is consistent with the grading in 2010 (**Table 3**).

For total fish consumption and the risk of AF, the 2023 Expert Consultation restated the evidence, grading it “limited, suggestive” of an *adverse* effect in the Background Document and in the 2022 VKM report (**Table 3**), as opposed to “emerging, possible, or probable” evidence for benefit, as per the 2010 Expert Consultation. The 2023 Expert Consultation did not emphasize the primary study by Frost and Vestergaard (2005), which was identified in the Background Document and in the 2022 VKM report (for exclusion reason, see Studies in the Background Document excluded by the 2023 Expert Consultation). The grading in the 2022 VKM report for the association between total fish and AF was based on five primary studies and the pooled relative risk from a high–low meta-analysis. The pooled relative risk was borderline statistically significant ($p = 0.05$) for an adverse association. The overall estimate was driven by the UK Biobank prospective cohort study reported in Zhang *et al.* (2021), but statistically significant between–study heterogeneity was not present.

Studies in the Background Document excluded by the 2023 Expert Consultation

After consideration, the 2023 Expert Consultation did not include the following four primary studies, which were included in the Background Document.

> Frost and Vestergaard (2005) was excluded as the exposure was n-3 polyunsaturated fatty acid consumption from fish, and not fish consumption per se.

> Gammelmark *et al.* (2016) was excluded as the study was included in the evidence grading in the 2022 VKM report.

> Tong *et al.* (2019) was excluded as the exposure was fish eaters, and not fish consumption per se.

> Petermann-Rocha *et al*. (2021) was excluded as the exposure was fish eaters, and not fish consumption per se.

However, the 2023 Expert Consultation found no reason to modify the grading of evidence from that reported in the Background Document.

Studies excluded in the Background Document but considered by the 2023 Expert Consultation

A prospective cohort study on fish consumption and the risk of stroke or transient ischemic attack in US twins by Bravata *et al.* (2007) was identified, but excluded in the Background Document. The 2023 Expert Consultation did not support the exclusion reason given (“not general population”), but the study was also excluded from the 2022 VKM report after quality assessment. The expert consultation found no reason to modify the grading of evidence from that reported in the Background Document.

The 2023 Expert Consultation concluded that there is strong evidence of an association between fish intake and reduced risk of CHD and total stroke. The strength of the evidence justifies recommendations made to reduce the disease risk. The strength of the evidence was graded “limited, suggestive” or lower for the other CVD outcomes assessed by the expert consultation.

3.3.6 TYPE 2 DIABETES, OVERWEIGHT AND OBESITY

3.3.6.1 Type 2 diabetes

The Background Document included seven systematic reviews and meta-analyses and one primary study, in addition to the 2022 VKM report.

The 2023 Expert Consultation weight-of-evidence conclusions on the relationship between consumption of fish (total, fatty or lean) and type 2 diabetes are shown in **Table 8**. The grading of evidence is consistent with the proposed grading in the Background Document for type 2 diabetes, except for the relationship between lean fish consumption and the risk of type 2 diabetes, which is downgraded from “limited suggestive” of no effect, to “limited, no conclusion”, due to limited evidence (**Table 3**). The 2023 Expert Consultation interpreted the WCRF criteria as indicating that "limited, no conclusion" should be used until there is sufficient evidence to judge "limited, suggestive" of a *direction* of effect or "substantial effect on risk unlikely".

Studies excluded in the Background Document but considered by the 2023 Expert Consultation

The European Prospective Investigation into Cancer (EPIC)-InterAct case-cohort study on fish consumption in place of red meat and processed red meat in relation to the risk of type 2 diabetes by Ibsen *et al.* (2020) was identified but excluded in the Background Document. In addition, a prospective cohort study on seafood consumption in place of red meat and the risk of type 2 diabetes by Würtz *et al.* (2021) was also identified but excluded in the Background Document. The 2023 Expert Consultation did not support the exclusion reason given ("wrong study design"), but found no reason to modify the grading of evidence from that reported in the Background Document.

Studies in the Background Document excluded by the 2023 Expert Consultation

After consideration, the 2023 Expert Consultation did not include one primary study identified and included in the Background Document, but found no reason to modify the grading of evidence from that reported in the Background Document.

The study by Chen *et al.* (2020) was excluded due to inadequacy of exposure considered for this evaluation. The exposure was protein consumption from fish, not fish consumption per se.

The 2023 Expert Consultation graded the strength of evidence for the association of total, fatty and lean fish consumption with type 2 diabetes "limited, no conclusion". Type 2 diabetes was not considered by the 2010 Expert Consultation.

3.3.6.2 Overweight and obesity

The Background Document included three primary studies in addition to the 2022 VKM report. No additional systematic reviews were included. Two primary studies were prospective cohort studies, with the outcome being changes in body weight (Smith *et al.*, 2015 and Beulen *et al.*, 2018). The third primary study was an epidemiological population-based study with the outcome being changes to metabolic syndrome components, including waist circumference (Tørris, Molin and Småstuen, 2017).

The 2023 Expert Consultation graded the strength of evidence for the association of total fish consumption with overweight and obesity "limited, no conclusion" (**Table 8**). These conclusions align with the conclusions of the Background Document and those of the 2022 VKM report. Overweight and obesity were not considered by the 2010 Expert Consultation.

TABLE 8. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH TYPE 2 DIABETES, OVERWEIGHT AND OBESITY**

OTHER OUTCOMES IN ADULTS	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Overweight and obesity					Total fish	
Type 2 diabetes					Total, fatty and lean fish	

3.3.7 MORTALITY OUTCOMES

In assessing mortality outcomes, it should be noted that, while studies on disease incidence may be seen as studies on etiology, studies on only fatal outcomes may be seen as studies exploring combined etiology and prognosis. This means that fatal outcomes may be affected by possible preventive factors, such as fish consumption, and by the quality of disease treatment provided by the health system (whenever there is a time lapse between the clinical threshold of declared disease and death) and other aspects (O'Flaherty, Buchan and Capewell, 2013). It may be difficult to extricate the etiological aspects from other aspects, thus rendering fatal-outcome studies less conclusive than disease-incidence studies in what concerns prevention.

3.3.7.1 Mortality from Alzheimer's disease and type 2 diabetes

The Background Document for these outcomes included only the 2022 VKM report. No new evidence was included.

Considering the evidence in the Background Document, the 2023 Expert Consultation determined the final weight of evidence for the associations between total fish consumption and mortality from both Alzheimer's disease and type 2 diabetes, which is summarized in **Table 9**. This conclusion aligns with the conclusions of the Background Document. Mortality from Alzheimer's disease and type 2 diabetes were not considered by the 2010 Expert Consultation.

3.3.7.2 Mortality from colorectal cancer and prostate cancer

The Background Document included one meta-analysis investigating the association between fish consumption and colorectal cancer mortality, and one meta-analysis investigating the association between fish consumption and prostate cancer mortality. Mortality from colorectal cancer and prostate cancer associated with fish consumption were not evaluated in the 2022 VKM report or considered by the 2010 Expert Consultation.

Considering the two meta-analyses identified in the Background Document, the 2023 Expert Consultation determined the final weight of evidence for the associations between total fish consumption and mortality from colorectal cancer and prostate cancer, which is summarized in **Table 9**. This conclusion aligns with the conclusions of the Background Document.

3.3.7.3 Mortality from cardiovascular disease

The final evidence summarized in the Background Document for this outcome included the 2022 VKM report as well as one systematic review and seven primary studies that were additionally identified. The specific outcomes included mortality from total CVDs (total CVD and total heart mortality), atherosclerotic CVDs (CHD, MI), and total stroke.

Considering the Background Document, the 2023 Expert Consultation determined the final weight of evidence for the association between total fish, fatty fish or lean fish consumption and mortality outcomes, as summarized in **Table 9**.

TABLE 9. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH MORTALITY OUTCOMES**

TYPE OF MORTALITY	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Cardiovascular						
CVD		Total fish				
Total heart disease					Total fish	
CHD		Total fish			Fatty or lean fish	
MI		Total fish				
Stroke		Total fish				
Ischemic stroke			Total fish			
Hemorrhagic stroke			Total fish			
Alzheimer's disease					Total fish	
Type 2 diabetes					Total fish	
Colorectal cancer					Total fish	
Prostate cancer					Total fish	
All-cause		Total fish			Fatty or lean fish	

Notes: CVD: cardiovascular disease, CHD: coronary heart disease, MI: myocardial infarction.

In the 2010 Expert Consultation, none of the cardiovascular-related mortality outcomes were included, with the exception of CHD mortality. For CHD mortality, the 2010 Expert Consultation concluded that there was "convincing" evidence of benefit. Although it appears that the conclusion of the 2023 Expert Consultation has been downgraded compared with that of the 2010 Expert Consultation, note that the 2010 report considers not only data from prospective observational and intervention human studies of fish consumption considered in this review, but also supportive evidence from retrospective, ecological, metabolic and experimental animal studies. Therefore, the conclusions are considered to be generally aligned.

Studies excluded in the Background Document but considered by the 2023 Expert Consultation

The 2023 Expert Consultation reviewed the studies excluded from the Background Document and the 2022 VKM report and identified two studies deserving a more attentive analysis. These were the prospective cohort study in initially healthy men and women on meat replacement by fish and risk of CVD, cancer and total mortality by Pan *et al.* (2012), and the prospective cohort study in postmenopausal women on associations of fried food consumption with all-cause, cardiovascular and cancer mortality by Sun *et al.* (2019). The 2023 Expert Consultation did not support the exclusion reasons given in both cases, since meat replacement by fish (Pan *et al.*, 2012) and by fried fish (Sun *et al.*, 2019) do not necessarily affect the validity of the conclusions. The studies were also not included in the 2022 VKM report. Despite this, the 2023 Expert Consultation found no reason to modify the grading of evidence regarding CVD mortality from that reported in the Background Document.

3.3.7.4 All-cause mortality

The Background Document included two primary studies in addition to the 2022 VKM report. Both additional studies report no significant association between total fish or seafood consumption and all-cause mortality in the general adult population (RR = 0.84, 95% CI: 0.66, 1.07) (Sun *et al.*, 2021) and in adults with prior myocardial infarction (RR = 0.97, 95% CI: 0.82, 1.15) for >40 g/day versus ≤5 g/day) (Pertiwi *et al.*, 2021). However, the direction of the associations was consistent towards a protective effect of total fish consumption on all-cause mortality.

As part of their 2022 report, VKM conducted four meta-analyses, all of which showed significant protective associations between total fish consumption and all-cause mortality in general populations and in specific subpopulations. The first meta-analysis of the association between total fish consumption and all-cause mortality in general populations (23 primary studies), showed a statistically significant protective association (RR = 0.93, 95% CI: 0.90, 0.97), however with significant heterogeneity between studies. Two further meta-analyses also suggested protective associations between total fish consumption and all-cause mortality in subpopulations with previous or at high risk of CVD from vascular disease (five primary studies), and in subpopulations with type 2 diabetes (five primary studies). A further meta-analysis (four primary studies) suggested a potentially small increased risk associated with fried fish, and a borderline statistically significant protective association with non-fried fish in general populations.

Considering the two additional primary studies identified in the Background Document and the evidence from the 2022 VKM report, the 2023 Expert Consultation determined the final weight of evidence for the association between total fish consumption and all-cause mortality and between fatty fish, lean fish and all-cause mortality, as summarized in **Table 9**. These conclusions align with the conclusions of the Background Document and those of the 2022 VKM report. All-cause mortality was not considered by in the 2010 Expert Consultation.

A key conclusion of the 2023 Expert Consultation is the existence of strong evidence of an association between fish intake and reduced risk of CVD, CHD, MI, stroke and all-cause mortality. The strength of the evidence justifies the recommendations made to reduce mortality risk. The strength of the evidence was graded "limited, suggestive" or lower for the other mortality types assessed by the 2023 Expert Consultation.

3.3.8 NEURODEVELOPMENT

3.3.8.1 Neurodevelopment in children

With regard to maternal fish consumption and neurodevelopment in children, the Background Document included one randomized controlled trial and one prospective study, as well as evidence from the 2022 VKM report. Most of the studies incorporated in the analysis originated from European countries, although five studies were conducted in the United States of America and one was conducted in Japan. The 2023 Expert Consultation also included one additional, recently published study from a mother–child cohort in a high-fish-eating population (Conway *et al.*, 2023). When assessing the relationship between fish consumption in children and child neurodevelopment, the evidence included the VKM report.

The direction of associations was consistent towards a protective effect of total maternal fish consumption on neurodevelopment in children. In children, there is moderate and consistent evidence that indicates total and fatty fish consumption during childhood has beneficial associations with neurocognitive outcomes (**Table 10**).

TABLE 10. **CONCLUSIONS OF THE EXPERT CONSULTATION REGARDING ASSOCIATIONS OF FISH CONSUMPTION WITH NEURODEVELOPMENT IN CHILDREN AND ADULTS**

NEURODEVELOPMENT AND NEUROLOGICAL DISEASES	CONVINCING	PROBABLE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (PROTECTIVE EFFECT)	LIMITED, SUGGESTIVE (ADVERSE EFFECT)	LIMITED, NO CONCLUSION	SUBSTANTIAL EFFECT ON RISK UNLIKELY
Children						
Neurodevelopment in children			Total fish (maternal consumption in pregnancy) Total and fatty fish (child consumption)		Fatty and lean fish (maternal consumption in pregnancy) Lean fish (Child consumption)	
Adults						
Neurocognitive and psychiatric endpoints (dementia, Alzheimer's disease and cognitive decline)		Total fish			Fatty or lean fish	
Depression and post-partum depression			Total fish		Fatty or lean fish	

The 2023 Expert Consultation concluded that a protective effect of maternal and child total fish consumption is apparent for child neurodevelopment. The expert consultation graded this evidence "limited, suggestive". This differs from the 2010 report, which indicated "convincing" evidence of beneficial health outcomes from fish consumption for improved neurodevelopment in infants and young children when fish is consumed by the mother before and during pregnancy. Differences in the approach taken between the 2010 (fish and nutrients) and 2023 (only fish) reports may explain differences in the grading. Children's fish consumption was not considered in the 2010 report.

The 2023 Expert Consultation noted that the protective effect of maternal fish consumption and childhood neurodevelopment was reported in studies where maternal fish consumption was equal to or greater than three meals/week or 340 g/week (Julvez *et al.*, 2016). Importantly, no adverse association with child neurodevelopment was observed in any study, even with maternal fish consumptions as high as ~800 g/week (Conway *et al.*, 2023 and Julvez *et al.*, 2016). In addition, no additional benefit was reported for consuming fish in higher amounts.

It is important to recognize that neurodevelopment is assessed using a variety of scales in children, and each scale can include subscales, making the comparison of findings between studies difficult and introducing the potential of bias due to multiple comparisons. Furthermore, the majority of the studies reviewed in the 2023 Expert Consultation are based on cohorts in developed countries.

3.3.8.2 Neurodevelopment in adults

The final evidence for this outcome included the 2022 VKM report (4 systematic reviews and 13 primary prospective studies). Specific associations between fish consumption and neurodevelopment in adults included neurocognitive and psychiatric endpoints in adults, depression and other psychiatric symptoms, incidence of dementia and Alzheimer's disease, risks or symptoms of cognitive decline, and general cognition.

The evidence supports a positive relationship between total fish consumption and reduced risk of dementia, Alzheimer's disease and cognitive decline. Benefits were seen with consumptions higher than 100 g/week (Zeng *et al.*, 2017). There is a lack of evidence with respect to the association of fatty fish and lean fish with the risk of dementia, Alzheimer's disease and cognitive decline (**Table 10**).

The 2023 Expert Consultation concluded that there is strong evidence that total fish consumption reduces the risk of psychiatric endpoints. In children, there is suggestive evidence that maternal total fish consumption during pregnancy and fatty fish consumption in childhood are associated with a protective effect on neurodevelopment in children.

3.4 OVERALL CONCLUSIONS AND LIMITATIONS

> Strong evidence exists for health benefits of total fish consumption during all life stages: pregnancy, childhood and adulthood. For example, positive associations are found for maternal consumption during pregnancy with selected birth outcomes and for adult consumption with cardiovascular and neurological disease outcomes. This evidence for health benefits of total fish consumption incorporates the effects of all nutrients and contaminants in fish on the outcomes studied, including nutrients and contaminants not specifically considered in the evidence review.

> Among the general population, few if any harms exist for total fish consumption.

> Benefits will vary depending on overall diet and on the characteristics of the consumers and the fish consumed. For example, n-3 LCPUFA status, Se intake, exposure to other contaminants, food preparation methods and individual susceptibility may modify health effects.

> Healthy dietary patterns that include fish consumption and are established early in life could influence nutritional habits and health during adult life. There is also emerging, possible or probable evidence that fish consumption may reduce the risk of multiple other adverse health outcomes (such as anxiety and inflammatory disease). More cohort studies are needed to generate data among infants, young children and adolescents to derive a quantitative framework of the health risks and benefits of eating fish and its effects in the long term.

3.5 RECOMMENDATIONS

The 2023 Expert Consultation considers that different subtypes of seafood differ in both nutritional components and contaminant burden. Thus, the expert consultation recommends that Member Nations consider the different seafood subtypes consumed in different settings for local guidelines.

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CHAPTER 4

TOXIC EFFECTS OF DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

4.1 BACKGROUND

Dioxins and dl-PCBs are lipophilic and persistent. Consequently, they accumulate in the food chain. Foods of animal origin are the main contributors to total dietary exposure, particularly fatty fish, dairy products (butter and cheese), and livestock meat.

In this section, the term “exposure to dioxins and dl-PCBs” refers to the overall exposure, not only to exposure due to fish consumption. Fish may be an important contributor to dietary dioxin and dl-PCB exposure in some regions (for Europe, see EFSA, 2018; for China, including Hong Kong SAR, see Zhang *et al.*, 2015; and for the Republic of Korea, see Shin *et al.*, 2022), but not in others (for Australia, see Food Standards Australia New Zealand, 2020; and for the United States of America, see USDA, 2004).

PCDDs and PCDFs are two groups of persistent organic pollutants (POPs) that together are often referred to as “dioxins” (PCDD/Fs). There are 75 chemical forms (congeners) of PCDDs and 135 forms of PCDFs. Dioxins are not intentionally produced but can be formed during several industrial and thermal processes, such as waste incineration or the production of various chlorinated chemicals, including the herbicide 2,4,5-trichlorophenoxy acetic acid (part of Agent Orange), polychlorinated biphenyls (PCBs), and chlorophenols. The toxicity of the various congeners depends on the number and position of chlorine substitution, and the most toxic congener is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

In contrast to dioxins, PCBs had widespread use in numerous industrial applications, generally in the form of complex technical mixtures. There are 209 congeners of PCBs, 12 of which show toxicological properties similar to dioxin. These are called dioxin-like PCBs (dl-PCBs).

In order to compare the toxicity of a mixture of congeners, the concept of toxic equivalency (TEQ), based on different toxic equivalency factors (TEFs), was introduced. The concept assumes that the relevant PCDD/Fs and dl-PCBs bind to the intracellular aryl hydrocarbon receptor (AHR) and cause the same type of AHR-mediated biochemical and adverse effects. Another important requirement of the TEQ concept is the persistence and accumulation of the compounds in the body. TCDD was assigned a value of 1, and the TEFs for the other 16 toxic PCDD/Fs with 2,3,7,8-chlorine substitution and 12 dl-PCBs have values between 0.00003 and 1. Thus, a TEF indicates an order-of-magnitude estimate of the potency of a dioxin-like compound relative to TCDD. TEF values have been evaluated and reevaluated several times, taking into account the multiple endpoints known to be affected by dioxins and dl-PCBs. To calculate the total TEQ value of a sample, the concentration of each congener is multiplied by its TEF and the products are then added together. The resulting TEQ value expresses the toxicity of PCDD/Fs and dl-PCBs in a complex sample in terms of TCDD. The TEF values considered by the 2023 Expert Consultation were proposed by an expert meeting of the WHO in 2005 and are termed WHO 2005 TEFs (van den Berg *et al.*, 2006).

The current Provisional Tolerable Monthly Intake (PTMI) for dioxins and dl-PCBs, developed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), was established in 2001 at 70 pg WHO1998-TEQs/kg of body weight (WHO, 2002). More recently, EFSA established a tolerable weekly intake (TWI) of 2 pg WHO2005-TEQ/kg of body weight per week (EFSA, 2018).

4.2 APPROACH

To assess the new evidence on the health-related effects of exposure to dioxins and dl-PCBs, the 2023 Expert Consultation considered the EFSA report, Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food (EFSA, 2018), and the health effects reported in the Background Document. The latter included studies published after the 2018 EFSA report (between 5 July 2016 and 13 December 2021). The health outcomes considered for dioxins and dl-PCBs in the expert consultation were based on those considered in the Background Document and in the 2018 EFSA report. EFSA conducted a comprehensive systematic literature search, including studies published between 1 July 1998 and 5 July 2016. The EFSA report was rated in the Background Document using a risk-of-bias tool (AMSTAR 2, a measurement tool to assess systematic reviews) and was rated “high”.

A weight-of-evidence approach was not provided since the section in the Background Document on toxic effects of dioxins and dl-PCBs only included literature published after 2010, and thus it was not possible to calculate an overall grading of the available evidence.

4.3 SUMMARY OF THE EFFECTS OF DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS ON HEALTH OUTCOMES

4.3.1 CHLORACNE AND OTHER DERMAL EFFECTS

Chloracne is a cystic and hyperkeratotic skin disorder, which is a typical effect of acute dioxin exposure. The systematic literature review carried out for the development of the Background Document did not identify any additional evidence for dermal effects of dioxins and dl-PCBs at general-population-relevant exposure levels beyond that discussed in the 2018 EFSA report. As such, the expert consultation concluded that there is no evidence for this toxicity following chronic exposure. This outcome was not discussed in the 2010 Expert Consultation.

4.3.2 MALE REPRODUCTIVE EFFECTS (INCLUDING ORGANS)

Sex hormones

The review conducted for the Background Document identified eight additional studies investigating changes in sex hormones following dioxin and dl-PCB exposure published after the EFSA 2018 report. These studies showed conflicting results. EFSA reported that observed changes in serum sex hormones were mainly studied in males and most often reported no association. Changes in hormone levels were not considered to be an adverse effect by the EFSA 2018 report.

The 2010 Expert Consultation reviewed one cohort study that reported increased feminized play behavior observed in both boys and girls upon prenatal exposure to dioxin. These observations were suggested to be due to steroid hormone imbalances in early development, which could be due to prenatal exposure to PCBs, dl-PCBs and dioxins, their metabolites, or related compounds. However, the 2010 Expert Consultation did not draw any conclusions regarding potential associations between dioxin and dl-PCB exposure and changes in sex hormones.

In conclusion, there is insufficient evidence to support an association between dioxin and dl-PCB exposure and changes in sex hormones, in line with the findings of the 2010 Expert Consultation.

4.3.3 SEMEN QUALITY

The Background Document identified one study published after the 2018 EFSA report. The study, a case-control study from a fertility clinic in Spain, compared measured dl-PCB levels in serum in a group of men with low sperm quality (n = 24) with those of a group of men with normal sperm quality (n = 26). The study did not measure levels of PCDD/Fs. The study found no clear association between dl-PCB exposure and semen volume. No studies on the association between PCDD/Fs and semen quality published after the 2018 EFSA report were identified.

The EFSA report considered seven epidemiological studies. Among these, the strongest associations were seen in three of these studies: two Seveso studies (epidemiological studies following up on an accidental release of TCDD in Seveso, Italy) (Mocarelli *et al.* 2008 and 2011), and the Russian Children's Study (an epidemiological study performed on Russian boys in the town of Chapayevsk) (Mínguez-Alarcón *et al.*, 2017). Associations between TCDD exposure during infancy (breastfed children in the Russian Children's Study) or prepuberty (men in the Seveso study) and impaired semen quality was considered causal by EFSA, based on weight of evidence from epidemiological observational studies and supported by experimental animal studies. Effects on semen quality upon pre- and postnatal exposure were considered the critical effect by EFSA. The study by Mínguez-Alarcón *et al.* was identified as the critical study and formed the basis for the derivation of the TWI. The TWI for dioxins and dl-PCBs was based on the no-observed-adverse-effect level for dioxins of 7 pg 2005 WHO-TEQ/g fat in serum from Mínguez-Alarcón *et al.*

The 2010 Expert Consultation considered only experimental animal studies on male reproductive effects. It was noted that adverse effects on the developing reproductive systems of both male and female offspring in rats, as well as decreased sperm counts in male pups, had been observed. However, no conclusions were drawn regarding potential associations between dioxin and dl-PCB exposure and semen quality in humans.

The 2023 Expert Consultation noted that the study by Mínguez-Alarcón *et al.* only found an association for dioxin exposure and semen quality, but not when considering dl-PCB exposures alone or total TEQ dioxin and dl-PCB exposures. Despite the absence of documented associations between total TEQ dioxin and dl-PCB exposure from this study, the TWI set by EFSA 2018 was for total TEQ dioxins (PCDD/Fs) and dl-PCBs.

The 2023 Expert Consultation concluded that there is consistent evidence for an association between exposure to dioxins (in particular, TCDD), but not dl-PCBs alone or total TEQ dioxins and dl-PCBs, and semen quality. The expert consultation furthermore emphasized that these associations are observed for total exposures and not for exposures from fish alone.

4.3.4 CRYPTORCHIDISM

The Background Document did not identify additional studies on potential associations between dioxin and dl-PCB exposure and cryptorchidism published after the 2018 EFSA report. The EFSA report identified two nested case-control studies, one that reported no association and one that found sum PCDD/F levels in subcutaneous adipose tissue biopsies to be associated with cryptorchidism (after adjusted analysis). (Cryptorchidism was not considered in the 2010 Expert Consultation.)

In conclusion, there is insufficient evidence to support an association between dioxin and dl-PCB exposure and cryptorchidism.

4.3.5 MALE PUBERTAL DEVELOPMENT

The Background Document did not identify additional studies on potential associations between dioxin and dl-PCB exposure and male pubertal development published after the 2018 EFSA report. Seven epidemiological studies on male pubertal development were described in the EFSA report. Male pubertal development was not considered in the 2010 Expert Consultation.

In conclusion, there is insufficient evidence to conclude on the effects of dioxins and dl-PCBs on male pubertal development.

4.3.6 FEMALE REPRODUCTIVE EFFECTS

The Background Document did not identify additional new studies investigating an association between exposure to dioxins and dl-PCBs and female reproductive effects. The 2018 EFSA report identified 12 studies that considered associations between dioxins and dl-PCBs and endometriosis. Most studies were cross-sectional and case-control studies. One study was a prospective cohort study, but it did not derive a dose–response. EFSA concluded that there was insufficient evidence to make a conclusion. Four studies considered pubertal development, none of which identified an association. EFSA reported studies that investigated the association between dioxins and dl-PCBs and menstruation, time-to-pregnancy, ovarian function, leiomyomas, or age-at-menopause. Because there was only one study per outcome, EFSA concluded that there was insufficient evidence on the association between dioxins and dl-PCBs and these effects. The 2010 Expert Consultation drew no conclusions regarding associations between dioxin and dl-PCB exposure and female reproductive effects in humans.

In conclusion, there is insufficient evidence on the association between exposure to dioxins and dl-PCBs and female reproductive effects.

4.3.7 BIRTH OUTCOMES

The Background Document identified a prospective birth cohort study that suggests possible gene-environment interactions for birth weight.

The 2018 EFSA report considered the association between dioxins and dl-PCBs and sex ratio, birth weight and other outcomes. Decreased sex ratio (newborn male/total births) was observed across three cohorts, but there were some uncertainties in the back calculations of the levels of dioxins in the parents. Thus, the relationship was declared as likely causal. Eighteen studies considered birth weight and other outcomes, specifically Yusho disease, gestational age, child head circumference, birth defects, parity, spontaneous abortion, preterm delivery, pregnancy loss, congenital abnormalities and infant death. EFSA determined that the studies were inconclusive and did not find association between exposure and effect. Taken together with the new study identified in the Background Document, there was insufficient evidence to conclude on associations between exposure to dioxins and dl-PCBs and birth weight in the general population. However, effects may vary across susceptible populations. The 2023 Expert Consultation reviewed the evidence available at the time and made no conclusions on the associations between dioxin and dl-PCB exposure and birth outcomes in humans. Potential associations between dioxin and dl-PCB exposure and birth outcomes in humans were not discussed in the 2010 Expert Consultation.

In conclusion, associations have been reported between exposure to dioxins and dl-PCBs and decreased sex ratio, but there was insufficient evidence to conclude on associations with birth weight.

4.3.8 THYROID DISEASE AND THYROID HORMONES

The Background Document identified two studies in adults and two studies in children for thyroid disease and thyroid hormones, in addition to those reviewed in the 2018 EFSA report. However, both studies in adults had limited power due to small sample sizes. The EFSA report concludes that there is relatively strong support for a causal association between predominantly prenatal exposure to TCDD and increased thyroid stimulating hormone (TSH), indicating possible subclinical hypothyroidism. These results are in line with the results of the studies reviewed in the 2010 Expert Consultation, which found that in adults, adolescents and children from highly PCB-exposed areas the concentration of PCBs in blood samples correlated negatively with levels of circulating peripheral thyroid hormones and demonstrated a positive correlation between PCB exposure and TSH.

In conclusion, there is some evidence that prenatal high level exposure is associated with higher TSH in children.

4.3.9 OBESITY AND DIABETES

The Background Document identified an additional birth cohort study beyond those considered in the 2018 EFSA report: an analysis of Seveso children's health that found negative associations with body mass index (BMI) trajectories in girls, and positive associations with incident metabolic syndrome in boys. For obesity-related outcomes, EFSA emphasized a prospective association between serum TEQ in Russian children ages 8 to 9 years old and trajectories of BMI z-scores over the following 3 years, which was interpreted as suggesting a distinct mechanism from AHR-mediated toxicity.

The EFSA report emphasized two cohorts for diabetes, both of Vietnam War veterans: one reporting an association of TCDD with incident diabetes and the other reporting a positive prospective association of spraying herbicides with an insulin-sensitivity index. Diabetes and obesity outcomes were not discussed in the 2010 Expert Consultation, but metabolic disorders were considered in the Background Document.

In conclusion, evidence regarding these outcomes is still emerging, but is lacking for the low-dose exposure ranges most relevant to general populations eating fish, whereas there may be associations at high-exposure ranges.

4.3.10 CARDIOVASCULAR EFFECTS

The Background Document did not identify additional studies on cardiovascular risks of dioxins beyond the evidence in the 2018 EFSA report, which found that evidence was lacking regarding low-exposure health effects. Cardiovascular outcomes might pertain to high-level dioxin exposures, but study findings were mixed (including, for instance, different relationships across cohorts), and it is unclear if the high-exposure results would be informative for low-exposure toxicity. In conclusion, evidence was lacking regarding potential cardiovascular hazards of low-level, general-population-relevant exposures, but was suggestive for high exposures. The 2010 Expert Consultation did not discuss the potential role of dioxins in cardiovascular health.

4.3.11 HEPATIC DISORDERS AND DIGESTIVE EFFECTS

There were no additional studies identified by the systematic search conducted for the Background Document beyond the five high-exposure cohorts discussed in the 2018 EFSA report. ESFA concluded that there was insufficient evidence to conclude hepatic or digestive toxicity. The 2023 Expert Consultation concluded that there is insufficient evidence to suggest hepatic disorders and digestive effects from low-level exposures expected of fish consumers in the general population. Non-cancerous hepatic disorders and potential digestive effects of dioxins were not discussed in the 2010 Expert Consultation.

4.3.12 EFFECTS ON THE IMMUNE SYSTEM

The Background Document did not find additional studies, but 14 studies were reviewed for the development of the 2018 EFSA report. Dioxins can have a variety of effects on the immune system, including immunosuppression; however, the 2010 Expert Consultation considered that there was insufficient evidence for adverse health effects associated with exposure to dioxins from fish consumption with this endpoint. In conclusion, the available studies did not provide sufficient evidence for an association between PCDD/Fs or dl-PCBs and effects on the immune system.

4.3.13 EFFECTS ON TEETH AND BONE HEALTH

The Background Document did not find additional studies on the effect of dioxins on teeth and bone health beyond those identified in the 2018 EFSA report. These endpoints were not mentioned in the 2010 Expert Consultation report. In the EFSA report, dose–response relationships were reported for childhood exposure to dioxins and tooth enamel, hypomineralization and enamel defects in three different population groups (Seveso, Helsinki and Yucheng). Hypomineralization weakens the enamel and increases the risk of caries and impaired tooth health later in life. In contrast to teeth, bone has a continuous turnover. EFSA reported limited evidence from one cohort, which indicated some changes in bone parameters related to early-life dioxin exposure.

In conclusion, there was an association between dioxins and dl-PCBs and weakened tooth enamel, but there was insufficient evidence regarding an association with bone health.

4.3.14 EFFECTS ON THE NERVOUS SYSTEM

Various neurodevelopmental outcomes have been investigated in children of different ages, but few outcomes have been assessed in several cohorts or at a similar age. Other endpoints have only been investigated in single cohorts, and while there are some sex-specific associations for some outcomes, these are either inconsistent or are not confirmed in several cohorts. EFSA reported on 22 studies (15 in children and 7 occupational studies in adults) for outcome effects on the nervous system, and concluded that the available information was insufficient to draw conclusions on the effects of dioxins and dl-PCBs on the nervous system in both children and adults. One additional study was described in the Background Document on the effect of TCDD exposure on neurodevelopment in children; however, the findings were not conclusive.

Several studies were described in the report of the 2010 Expert Consultation that examined the effects of dioxins and non-dioxin-like PCBs on neurobehavioural development in children. (These include the Great Lakes cohort, the Dutch cohort and the US Oswego cohort.) Effects included reduced neonatal neurological optimality in infants, delayed brain maturation, neurobehavioural alterations and reduced IQ development. However, it was not possible to separate the effects of dioxins and dl-PCBs from other contaminants in these studies. Consequently, a quantitative evaluation of developmental exposure to dioxins with relation to body burden and IQ was not carried out by the 2010 Expert Consultation.

Associations have been suggested between dioxin and dl-PCB exposure and several nervous system outcomes, but replication is needed to draw firm conclusions.

4.3.15 CANCER

The Background Document identified two case-control studies in addition to the five cohort studies already identified by the 2018 EFSA report. Several of the high-exposure cohort studies showed a positive association with all cancers combined, but there was no clear link to any specific cancer site. In addition, there was no clear dose–response relationship between exposure and cancer development. In a general-population study assessing the effect of chronic exposure to dioxins and dl-PCBs there was a graded dose–response trend for cancer mortality, but that association did not reach statistical significance. These findings are in line with the findings of the 2010 Expert Consultation, which found that the epidemiological evidence from the most highly TCDD-exposed cohorts studied produced the strongest evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites. The report noted that the general population exposures are 2 to 3 orders of magnitude lower than those observed in these high-exposure cohorts.

In conclusion, there is some evidence of an association between high dioxin and dl-PCB exposures and cancer.

4.4 CONCLUSIONS AND RECOMMENDATIONS

4.4.1 CONCLUSIONS AND LIMITATIONS

Studies are lacking regarding the effects of dioxin and dl-PCB exposure from fish consumption on human health in general populations. The current evidence base is mainly from populations highly exposed because of occupational exposure or local contamination.

Dietary exposure to dioxins and dl-PCBs comes from multiple different foods of animal origin, including fish. The contribution of fish consumption to these exposures will vary based on the region of residence and the amount, source and types of fish consumed.

There is consistent evidence for an association between dioxin exposure and reduced semen quality, but not for sum dioxins and dl-PCBs. Exposure to total dioxins and dl-PCBs has been associated with altered sex ratio and weaker tooth enamel.

In children, there was some evidence for association of dioxin and dl-PCB exposure with BMI z-scores, and increased TSH with prenatal high-level exposures. In adults, there was some evidence for associations of high exposure with cancer, cardiovascular effects and diabetes.

4.4.2 RECOMMENDATIONS

The 2023 Expert Consultation considered there to be a need for further studies on the potentially adverse health effects of dioxins and dl-PCBs due to fish consumption. There are several health outcomes that may especially merit further study in fish consumers based on the hazard assessment for dioxins and dl-PCBs, in particular semen quality which, to date, is the most sensitive endpoint identified in humans.

The expert consultation recommends that the JECFA update the health-based guidance value for dioxins and dl-PCBs, taking into consideration the new evidence and updated WHO 2022 TEF values (DeVito *et al.*, 2024).

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CHAPTER 5

TOXIC EFFECTS OF METHYLMERCURY AND THE ROLE OF SELENIUM IN RELATION TO THE HEALTH EFFECTS OF METHYLMERCURY

5.1 TOXIC EFFECTS OF METHYLMERCURY

5.1.1 BACKGROUND

Mercury (Hg) is a persistent, non-essential element that can be toxic at high exposures due to its ability to cross the blood–brain barrier and other biological membranes. The emission of Hg into the environment occurs through both natural and anthropogenic processes, such as volcanic eruptions, erosion, mining, coal incineration and other industrial activities. In its biogeochemical cycle, Hg undergoes complex changes during transformation and transposition between the atmosphere, the soil and aquatic ecosystems (ATSDR, 2022). According to the WHO (2017), Hg is considered “one of the top ten chemicals or groups of chemicals of major public health concern”. The significance of Hg as a global pollutant is acknowledged in the establishment of the Minamata Convention, which aims to protect human health and the environment from anthropogenic emission of Hg. The most common organic form of Hg in the environment is MeHg, which is formed when Hg combines covalently with carbon. This form can be bioaccumulated by organisms and transferred up the food web, from prey to predator (a process known as biomagnification), reaching its highest concentrations in the oldest and most predatory fish and mammalian species. In the absence of occupational exposure, humans are primarily exposed to MeHg through the consumption of fish and other seafood.

Although high exposures to bioavailable forms of Hg are toxic to humans in general, the level of toxicity depends on various factors, including the chemical form, the duration and route of exposure and the aggregate dose per unit of body weight, as well as the age, health and nutritional and dietary status of the exposed individual (Ralston and Raymond, 2018; Raymond and Ralston, 2020; Spiller, 2018; Spiller, Hays and Casavant, 2021). Of particular importance in this regard is the Se content of the food consumed (fish and seafood), which can influence the level of risks, if any, associated with MeHg exposure.

In 2003, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a provisional tolerable weekly intake (PTWI) of MeHg of 1.6 µg/kg of body weight. In 2012, the European Food Safety Authority (EFSA) established a tolerable weekly intake (TWI) of MeHg of 1.3 µg/kg of body weight. Furthermore, in 2011, JECFA established a PTWI of 4 µg/kg of body weight for inorganic mercury.[1]

5.1.2 APPROACH

This section is based on the findings of the literature review presented in the Background Document, which were reviewed by the experts participating in the expert consultation, bringing to bear their diverse experience and expertise. The expert consultation also considered the findings and conclusions of the 2010 Expert Consultation (FAO, 2011). It should be noted that the 2010 Expert Consultation assessed the effects of high exposures to MeHg and additional contaminants from eating meat and blubber from whales and other mammals, which are very different from the effects of eating ocean fish.

The findings presented in the Background Document in Chapter 5, Results and summarization of the literature review “Toxic effects of MeHg”, are based on a systematic literature review of epidemiological evidence on MeHg and human health performed by the IMR. The literature search was performed in the databases PubMed and Web of Science on 15 December 2021. The literature review, which included systematic reviews and original primary studies, was limited to papers published since 2010; that is, the period after the publication of the prior FAO/WHO report. The health outcomes were subsequently categorized into four groups: neurological outcomes, cardiovascular outcomes, growth and other health outcomes.

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

In addition to the findings extracted from the systematic reviews and original articles, the Background Document also considered the main findings of two published 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). Both reports include reviews of literature related to the health effects of MeHg exposure. The EFSA report considers only original primary studies published between 2004 and 2012, while the VKM report considers only systematic reviews published since 2012. Because the Background Document considers only evidence published since 2010, it does not provide an overall grading of the available evidence.

Prior to recognition of the importance of Hg–Se interactions, it was not generally known that effects of Hg exposures from consuming marine mammals, freshwater fish or other environmental sources may be different from the effects of eating ocean fish. The Background Document includes studies reporting effects from the consumption of marine mammals, freshwater fish and other sources, in addition to exposure from the consumption of ocean fish. The assessment and stated conclusions do not necessarily reflect the conclusions of studies assessing MeHg risks exclusively from ocean fish consumption.

5.1.3 SUMMARY OF TOXIC EFFECTS OF METHYLMERCURY

5.1.3.1 Neurological outcomes

The Background Document included findings from 6 systematic reviews and 31 primary studies evaluating neurological outcomes. The systematic reviews considered autism spectrum disorders (n = 3), autism and attention deficit hyperactivity disorder (ADHD) (n = 1 for each outcome), neurological effects in adults (n = 1) and the neurodevelopment of children exposed prenatally to MeHg (n = 1).

The 31 primary studies, including data from 13 unique cohorts, evaluated a range of outcomes, including depression, neurotoxicity, neurodevelopment, behaviour, brain morphology, intelligence/cognition, memory and learning, mental and psychomotor development, motor function, nerve signalling, reactions and reflexes, speech and language outcomes. (Nineteen primary studies evaluated more than one outcome.) Three primary studies focused on adults (two of these on the relationship between MeHg and fish consumption in the postnatal period), and 28 primary studies focused on effects observed in childhood. The studies of adults did not observe relationships between MeHg exposures and neurological effects. The other 28 studies showed heterogenous results, with 11 reporting negative, unclear or inconsistent effects, and 17 indicating neurological effects associated with MeHg. After separating studies which included exposures to MeHg and other toxicants originating from eating marine mammals, freshwater fish, and/or other atypical exposures from those involving the consumption of ocean fish, the inconsistencies were reduced. Considering ocean fish separately, either no effects or beneficial outcomes were evident. In contrast, high MeHg exposures from consumption of marine mammals or freshwater fish from Se-poor areas were associated with subtle adverse effects.

The EFSA (2012) report did not reach conclusive findings regarding postnatal Hg exposure and neurological effects in childhood due to inconsistent results from the literature. In studies addressing neurotoxicity in adults, EFSA found no significant associations with low levels of MeHg exposure. The 2022 VKM report was a systematic review of 30 epidemiological studies, concluding that Hg exposures from fish had inconclusive relationships with autism and/or ADHD and with inhibitory control.

It is important to note that, in 2012, JECFA established a PTWI of MeHg of 1.6 µg/kg of body weight, based on data generated from early 2000. JECFA concluded that intakes above this PTWI would pose a risk of developmental neurotoxicity. However, fish consumption is not the only source of MeHg, and individuals may not reach the PTWI solely through the consumption of fish. Therefore, considering fish alone as a source of MeHg may not reflect the actual situation in terms of risk or benefits of fish consumption. Indeed, it is necessary to consider the combination of potential sources of MeHg that will add to the exposure from fish, whether from diet or other sources, and the corresponding health effects.

5.1.3.2 Cardiovascular outcomes

For cardiovascular outcomes, the Background Document reviewed four systematic reviews and four primary studies. Of the systematic reviews, one focused on blood pressure in children and adolescents, one on blood pressure and hypertension in adults, and the other two on various cardiovascular endpoints. One of the systematic reviews concluded that MeHg exposure was not associated with any cardiovascular risk, one concluded that the results were inconclusive, and the other two reported negative effects of MeHg only at levels exceeding hair concentrations of 2 µg/g. Among the primary studies, three focusing on adults and one focusing on children and adolescents, three showed no clear negative outcomes or showed inconsistent outcomes, while one identified a negative effect on cardiac autonomic function in children, though this was observed only for pre- and not post-natal exposure (Chan *et al.*, 2021).

The 2012 assessment by EFSA highlighted the potential importance of observations on MeHg exposure related to myocardial infarction, heart rate variability and possible blood pressure changes, but did not yield conclusive results. The 2022 VKM report emphasized the importance of considering the beneficial effects of fish consumption in the context of studying the association between MeHg and cardiovascular outcomes.

Based on the studies included for assessment in the Background Document, the expert consultation concluded that the evidence in relation to MeHg exposure and cardiovascular health outcomes is inconclusive. When MeHg exposures were limited to only those arising from ocean fish, no adverse effects were evident.

5.1.3.3 Growth

With regard to Hg exposure and growth outcomes, identified studies examined associations of prenatal Hg exposure with growth outcomes mainly at birth, although one evaluated postnatal growth. The Background Document included one systematic review on Hg and prenatal growth, which showed no strong evidence of an effect, but did find inverse associations with birth weight in populations with the highest mean Hg concentrations. Six primary studies found no consistent associations between prenatal Hg exposure and ultrasound or birth measures of growth. However, two studies found a small reduction in biparietal diameter in early to mid-pregnancy, but no associations with other growth parameters, and the only postnatal study found an association between the highest decile of Hg exposure and weight growth in girls.

The EFSA report generally also found null or isolated associations with growth outcomes, and the VKM report had overlapping findings (also summarized the Background Document).

Based on the studies included for assessment in the Background Document, the expert consultation considered the evidence in relation to MeHg exposure and growth outcomes to be inconclusive.

5.1.3.4 Other outcomes

In the category of "Other outcomes", the Background Document considered various health outcomes and included studies assessing associations between MeHg exposure from seafood and diabetes and metabolic syndrome, the immune system, reproduction, vision, osteoporosis, multiple sclerosis, hypertension and renal disease, thyroid hormones, pulmonary function, cancer and sexual maturation. Five systematic reviews and fifteen primary studies were included, with mixed results. Some found effects, while others did not reach a clear conclusion. EFSA's 2012 report indicated mixed results. The VKM report did not provide clear information on these other outcomes.

Based on the studies included for assessment in the Background Document, the expert consultation considered evidence regarding MeHg exposure and other outcomes to be limited and inconclusive.

5.1.4 CONCLUSIONS: TOXIC EFFECTS OF METHYLMERCURY

Based on the studies in the Background Document, the 2023 Expert Consultation concluded that the evidence regarding MeHg exposure and neurological health and growth outcomes is inconclusive for children when considering fish consumption only. The evidence indicates a limited but suggestive association between MeHg exposure and neurological health when considering all sources, but no specific association was found when considering only fish consumption. For cardiovascular health outcomes and other outcomes of interest, the evidence was inconclusive. These conclusions are summarized in **Table 11**.

TABLE 11. **FINAL WEIGHT OF EVIDENCE REGARDING ASSOCIATIONS BETWEEN MeHg AND NEUROLOGICAL, CARDIOVASCULAR, GROWTH AND OTHER OUTCOMES**

HEALTH OUTCOME	HEALTH EFFECTS OF MEHG BASED ON EVIDENCE FROM ALL SOURCES	HEALTH EFFECTS OF MEHG EXCLUSIVELY BASED ON OCEAN FISH EXPOSURES
Neurological outcomes	Limited, suggestive	Either no effects or beneficial effects were associated with increasing MeHg exposures in nearly all studies
Cardiovascular outcomes	Limited, no conclusion	No adverse effects associated with ocean fish MeHg
Growth	Limited, no conclusion	Limited, no conclusion
Other outcomes	Limited, no conclusion	Limited, no conclusion

5.2 THE ROLE OF SELENIUM IN THE HEALTH EFFECTS OF METHYLMERCURY

5.2.1 BACKGROUND

5.2.1.1 The importance of selenium and fish as a source of selenium

Selenium (Se) is a nutritionally essential trace element required for the synthesis of selenocysteine, the twenty-first genetically encoded amino acid (Chambers *et al.*, 1986). Selenoenzymes with critical roles in foetal brain development, growth, thyroid hormone metabolism, calcium regulation and prevention/reversal of oxidative damage in the brain and other tissues, employ selenocysteine in their active sites to perform their catalytic roles (Rayman, 2000; Taylor *et al.*, 2009; Ralston and Raymond, 2010; Ralston and Raymond, 2018).

Many metabolic processes depend on Se physiology, and disruptions of selenoenzyme metabolism are recognized as causative or contributing factors in increasing the incidence of diseases and clinical conditions (Rayman, 2000; Taylor *et al.*, 2009; Ralston and Raymond, 2010). A high Hg exposure is the only environmental insult known to induce a conditioned Se deficiency in the brain and impair the activities of essential selenoenzymes.

Selenium is effectively absorbed at the intestinal level from usual diets, with the Institute of Medicine of the United States of America (IOM, 2000) indicating over 90 percent absorption, and EFSA (2014) suggesting 70 percent absorption. The IOM advises a recommended daily allowance of 30 µg of Se for children between 4 and 8 years of age, 55 µg for individuals between 14 and 52 years of age, and 60 to 70 µg/day for pregnant and lactating women (IOM, 2000). EFSA (2014b), for its part, has set an adequate intake of 70 µg/day for adults (including pregnant women but not lactating women, for whom an adequate intake of 85 µg/day was set) and a range of 15 µg/day for children 1 to 3 years old to 70 µg/day for adolescents 15 to 17 years old.

Ocean fish and other seafoods are a valuable source of Se (Afonso *et al.*, 2019; USDA, 2019; EFSA, 2014a). Tissue concentrations of Se in ocean fish and other seafoods tend to vary depending on the species, geographic location and amounts of Se available in their local habitats. In contrast to MeHg, which can vary several orders of magnitude, concentrations of Se in fish and other seafoods are homeostatically modulated and typically vary less than a single order of magnitude; that is, between 10 and 100 µg/100 g (Afonso *et al*., 2014) or, in the case of pelagic ocean fish, between ~4.0 to ~20 µmole/kg, when reported in the recommended SI units (Ralston, Kaneko and Raymond, 2019). Furthermore, the Se obtained from eating fish is highly bioaccessible and bioavailable as it reaches the systemic circulation and is stored and available for use by the human body (Fox *et al.,* 2004; Cardoso *et al*., 2018; Afonso *et al.,* 2019). The variation in geologic distributions and availability of Se influences the amounts present in foods and freshwater fish, potentially predisposing for or protecting against potential risks of Hg exposures (Peterson *et al.*, 2009; Ralston, Kaneko and Raymond, 2019), as is explained in Section 5.2.1.2.

5.2.1.2 Interactions of methylmercury and selenium

MeHg and Se interact in a number of ways, each of which has implications for human health, in particular in relation to the consumption of fish, which can be a source of both MeHg and Se. MeHg has an extraordinarily high affinity for Se and high MeHg exposures can inhibit selenoenzyme activities (Ralston and Raymond, 2018; Spiller, 2018; Spiller, Hays and Casavant, 2021). Selenoenzymes have roles in foetal brain development, growth, thyroid hormone metabolism, calcium regulation, and in the prevention and/or reversal of oxidative damage in the brain and other tissues (Ralston and Raymond, 2010, 2018; Rayman, 2000; Taylor *et al.*, 2009). MeHg is a highly specific irreversible inhibitor of selenoenzymes that subsequently trap Se as HgSe, rendering it unavailable for further cycles of selenoenzyme synthesis (Moler-Madsen and Danscher, 1991; Moller-Madsen, 1990; Ralston and Raymond, 2018). The cellular dysfunctions that arise once Hg has disabled selenoenzymes, especially in brain regions requiring continual activities, can explain the signs and symptoms of MeHg toxicity (Ralston and Raymond, 2018; Raymond and Ralston, 2020; Spiller, 2018; Spiller, Hays and Casavant, 2021).

Research also indicates that Se is involved in decreasing Hg accumulation in lake fish. Se bioavailability in Hg-contaminated lakes is inversely related to the bioaccumulation of MeHg in fish (Paulsson and Lundbergh, 1989; Southworth, Peterson and Ryon, 2000; Southworth, Peterson and Turner, 1994; Turner and Rudd, 1983; Yang *et al.*, 2010). Due to the affinity of MeHg for Se, HgSe forms at each level of the aquatic food web. However, since it is not digestively absorbed, it is excreted and deposited in sediments. Therefore, higher levels of environmental Se increase HgSe formation in tissues of prey, resulting in increased deposition in sediments. This Se-dependent Hg retirement diminishes MeHg bioaccumulation in fish, whereas low Se availability accentuates MeHg bioaccumulation. Evidence for this effect has been reported in intervention studies (Paulsson and Lundbergh, 1989) and in natural experiments (Belzile *et al.*, 2006, 2009; Chen, Belzile and Gunn, 2001; Peterson *et al.*, 2009). Because physiological and environmental outcomes are proportional to Se:Hg molar ratios; Hg and Se must both be measured in exposure and health assessments.

Recognizing the interactions between MeHg and selenoenzyme synthesis and activities provides a consistent basis for understanding the impacts of MeHg toxicity and may explain discrepancies noted between the findings of various studies. The protective effect of Se with regard to MeHg toxicity was first recognized over 50 years ago (Pařízek and Ošťádalová, 1967), but recent awareness of the vital functions of Se in the brain and endocrine system has shed new light on the mechanisms of MeHg toxicity. Based on current understanding, the consequences of the effects of MeHg arise due to the inhibition of brain selenoenzyme synthesis and activities. Therefore, supplemental Se does not "protect against MeHg toxicity". Instead, the beneficial effects of additional dietary Se arise through the preservation of selenoenzyme activities and preventing loss of these activities due to MeHg. Although this may seem to only be a nuanced definition, it changes how MeHg toxicity is understood and directly impacts considerations regarding exposure risks and assessment. When brain Se concentrations remain sufficient to maintain Se metabolism, the adverse effects that would otherwise be associated with high MeHg exposures do not occur (Ralston and Raymond, 2018; Spiller, 2018; Spiller, Hays and Casavant, 2021).

In the marine food web, Se is typically far more abundant than MeHg, with only minor regional differences observed among fish of the same species collected in different regions of the world (Kaneko and Ralston, 2007; USDA, 2019). However, in freshwater fish, MeHg and Se levels can differ considerably depending on location (Turner and Rudd, 1983; Paulsson and Lindbergh, 1989; Southworth *et al*., 1994, 2000; Yang *et al*., 2010). The Se content of freshwater fish and fish from estuaries of rivers reflect Se availability in their respective watersheds. Waterbodies with low Se tend to exhibit greater MeHg accumulation because there is less HgSe formation at lower levels of the aquatic food web. As concentrations of HgSe approach or exceed a 1:1 molar ratio in fish, their consumption poses an increased risk of selenoenzyme hindrance, especially in regions where other food sources are also likely to be low in Se (Combs, 2001). For this reason, MeHg risk assessments should also consider the concentrations of Se in fish and/or blood samples of the exposed population.

5.2.2 APPROACH

This section is based on the findings presented in Chapter 6 of the Background Document on the role of Se with regard to the health effects of MeHg. The findings of the chapter were drawn from a systematic literature review conducted on 13 December 2021, in PubMed NCBI and Web of Science Core Collection, with no restrictions on time. After comparison with inclusion and exclusion criteria, removal of duplicate records, and risk-of-bias assessment, 45 human studies were included for further review. Additionally, 119 animal studies were identified and used for background information for mechanistic and biologically plausible evidence.

In the Background Document, the included studies are grouped according to the following outcomes: cardiovascular, oxidative stress, immune system, reproduction, thyroid hormones, prenatal somatic development, neurodevelopment/cognition, vision function, and motor function. A weight-of-evidence approach was used to determine a final grading of the available literature, following the WCRF guidelines. In the expert consultation, the effects of Se on the health effects of MeHg were further categorized into four main categories: neurological outcomes, cardiovascular outcomes, growth-related effects and other outcomes.

In addition to the evidence summarized in the next section (Section 5.2.3), it is worth noting that additional publications were identified in the Background Document that either did not study effects of Se on MeHg toxicity or did not show toxicity of Hg on the studied outcomes, and thus it was not possible to investigate the modification of MeHg toxicity by Se in those studies. As stated in the Background Document (FAO & WHO, 2024, p. 216), “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.” This might be of relevance since MeHg toxicity only occurs when exposures are high enough to compromise Se availability and impair brain selenoenzyme activities (Ralston and Raymond, 2018).

5.2.3 SUMMARY OF THE ROLE OF SELENIUM IN THE HEALTH EFFECTS OF METHYLMERCURY

5.2.3.1 Neurological outcomes

In the Background Document, the research on neurological outcomes is categorized into the areas of neurodevelopment and cognition, vision function and motor function.

When focusing on neurodevelopment and cognition, only human studies were identified for this assessment. Among these, there were five primary studies, all of which were cohort studies. Of these five studies, one reported an indirect positive effect of Se, while the other four did not find a protective effect of Se because MeHg exposures in those studies were too low to reduce Se availability, possibly because Se status was too consistent among the groups.

With regard to vision, the Background Document synthesized findings from four primary studies, all cross-sectional studies. Two of these studies found positive effects of Se counteracting Hg toxicity, while the other two did not. Outcomes and age groups studied varied across the studies. No animal studies were identified for this category.

For motor function, one cross-sectional study found that high plasma Se correlated positively with motor function outcomes, while Hg was a negative confounder. Furthermore, in mice, it was shown that MeHg causes a significant decrease in motor activity, which was reduced by selenomethionine co-exposure. Based on the human studies included in the assessment, the conclusion in the Background Document is that there was “limited evidence, no conclusion” for the effect of Se on Hg toxicity for neurological outcomes. On the same basis, the 2023 Expert Consultation also graded the evidence provided as “limited evidence, no conclusion”.

5.2.3.2 Cardiovascular outcomes

For cardiovascular outcomes, four primary studies were examined, including three cohort studies presented in four publications, and one cross-sectional study. Three studies (including one of the cohort studies) showed an effect of Se on reducing MeHg toxicity in cardiovascular outcomes.

Based on the systematic review, the Background Document indicates that there was "limited, suggestive evidence of a protective effect of Se on MeHg toxicity on cardiovascular outcomes." There were no animal studies identified for this outcome. Based on the human studies included in the Background Document, the 2023 Expert Consultation agreed that the evidence provided was "limited, suggestive", but also determined that, when limited to evidence from ocean fish studies, "protective effects" were noted.

5.2.3.3 Growth (birth outcome)

Regarding growth, which was referred to as "birth outcomes" in the Background Document, two primary studies were included. One cross-sectional study found a protective effect of Se against the negative association of Hg with birth weight and ponderal index; while the other, a large cohort study, found no protective effect of Se for a weak correlation of Hg with head circumference. No animal studies were identified for this outcome.

Based on the human studies included in the assessment, the evidence was graded "limited evidence, no conclusion" in the Background Document for the effect of Se on Hg toxicity for birth outcomes. The 2023 Expert Consultation agreed with this conclusion.

5.2.3.4 Other outcomes

Regarding other outcomes, the Background Document explored the effects of Se on MeHg toxicity in relation to oxidative stress, the immune system, reproduction and thyroid activity.

In the context of oxidative stress, five primary studies were reviewed, with one cross-sectional study showing a protective effect of Se on Hg toxicity, and the others showing indirect or less clear effects. As such, all the studies found some effect of Se on Hg toxicity regarding oxidative stress. Animal studies provided further corroboration of these findings on the outcome oxidative stress.

As to the immune system, two cross-sectional studies were included. One of them indicated a protective effect of Se on Hg toxicity, while the other did not. In addition, one animal study was identified that demonstrated antagonistic effects between Se and Hg, and another found a protective effect of Se administered by diet.

Similarly, for reproduction, two primary studies were examined, with one case-control study suggesting a protective effect of Se on fertility, while the other, a cross-sectional study, did not find any association between Se and semen parameters. There is some evidence from animal studies pointing towards a protective effect of Se on Hg toxicity in reproduction, but studied outcomes varied.

A single human study of MeHg effects on thyroid hormones found no effect of Se, and no animal studies of this outcome were included in the assessment.

For all the "other outcomes", the Background Document indicates that there was "limited evidence, no conclusion" for the effect of Se on MeHg toxicity. Based on the human studies included in the assessment in the Background Document, the 2023 Expert Consultation agreed and graded the evidence for the other outcomes as "limited, no conclusion".

The findings regarding the role of Se in the health effects of MeHg are summarized in **Table 12**.

TABLE 12. **BACKGROUND DOCUMENT FINDINGS FOR THE ROLE OF SELENIUM IN THE HEALTH EFFECTS OF METHYLMERCURY**

HEALTH OUTCOME	SE-DEPENDENT PROTECTION AGAINST MEHG EXPOSURES FROM ALL SOURCES	SE-DEPENDENT PROTECTION AGAINST MEHG EXPOSURES FROM OCEAN FISH
Cardiovascular outcomes	Limited, suggestive	Protective effects noted
Oxidative stress	Limited, no conclusion	Protective effects noted
Immune system	Limited, no conclusion	Limited, no conclusion
Reproduction	Limited, no conclusion	Limited, no conclusion
Thyroid hormones	Limited, no conclusion	Limited, no conclusion
Birth outcomes	Limited, no conclusion	Limited, no conclusion
Neurodevelopment and cognition	Limited, no conclusion	No adverse effects, benefits noted
Vision function	Limited, no conclusion	No studies of ocean fish effects
Motor function	Limited, no conclusion	No studies of ocean fish effects

5.3 ADDITIONAL REMARKS FROM THE EXPERT CONSULTATION ON THE ROLE OF SELENIUM WITH REGARD TO THE HEALTH EFFECTS OF METHYLMERCURY

The levels of Se in fish in relation to the effects of MeHg exposure were not considered in the 2010 Expert Consultation. Furthermore, several key studies that clarify the significance of selenoenzyme activities in the toxic effects of MeHg were not considered in the Background Document. These studies include quantum chemical assessments that explain why the affinity of Hg for Se is orders of magnitude higher than its affinity for sulphur (Dyrssen and Wedborg, 1991; Khan and Wang, 2009); studies that explain the toxicokinetic and toxicodynamic interactions between MeHg and Se in *in-vitro* (Seppänen *et al.*, 2004), cellular (Branco *et al.*, 2014; Carvalho *et al.*, 2008; Kleinschuster, Yoneyama and Sharma, 1983) and animal (El-Demerdash, 2001; Ganther *et al.*, 1972; Parizek *et al.*, 1971; Prohaska and Ganther, 1977; Ralston, Blackwell and Raymond, 2007a; Ralston and

Raymond, 2010) models; and tissue assessments demonstrating the binding between Hg and Se in the brains of people exposed to lethal amounts of Hg (Korbas *et al.*, 2010). In addition, animal studies that were also not considered in the Background Document demonstrate the effects of toxic amounts of MeHg, which are lethal when Se availability is limited but are without observable effects when dietary Se intakes are enriched to levels approximating those present in ocean fish (Ralston, Blackwell and Raymond, 2007a; Ralston and Raymond, 2010). Due to the method used in the Background Document to review the effects of Se on MeHg toxicity outcomes, these relevant studies, and possibly others, were excluded, and the evidence was graded “limited, no conclusion”.

The final literature review conducted for the Background Document on Se and MeHg included 45 articles (after exclusions), comprising 34 different studies (some studies were published in more than one article) from 12 countries in Asia, Europe, North America or South America (see **Appendix 6, Table A6.3** in the Background Document). Of the 45 studies, 23 were cohort studies, 6 were case-control studies, and 16 were cross-sectional studies. Although all the studies measured Se and Hg levels in different human tissues, 15 studies could not assess the potential effects of Se on Hg toxicity since they did not find any toxic effects of Hg on the investigated health outcomes. While these studies could not assess the effects of Se on Hg toxicity, they did demonstrate that selenium levels were sufficient to prevent any selenoenzyme impairments by MeHg.

Additionally, 30 peer-reviewed scientific articles describe studies in which the independent variables were the quantities of ocean fish consumed by mothers during pregnancy and the dependent variables were the neurodevelopmental outcomes observed in their children (Spiller *et al.*, 2023). These assessments collectively involved over 200 000 mother—child pairs, with fish consumption levels ranging up to more than 2.8 kg per week. A total of 52 beneficial outcomes were reported in 24 of these studies, and 28 of the studies found no adverse outcomes. Two studies reported a single adverse outcome, but the findings were inconsistent with each other and with the remaining 28 studies.

Considerations

Ocean fish tend to be richer in Se than in Hg (having a Se:Hg molar ratio higher than 1). As such, the findings of no observed adverse effects in the studies of the 30 peer-reviewed scientific articles conform with the expected outcomes (Ralston *et al.*, 2024). Those studies provide strong evidence in support of the expected finding that the rich levels of Se present in the fish were adequate to prevent adverse effects due to MeHg exposure, since the relatively small amounts of Hg compared to the amounts of Se were not sufficient to induce a conditioned Se deficiency.

Since most of the studies were not methodologically designed to measure the effects of MeHg on Se metabolism, a reassessment of current literature will need to be performed. Furthermore, since Se levels appear to be adequate in most of the study populations, there was little to no heterogeneity in Se status in relation to MeHg exposure, and no Se-dependent effects would be expected. In addition, numerous fish-consumption studies have been performed throughout the world assessing health outcomes at various MeHg exposure levels. Many include physiological and/or Se measurements in the data, and fish Hg and Se concentrations are often known or can be estimated by type or geographical location. Therefore, although assessments and conclusions may be made regarding the influence of MeHg on Se, due to the inclusion and exclusion criteria considered for the Background Document, relevant studies were omitted.

Other discrepancies are noted in the inclusion/exclusion process that could have affected the conclusions of the Background Document regarding Se and Hg. For instance, the Background Document includes the EFSA 2012 report, which includes consideration of the 14 years of data from the Faroe Islands, stating that the results consistently point to a detrimental effect of MeHg on some neurological outcomes. This study is the main cause of concern for MeHg exposures from fish consumption. However, in the Faroe Islands study, over 85 percent of the MeHg exposures were due to consumption of whale meat instead of ocean fish. Pilot whale is one of the rare few “seafoods” that contains a molar excess of Hg in relation to Se. Due to their long lives and status as apex marine predators, pilot whales accumulate all persistent bioaccumulative toxicants (PBTs) including cadmium and other notable Se-binding metals, as well as dioxins, PCBs, dl-PCBs and other organic agents that persist throughout the food web and contribute adverse effects that would arise concurrently with Hg exposures. The aggregate effects of PBT exposures will be highly correlated with the Hg “index”, which reflects total seafood intake. However, Hg itself may not be causing the adverse effects. Therefore, studies of ocean-fish-consuming populations must be considered in contrast to studies from the northern parts of Canada or the Faroe Islands where marine mammals are abundant sources of Hg and other PBTs in the diets. Similarly, in contrast to ocean fish, which tend to be Se-rich, freshwater fish contain variable amounts of Se, reflecting its availability in local soils. While most freshwater lakes and rivers of the world contain adequate amounts of Se, some regions are notably poor. The risk of adverse effects from high exposures to MeHg and other Se-binding electrophiles will be higher in Se-poor populations.

5.4 CONCLUSIONS AND RECOMMENDATIONS

5.4.1 CONCLUSIONS AND LIMITATIONS

For MeHg exposure and health outcomes from all sources of fish, the 2023 Expert Consultation concluded that the evidence provided was “limited, suggestive” for MeHg-related neurological health outcomes, and “limited, no conclusion” for cardiovascular health outcomes, growth and other health outcomes. For many of the health outcomes, especially in studies of children (except for neurological health outcomes), few studies were available in this assessment.

The expert consultation noted that numerous studies that would have provided pivotal information addressing the question of MeHg and Se interactions when consuming fish did not fit the criteria used in this systematic review, and thus were excluded from the literature review conducted for the Background Document. Among the evidence provided in these studies it is noted that there is heterogeneous evidence regarding associations of childhood MeHg exposure and neurological outcomes in childhood, possibly reflecting differences in study populations, including Se status. Articles in the Background Document that were excluded or graded as "Limited, no conclusion" could have provided evidence that the Se physiology of the study population was unaffected by MeHg exposures since ocean fish are rich in Se and improved, rather than diminished, Se:MeHg molar ratios.

Consumption of ocean fish rich in Se (with a Se:MeHg molar ratio greater than 1) prevents MeHg from inducing a conditioned Se deficiency, thus alleviating risks of MeHg toxicity. This paradigm also suggests that risks from high Hg exposures among subsistence freshwater-fish consumers will be accentuated in regions where environmental Se availability is low, resulting in a low Se:MeHg molar ratio. Although the number of human studies cited in this assessment were limited, those studies and evidence from animal studies indicate MeHg health effects from fish consumption will vary according to Se status and intake.

5.4.2 RECOMMENDATIONS

The 2023 Expert Consultation recommends that Member Nations:

> leverage existing efforts in their regions to overcome identified data and knowledge gaps, including, for instance, efforts to analyze the Se and Hg compositions of commonly consumed ocean fish, marine mammals and other seafood, as well as freshwater fish;

> strengthen ongoing monitoring of Hg levels in humans and seafood, which will be important to understand how exposures are changing over time;

> develop statistical models to describe and predict the variability of contamination in different species of fish, which can be used to assess contaminant exposures; and

> collect and report data in molar concentrations and harmonize using GEMS/Food guidelines for submission to the GEMS/Food database.

Despite heterogeneous evidence regarding the toxicity of prenatal and childhood exposure to MeHg, the expert consultation recommends against using individual toxicants found in seafood in developing risk–benefit guidance. Rather, the expert consultation supports the approach of considering seafood as a whole food, for which evidence demonstrates net benefits for many health outcomes.

CHAPTER 6

OCCURRENCE IN FISH OF MERCURY, METHYLMERCURY, DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS AND COMBINED SELENIUM/ MERCURY OCCURRENCE AND SELENIUM: METHYLMERCURY MOLAR RATIO

6.1 OCCURRENCE IN FISH OF MERCURY, METHYLMERCURY, DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

6.1.1 BACKGROUND

In addition to reviewing scientific literature on the risks and benefits of fish consumption, the 2010 Expert Consultation reviewed data on the levels of MeHg and dioxins in a range of fish species. It is interesting to note that one of the recommendations of the 2010 Expert Consultation was to develop, maintain and improve existing databases on specific nutrients and contaminants (particularly MeHg and dioxins) in fish consumed. The 2023 Expert Consultation noted that data on Hg and/or MeHg levels were available for 1 584 fish species in 2023 (defined by the scientific name, when possible, or by the common name) versus only 103 species in 2010, and that data on dioxin and dl-PCB levels were available for 161 fish species in 2023, versus only 80 fish species in 2010. Thus, the 2023 Expert Consultation concluded that there are now more comprehensive worldwide data that provide a better and more useful description of levels of contamination in fish per region.

6.1.2 APPROACH

To obtain new data published over the last 10 years (2011–2021) for the Background Document on the occurrence of Hg, MeHg, dioxins and dl-PCBs in fishery and aquaculture products, the IMR conducted a systematic literature search in the database Web of Science and extracted data from the public databases GEMS (WHO) and Chemical Monitoring Database (EFSA). Only published literature data with scientific names and FAO-area origin for fish species were considered for the analysis of the occurrence of the contaminants described in this section.

Concentration data on Hg, MeHg, dl-PCBs and dioxins were retrieved from the literature for diverse types of fish, molluscs and crustaceans. In total, 1 642 fish species were identified. These were grouped by family (n = 340) and order (n = 96), based on the following classification systems:

> for fishes: Eschmeyer’s Catalog of Fishes: Genera, Species, available at: http://researcharchive.calacademy.org/research/ichthyology/catalog/fishcatmain.asp (Fricke, R., Eschmeyer, W.N. and Van der Laan, R., 2023);

> for Mollusca and Crustacea: the World Register of Marine Species (WoRMS) Taxon Match Tool, available at: https://www.marinespecies.org/aphia.php?p=match (World Register of Marine Species, n.d.).

The levels of the above-mentioned contaminants were taken into account, considering the mean concentration of these chemical contaminants in fish reported by the identified literature. The number of samples for each species in the studies was not considered in estimating the mean concentration. Estimations of the levels were calculated considering the orders and families of the fish species; their origin, in terms of inland or marine FAO-areas; and the different types of habitats or combination of habitats: ocean, river, lake, estuary, river/lake/estuary, ocean/estuary, river/lake, river/ocean or unknown.

With regard to dioxins and dl-PCBs, although new toxic equivalency factors have been published (DeVito *et al.*, 2024), in this document, the levels were estimated with the previous TEFs set by WHO in 2005 (Van den Berg *et al.*, 2006).

6.1.3 SUMMARY OF THE OCCURRENCE OF MERCURY, METHYLMERCURY, DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS IN FISH

6.1.3.1 Mercury and methylmercury

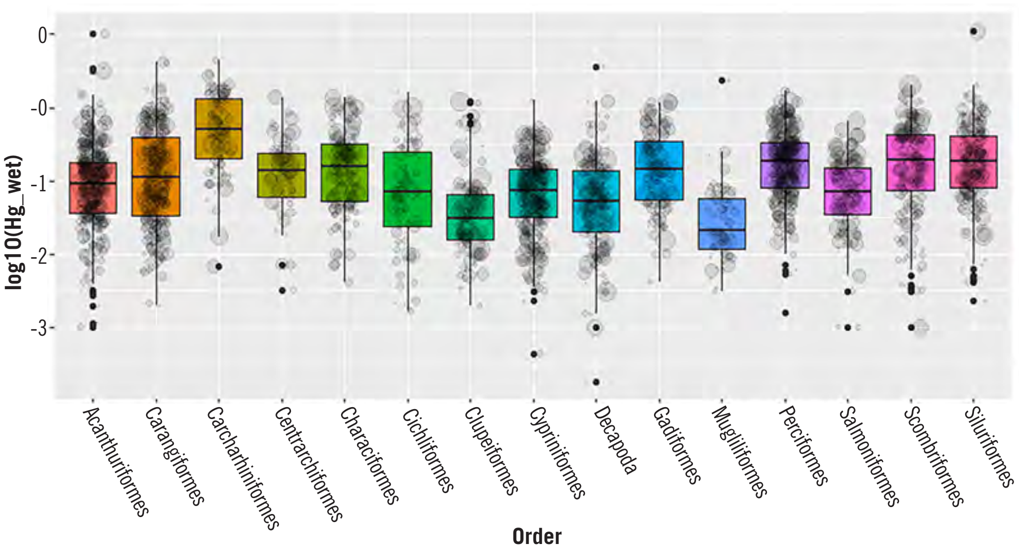
Summarized literature data for total Hg and MeHg were available from 513 articles. Most of them reported data on total Hg, adding up to a total sample number of 66 743, while only 69 articles reported results for MeHg, with a total sample number of 7 720. More than half the analysed fish were from marine waters (n = 31 440 for total Hg, and n = 4 819 for MeHg) compared to freshwaters (n = 23 718 for total Hg, and 2 138 for MeHg). In the Appendices section, Supplementary Material A1 gives information about the occurrence data from the literature. Supplementary materials A2, A3 and A4 give summarized levels of Hg and MeHg per family, order and order/region of fish from the literature, respectively.

Mercury

Fish species of the order Acanthuriformes were the most reported order quantifying the level of Hg, with 370 mean values. The mean concentration of Hg in this order was 0.2 mg/kg wet weight, but with large variability (median = 0.09 mg/kg wet weight, P2.5 = 0.005 mg/kg wet weight and P97.5 = 0.859 mg/kg wet weight). The most contaminated fish in this order were from the ocean/estuary (mean = 0.72 mg/kg wet weight, median = 0.01 mg/kg wet weight, P2.5 = 0.001 mg/kg wet weight and P97.5 = 6.597 mg/kg wet weight). The levels of Hg in the Acanthuriformes-order fish were highest in South America (mean = 0.38 mg/kg wet weight, n = 56), followed by Europe (mean = 0.33 mg/kg wet weight, n = 59) and North America (mean = 0.20 mg/kg wet weight, n = 75) (without considering habitat). In terms of the number of studies quantifying the levels of Hg in fish, the second most reported order (n = 292) was Cypriniformes (mean = 0.11 mg/kg wet weight, median = 0.07 mg/kg wet weight, P2.5 = 0.004 mg/kg wet weight and P97.5 = 0.43 mg/kg wet weight) with 79 different species identified within this order. The highest concentration of Hg in this order was found in the African region (0.28 mg/kg wet weight, n = 6).

The Cyprinidae family, which includes 37 species, is the most reported family when measuring the levels of Hg (n = 151, mean = 0.12 mg/kg wet weight, median = 0.07 mg/kg wet weight, P2.5 = 0.004 mg/kg wet weight and P97.5 = 0.44 mg/kg wet weight), with the most contaminated habitats being rivers and/or lakes.

FIGURE 2. **AVERAGE CONCENTRATIONS OF Hg BY ORDER OF FISH SPECIES IN MG/KG WET WEIGHT**

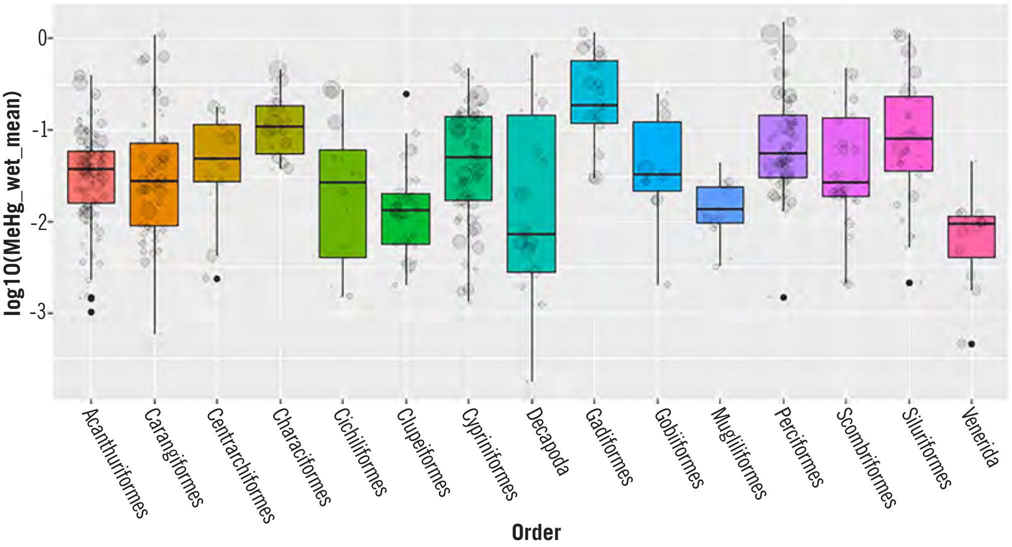


Notes: The size of the grey dots is proportional with the number of individual analyses in the study reported. Only orders with more than 50 mean values reported are represented.

Methylmercury

Carcharhiniformes were quantified as the most MeHg-contaminated order, with a mean level of 0.70 mg/kg wet weight from ten studies, corresponding to ten different species of fish (median = 0.16 mg/kg wet weight, P2.5 = 0.075 mg/kg wet weight and P97.5 = 2.886 mg/kg wet weight) and with the highest contamination in Europe (mean = 2.67 mg/kg wet weight, n = 2). As for Hg, the Acanthuriformes order was also the most reported order quantifying the level of MeHg, with 89 studies containing 66 different species. The mean concentration of MeHg in this order was 0.05 mg/kg wet weight (median = 0.04 mg/kg wet weight, P2.5 = 0.002 mg/kg wet weight and P97.5 = 0.249 mg/kg wet weight), with the highest levels being in North America (mean = 0.25 mg/kg wet weight, n = 3). When considering the habitat, Anguilliformes and Gadiformes orders from estuaries were the most contaminated fish order, with an average of 1 mg/kg wet weight of MeHg (in the case of *Anguilla Anguilla*, n = 2) and 0.9 mg/kg wet weight of MeHg (in the case of *Brosme brosme*, n = 3). This order was followed by Carcharhiniformes, Ophidiiformes and Trachichthyiformes from the ocean, with an average MeHg of 0.76 mg/kg wet weight (for *Scyliorhinus canicular, Galeus melastomus, Rhizoprionodon oligolinx, Scoliodon sorrakowah, Carcharhinus obscurus, Carcharhinus brachyurus, Cephaloscyllium umbratile, Mustelus manazo, Triakis scyllium*, n = 9), 0.46 mg/kg wet weight (for *Genypterus blacodes*, n = 1), and 0.43 mg/kg wet weight (for *Hoplostethus atlanticus*, n = 1).

FIGURE 3. **AVERAGE CONCENTRATIONS OF MeHg BY ORDER OF FISH SPECIES IN MG/KG WET WEIGHT**



Notes: The size of the grey dots is proportional with the number of analyses by study reported. Only orders with more than 10 mean values reported are represented.

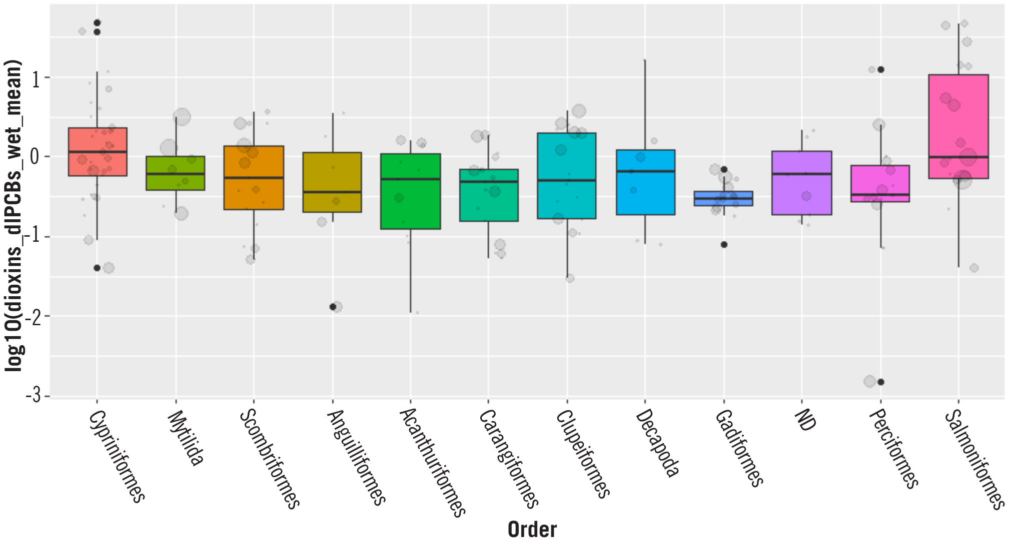
The Cyprinidae family is the most reported family when measuring the levels of MeHg (n = 36, mean = 0.08 mg/kg wet weight), followed by Sciaenidae (n = 28, mean = 0.04 mg/kg wet weight) and Leuciscidae (n = 21, mean = 0.12 mg/kg wet weight). Without considering the habitat, the Pentanchidae family were reported to have the highest levels of MeHg, with an average of 2.27 mg/kg wet weight. However, this was reported only by one study considering *Galeus melastomus*, from the ocean, with six analytical samples. This was followed by the Scyliorhinidae family, with an average concentration of 1.59 mg/kg wet weight, with large variability (percentile 2.5 = 0.183 mg/kg wet weight and percentile 97.5 = 2.991 mg/kg wet weight) from two studies with few samples each. Within this family, *Scyliorhinus canicula* had the highest concentration of MeHg (mean = 3.07 mg/kg wet weight from six samples), and *Cephaloscyllium umbratile* had the lowest concentration (0.11 mg/kg wet weight from one sample).

6.1.3.2 Dioxins and dl-PCBs

In the Appendices section, Supplementary Material A1 gives information about the occurrence data from the literature. Supplementary materials A2, A3 and A4 give summarized levels of dioxins and dl-PCBs per family, order and order/region of fish from the literature, respectively.

When considering dioxins and dl-PCBs together, the orders Cypriniformes (n = 33) and Salmoniformes (n = 18) were the most reported orders evaluated in the studies, with average concentrations of 4.55 and 9.14 ng TEQ/kg wet weight, respectively, with diverse levels of intra-order variability. Cypriniformes from Europe were the most reported (mean = 2.36 ng TEQ/kg wet weight, n = 26), followed by Scombriformes from Asia (0.56 ng TEQ/kg wet weight, n = 12).

FIGURE 4. **AVERAGE CONCENTRATIONS OF DIOXINS (PCDD/F) AND dl-PCBs BY ORDER OF FISH SPECIES IN NG TEQ/KG WET WEIGHT**



Notes: The size of the grey dots is proportional with the number of analyses by study reported. Only orders with more than five mean values reported are represented. ND: Order not determined.

The Salmonidae family, which includes seven species (*Onchorhynchus mykiss*, *Salmo salar*, *Salmo trutta*, *Salvelinus namaycush*, *Coregonus renke*, *Onchorhynchus masou* and *Onchorhynchus keta*), was the most reported family in the studies, with an average of 9.14 ng TEQ/kg wet weight (P2.5 = 0.117 ng TEQ/kg wet weight, P97.5 = 46.053 ng TEQ/kg wet weight) reported by 18 studies. It was also one of the most contaminated fish families (fourth position). The lake was the habitat where the Salmonidae family had the highest concentration (mean = 29.45 ng TEQ/kg wet weight, P2.5 = 13.736 ng TEQ/kg wet weight, P97.5 = 46.930 ng TEQ/kg wet weight) according to the results of five studies.

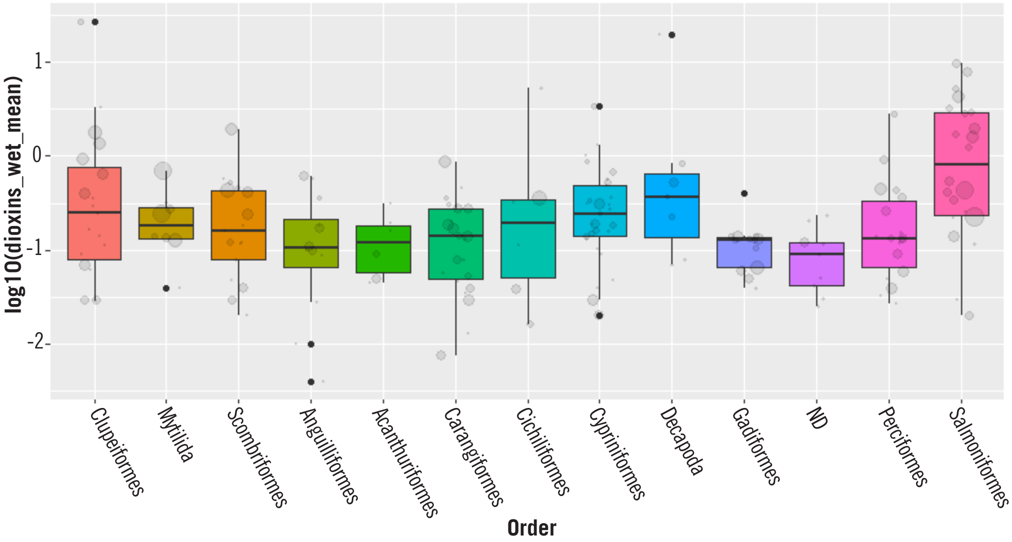
Dioxins

The most reported orders in the literature for dioxin contamination were Cypriniformes (n = 29), Carangiformes (n = 23) and Salmoniformes (n = 22), with mean values of dioxins of 0.43, 0.18 and 2.04 ng TEQ/kg wet weight, respectively.

The most contaminated order by dioxins (PCDD/F) reported was Elopiformes, corresponding to the Elopidae family, which includes the *Elops machnata* and *Elops hawaiensis* species, with an average level of dioxins of 110.06 ng TEQ/kg wet weight, but with large variability (median = 0.33 ng TEQ/kg wet weight, P2.5 = 0.242 ng TEQ/kg wet weight and P97.5 = 313,137 ng TEQ/kg wet weight). This was followed by the Gonorynchiformes order, specifically the *Chanos*

chanos species, with a mean of 27.68 ng TEQ/kg wet weight (n = 2) and by the Mugiliformes order, including the *Liza macrolepis* and *Mugil cephalus* species, with a mean of 14.81 ng TEQ/kg wet weight (n = 4). However, these levels of contamination must be taken with caution as the mean values were impacted by the high level of dioxins detected and reported in one study (Liao *et al.*, 2016), which collected analytical samples from a closed saltwater pond located at a former chloralkali factory. The results for the Cichlidae, Dorosomatidae and Portunidae families, corresponding to *Oreochromis mossambicus*, *Nematalosa come* and *Scylla serrata* species, respectively, may also be overestimated, as contamination levels were reported by the same study.

FIGURE 5. **AVERAGE CONCENTRATION OF DIOXINS (PCDD/F) BY ORDER OF FISH SPECIES IN NG TEQ/KG WET WEIGHT**

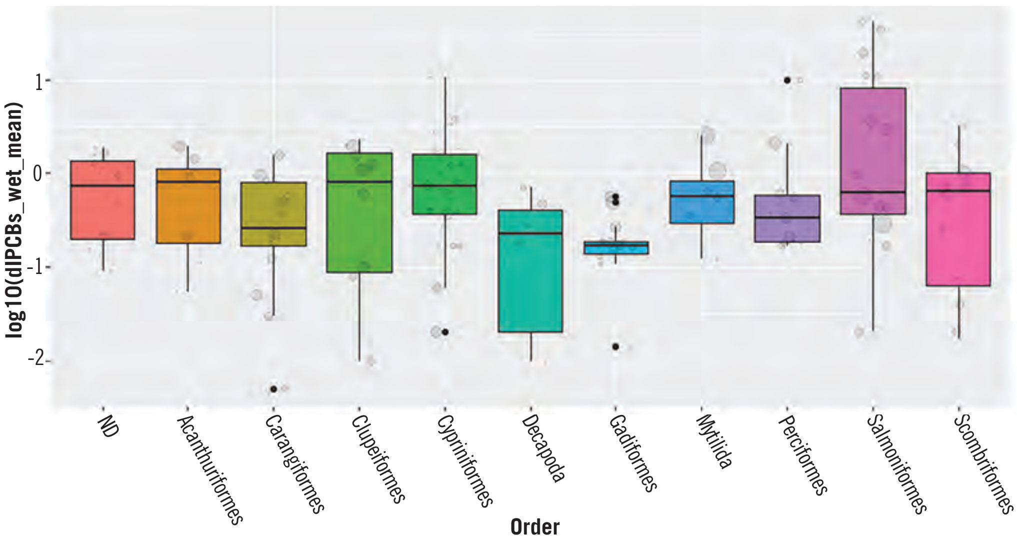


Notes: The size of the grey dots are proportional with the number of analyses by study reported. Only orders with more than five mean values reported are represented. ND: Order not determined.

Dioxin-like polychlorinated biphenyls

Within the 195 studies that quantified the level of dl-PCBs in fish, the most reported orders were Cypriniformes (n = 27), including nine species (*Squalius cephalus*, *Barbus barbus*, *Abramis brama*, *Leuciscus cephalus*, *Rutilus rutilus*, *Abramis bjoerkena*, *Misgurnus anguillicaudatus*, *Carassius carassius* and *Cyprinus carpio*), with 1.6 ng TEQ/kg wet weight of dl-PCBs. This was followed by the Salmoniformes order (n = 18), including seven species (*Coregonus renke*, *Onchorhynchus keta*, *Onchorhynchus masou*, *Onchorhynchus mykiss*, *Salmo salar*, *Salmo trutta* and *Salvelinus namaycush)*, with 7.17 ng TEQ/kg wet weight of dl-PCBs. Carangiformes (n = 17), including 14 species, was in the third position, with an average of 0.46 ng TEQ/kg wet weight of dl-PCBs.

FIGURE 6. **AVERAGE LEVELS OF dl-PCBs BY ORDER OF FISH SPECIES IN NG TEQ/KG WET WEIGHT**



Notes: The size of the grey dots is proportional with the number of analyses by study reported. Only orders with more than five mean values reported are represented. ND: Order not determined.

The Salmoniformes order was also the most contaminated order reported, with the highest levels of contamination originating from lakes. The mean value of contamination from this habitat was 23.62 ng TEQ/kg wet weight, quantified from five lakes in North America (median = 19.2 ng TEQ/kg wet weight, P2.5 = 10.81 ng TEQ/kg wet weight and P97.5 = 41.56 ng TEQ/kg wet weight). Only the *Salvelinus namaycush* species from Salmonidae family was included. From the same family, the other five species (*Onchorhynchus mykiss*, *Salmo salar*, *Salmo trutta*, *Coregonus renke*, *Onchorhynchus masou* and *Onchorhynchus keta*) had lower contamination levels, ranging between 0.02 and 3.59 ng TEQ/kg wet weight. These were followed by the Percidae family species, including *Perca fluviatilis*, *Stizostedion lucioperca* and *Sander vitreusand*, with a mean of 2.19 ng TEQ/kg wet weight (n = 5).

6.2 MERCURY/METHYLMERCURY AND SELENIUM OCCURRENCE IN FISH

6.2.1 BACKGROUND

Given the growing understanding of the role of selenium (Se) in the health effects of MeHg, this was considered by the 2023 Expert Consultation. (This was not included in the scope of the 2010 Expert Consultation nor in the Background Document.) In addition, 2023 Expert Consultation developed a database of around 10 580 analytical data on Hg/MeHg and Se content for 155 fish species.

6.2.2 APPROACH

As the data on Se content in fish was not included in the scope of the systematic review of the Background Document, the expert consultation used Hg, MeHg and Se data analysed in fish from the waters of Brazil (Cusack *et al.*, 2017; Lino *et al.*, 2018 and Alcala-Orozco *et al.*, 2020), New Zealand (GEMS/Food database), Norway (Azad *et al.*, 2019) and Portugal (Afonso *et al.*, 2019). Most of these data have been peer reviewed or are from accredited laboratories, so the mean values used to create the dataset (Appendix 1, **Table A1.1**) are considered of sufficient quality for this report. These databases provided information to create a set of around 10 580 analytical data on Hg, MeHg and Se in 155 different species of finfish, including their taxonomic identification at the species level.

Using the available data, the expert consultation proposed a matrix combining Hg/MeHg and Se content (**Table 13**) and Se:Hg/MeHg molar ratio (**Table 14**) for each fish species, which could serve as a communication tool for advising consumers on nutritional and safety aspects of fish consumption at the national or regional level. However, the expert consultation recommends that a more comprehensive data review be performed to analyse the composition of fish by drawing up a matrix to compare Se levels with MeHg levels.

TABLE 13. **CLASSIFICATION OF FISH SPECIES BY Se AND Hg/MeHg CONTENT**

		Se (MG/KG WET WEIGHT)				
		X ≤ 0.1	0.1 < X ≤ 0.2	0.2 < X ≤ 0.4	0.4 < X ≤ 0.6	X > 0.6
Hg/MeHg (MG/KG WET WEIGHT)	X ≤ 0.1		Common dentex, catfish, trout	Cod, horse mackerel, Atlantic mackerel, turbot, salmon, haddock, saithe, Atlantic cod, cutthroat trout, rainbow trout, black crappie, yellow perch, Chinook salmon, sole	Sardine, mackerel, blue whiting, Atlantic herring, chub mackerel, lemon sole, red cod, albacore tuna	Atlantic wolffish, mountain white fish
	0.1 < X ≤ 0.5		Skate, brown trout	Meagre, gilthead seabream, silver scabbardfish, hake, ray, seabass, anglerfish, plaice, pollock, walleye, smallmouth bass, white sturgeon	Tuna, European conger, redfish, Atlantic halibut, Greenland halibut, tusk, eel, hoki, snapper, trevally	Jack mackerel
	0.5 < X ≤ 1			Bluemouth rockfish, blue ling	Black scabbardfish	Ling
	1 < X ≤ 2			Blue shark	Swordfish	
	X > 2					

Note: Grey cells indicate higher risks due to Se:Hg/MeHg ratio <1.
Source: Prepared by authors based on Hg/MeHg and Se content in: Afonso *et al.*, 2019; Azad *et al.*, 2019; WHO, n.d.

Se:Hg/MeHg molar ratios above 1 are expected to counteract the risks of MeHg-dependent diminishments in Se availability and selenoenzyme activities associated with Hg toxicity. Whenever molar ratios are below 1, there is an increased risk of MeHg-dependent diminishments in Se availability and selenoenzyme activities (**Table 14**). Regarding Se:Hg/MeHg molar ratios, only a few species have values <1 (Appendix 1, **Table A1.1**).

TABLE 14. **Se:MeHg MOLAR RATIOS IN FISH SPECIES WITH DIFFERENT MeHg AND Se CONTENTS**

			Se (MG/KG WET WEIGHT)				
			$X \le 0.1$	$0.1 < X \le 0.2$	$0.2 < X \le 0.4$	$0.4 < X \le 0.6$	$X > 0.6$
		Median	0.05	0.15	0.3	0.5	1
Hg/MeHg (MG/KG WET WEIGHT)	$X \le 0.1$	0.05	3.2	9.5	19.1	31.8	63.6
	$0.1 < X \le 0.5$	0.3	0.5	1.6	3.2	5.3	10.6
	$0.5 < X \le 1$	0.75	0.2	0.6	1.3	2.1	4.2
	$1 < X \le 1$	1.5	0.1	0.3	0.6	1.1	2.1
	$X > 2$	2	0.1	0.2	0.5	0.8	1.6

Source: Prepared by authors based on Hg/MeHg and Se content in: Afonso *et al.*, 2019; Azad *et al.*, 2019; WHO, n.d.

CHAPTER 7

RESEARCH DATA GAPS

The 2023 Expert Consultation evaluated all the literature included in the five systematic literature reviews presented in the Background Document. This exercise highlighted a number of aspects that still need to be addressed to better understand the benefits of fish consumption as well as the risks associated with dioxins, dl-PCBs, Hg and MeHg, and the role of Se. The research needs and data gaps identified during the expert consultation are the following:

- Future research on health effects associated with fish-derived nutrients or contaminants should include an overall estimate for the association of fish intake with the health outcome of interest.
- The 2010 Expert Consultation and the Background Document did not consider the effects of culinary treatment or processing treatments and processing on MeHg bioavailability. Some original articles highlight culinary treatments that significantly change the bioavailability (or bioaccessibility) of Hg.
- Likewise, future research could consider the effects of food processing and preparation on nutrient and contaminant concentrations and bioavailability (or bioaccessibility) associated with fish consumption. This information could feed future risk and benefit assessments.
- To the extent possible, future research should differentiate the type of fish consumed, including species, source (for instance, freshwater vs marine, capture vs aquaculture), fatty vs lean, and geographic location of catch.
- Dose–response studies and meta-regression analyses, especially for outcomes with probable benefits, will help refine public health guidance regarding optimal amounts of fish consumption.
- More research is needed on factors that explain observed heterogeneity in health effects of fish consumption across the life course, for example overall diet quality, genetic polymorphisms and nutrient profiles of fish consumed, including the Se:Hg/HeHg molar ratio, particularly in populations at risk of Se deficiency.
- Further information is needed on contaminant and nutrient concentrations in fish. The expert consultation recommends future work to: (i) collect more data and reassess currently available data on fish species in regions where data are sparse; especially in freshwater fish; (ii) develop a statistical model to describe

and predict the variability of the level of contamination in different species of fish, which can be used at FAO-area or country level for risk–benefit assessment in a target population, to assess the level of exposure to contaminants in fish; (iii) collect data using harmonized guidelines and submit them to the Global Environment Monitoring System (GEMS) – Food Contamination Monitoring and Assessment Programme.

> Future studies should consider the aggregate impacts of fisheries depletion (resulting from capture fisheries) for planetary health effects, population health outcomes, etc. (in connection with SDG 14, SDG 2 and SDG 3) as well as the impact of climate change on the net risk or benefit of fish consumption (in connection with SDG 13, SDG 2 and SDG 3).

> Mechanisms of biological effects are a key piece of evidence that allows for refining the strength of evidence estimation. The expert consultation was limited in that a comprehensive evaluation of mechanistic studies (for instance, for marine omega-3 fatty acids in fish or effects of MeHg and other toxic agents on Se physiology) were not considered in the Background Document.

> Available contaminant occurrence data can be used in a future risk–benefit assessment. However, data may be incomplete in terms of regional representativeness and fish and seafood species included. The expert consultation also noted that available data only includes two contaminants, while other hazards (such as non-dl-PCBS, PFAS, PBDE and lead) may be of relevance.

> Healthy dietary patterns that include fish consumption and are established early in life could influence nutritional habits and health during adult life. There is also emerging, possible or probable evidence that fish consumption may reduce the risk of multiple other adverse health outcomes (such as anxiety and inflammatory disease). More cohort studies are needed to generate data among infants, young children and adolescents to derive a quantitative framework of the health risks and benefits of eating fish and its effects in the long term.

> Studies are lacking regarding the effects of dioxin and dl-PCB exposure from fish consumption on human health in general populations. The current evidence base is mainly from populations highly exposed because of occupational exposure or local contamination. As such, the expert consultation could not draw firm conclusions.

> Since observed health effects of MeHg exposures can be proportional to Se:Hg/MeHg molar ratios, future MeHg exposure assessments will need to consider both Hg and Se concentrations.

> To ensure that conclusions and recommendations are based on the best available scientific studies, the inclusion/exclusion criteria of the systematic reviews should be updated to separately consider the effects of Se:Hg/MeHg interactions in relation to ocean fish, in distinction from marine mammal, freshwater fish and other Hg sources.

> - Geological distributions of Se are highly variable and tend to be inversely related to MeHg bioaccumulation in freshwater fish. Therefore, future research should focus greater attention on subsistence freshwater-fish consumers living in Se-poor regions.
> - To address the questions of the effects on MeHg on Se metabolism, integration of information and data across different research disciplines is required.

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CHAPTER 8

CONCLUSIONS AND RECOMMENDATIONS

The assessment of the benefits and risks associated with the presence of dioxins, dl-PCBs, Hg and MeHg and the role of Se is complex, and the science surrounding it is still evolving. However, the 2023 Expert Consultation agreed on key conclusions and recommendations, which are presented in this chapter.

8.1 CONCLUSIONS

8.1.1 RISK AND BENEFIT APPROACH

> Various methods to assess the risk–benefit balance of fish consumption patterns are available.

> Existing studies show high heterogeneity in methods and metrics applied; nutrient, contaminant and health outcomes included; and fish and seafood species and products considered.

> There are large disparities in the availability of nationally and regionally relevant risk–benefit assessments of fish and seafood across the globe. Most studies are conducted for European and North American populations, while only few are available for other regions of the world.

> RBAs at regional, national or subnational levels are needed to assess the risk–benefit balance of fish and seafood consumption levels, considering local consumption habits, fish and seafood contamination levels and nutrient content, nutritional status of populations, cultural habits and demographics.

8.1.2 HEALTH BENEFITS FROM FISH CONSUMPTION

> Strong evidence exists for health benefits of total fish consumption during all life stages: pregnancy, childhood and adulthood. For example, beneficial associations are found for maternal consumption during pregnancy with selected birth outcomes, and for adult consumption with cardiovascular and neurological disease outcomes. This evidence for health benefits of total fish consumption

incorporates the effects of all nutrients and contaminants in fish on the studied outcomes, including nutrients and contaminants not specifically considered in the evidence review.

> Among the general population, few if any harms exist for total fish consumption.

> Benefits will vary depending on the overall diet and characteristics of consumers and of the fish consumed. For example, n-3 LCPUFA status, Se intake, exposure to other contaminants, food preparation methods, and individual susceptibility may modify health effects.

8.1.3 TOXIC EFFECTS OF DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

> Dietary exposure to dioxins and dl-PCBs comes from multiple different foods of animal origin, including fish. The contribution of fish consumption to these exposures will vary based on the region of residence and the amount, source and types of fish consumed.

> There is consistent evidence for an association between dioxin exposure and reduced semen quality, but not for sum dioxins and dl-PCBs. Exposure to total dioxins and dl-PCBs has been associated with altered sex ratio and weaker tooth enamel.

> In children, there was some evidence of association of dioxin and dl-PCB exposure with BMI z-scores, and increased TSH with prenatal high-level exposures. In adults, there was some evidence for associations of high exposure with cancer, cardiovascular effects and diabetes.

8.1.4 EFFECTS OF MeHg AND THE ROLE OF Se

> Based on the studies included in the Background Document, the 2023 Expert Consultation considered evidence in relation to MeHg exposure and neurological health and growth outcomes as inconclusive for children when considering exposure from fish solely. For adults, the evidence is conclusive of no association in relation to MeHg exposure, but inconclusive for neurological health, cardiovascular health outcomes and other outcomes of interest. However, when considering only ocean-fish studies, the adverse effects noted for neurological and cardiovascular outcomes were eliminated. Health effects clearly vary depending on overall diet, the characteristics of consumers and the types of fish and seafood consumed. For example, n-3 LCPUFA status, exposure to other contaminants, food preparation methods and individual susceptibility may modify health effects.

> The expert consultation noted that numerous studies that would have provided pivotal information addressing the question of MeHg and Se interactions when consuming fish did not meet the criteria of the systematic review. Among the evidence provided it is noted that there is heterogeneous evidence regarding associations of childhood MeHg exposure with neurological outcomes in childhood, possibly reflecting differences in study populations, including

Se status. Articles in the Background Document that were excluded or graded "Limited, no conclusion" could have provided evidence that the Se-physiology of the study population was unaffected by MeHg exposures, since ocean fish are rich in Se and, thus, improve rather than diminish Se:Hg/MeHg molar ratios.

- Consumption of ocean fish rich in Se (with a Se:Hg/MeHg molar ratio greater than 1) prevents MeHg from inducing a conditioned Se deficiency, thereby alleviating risks of MeHg toxicity. This paradigm also suggests that high Hg exposures among subsistence freshwater-fish consumers will be accentuated in regions where environmental Se availability is low, resulting in a low Se:Hg/MeHg molar ratio. Findings of human and animal studies indicate the health effects of MeHg exposures from fish consumption will vary according to Se status and intake.

8.2 RECOMMENDATIONS

8.2.1 RISK AND BENEFIT APPROACH

The 2023 Expert Consultation recommends that Member Nations:

- allocate resources to conduct national or regional risk–benefit assessments of fish that can account for dietary patterns, food availability, food contamination, cultural preferences and cooking practices, and relevant subpopulations;
- collect standardized data on fish and seafood contamination, nutrient content and food consumption representative at regional, national or subnational levels;
- create capacity for risk–benefit assessment, risk–benefit communication and knowledge translation for policymaking;
- leverage existing regional efforts to overcome identified data and knowledge gaps in Member Nations; for example, applying data from neighboring countries and involving experts in risk–benefit assessment;
- engage stakeholders and experts from multiple disciplines across food safety and nutrition, including toxicology, microbiology, nutrition and epidemiology; and
- integrate other aspects of fish consumption, such as environmental impacts and long-term sustainability, considering, for example, specific topics such as fish populations and sustainable fishing.

8.2.2 HEALTH BENEFITS FROM FISH CONSUMPTION

- The 2023 Expert Consultation considers that different subtypes of seafood differ in both nutritional components and contaminant burden. Thus, the expert consultation recommends that Member Nations consider the different seafood subtypes consumed in different settings when establishing local guidelines.

8.2.3 TOXIC EFFECTS OF DIOXINS AND DIOXIN-LIKE POLYCHLORINATED BIPHENYLS

- The 2023 Expert Consultation considers that there is a need for studies on the potentially adverse health effects of dioxins and dl-PCBs from fish consumption. There are several health outcomes that may especially merit further study in fish consumers, based on the hazard assessment for dioxins and dl-PCBs – in particular semen quality which, to date, is the most sensitive endpoint identified in humans. Thus, the expert consultation recommends that Member Nations engage with stakeholders to obtain this information.
- The expert consultation recommends that the JECFA update the health-based guidance values for dioxins and dl PCBs, taking into consideration new evidence and the updated WHO 2023 TEF values.

8.2.4 EFFECTS OF METHYLMERCURY AND THE ROLE OF SELENIUM

The 2023 Expert Consultation recommends that Member Nations:

- leverage existing efforts in their region to overcome identified data and knowledge gaps; for example, analyzing the Se and Hg compositions of commonly consumed ocean fish, marine mammals and other seafoods as well as freshwater fish in their regions;
- strengthen ongoing monitoring of Hg levels in humans and in seafood, which will be important to understand how exposures are changing over time;
- develop statistical models to describe and predict the variability of contamination in different species of fish, which can be used to assess contaminant exposures; and
- collect and report data in molar concentrations and harmonize it according to GEMS/Food guidelines for submission to the GEMS/Food database.

Despite heterogeneous evidence regarding the toxicity of prenatal and childhood exposure to MeHg, the 2023 Expert Consultation recommends against using individual toxicants found in seafood in developing risk–benefit guidance. Instead, the expert consultation supports the approach of considering seafood as a whole food, for which evidence demonstrates net benefits for many health outcomes.

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APPENDIX 1

SUPPLEMENTARY MATERIAL ON THE OCCURRENCE OF Hg, MeHg, Se AND Se:Hg/MeHg IN FISH

Supplementary material A1.1 Occurrence data of Hg and MeHg in fish from the literature based on the Background Document (FAO and WHO, 2024).

Supplementary material A1.2. Occurrence levels of contaminants per family of fish from the literature based on the Background Document (FAO and WHO, 2024).

Supplementary material A1.3 Occurrence levels of contaminants per order of fish from the literature based on the Background Document (FAO and WHO, 2024).

Supplementary material A1.4 Occurrence levels of contaminants per order of fish and per region from the literature based on the Background Document (FAO and WHO, 2024).

TABLE A1.1 **OCCURRENCE LEVELS OF MeHg, Hg AND Se AND Se:Hg/MeHg MOLAR RATIO IN FISH**

COMMON NAME	SCIENTIFIC NAME	N	MeHg (MG/KG)	Hg (MG/KG)	Se (MG/KG)	Se:Hg MOLAR RATIO
Albacore tuna	*Thunnus alalunga*	19	–	0.091±0.024	0.344±0.125	9.7
Anglerfish	*Lophius spp (Lophius piscatorius, Lophius budegassa e Lophius spp.)*	31*	0.31±0.19	–	0.30±0.11	2.5
Atlantic cod	*Gadus morhua*	2105	–	0.08±0.002	0.27±0.001	16.4±0.3
Atlantic halibut	*Hippoglossius hippoglossius*	53	–	0.31±0.037	0.46±0.013	12.1±1.3
Atlantic herring	*Clupea harengus*	1810	–	0.05±0.001	0.52±0.003	39.3±0.5
Atlantic mackerel	*Scomber scombrus*	7*	0.08±0.03	–	0.34±0.08	10.8
Atlantic wolffish	*Anarhichas spp.*	89	–	0.09±0.008	0.78±0.082	32.8±3.5
Black crappie	*Pomoxis nigromaculatus*	12	–	0.1 ± 0.02	0.35 ± 0.03	10.0 ± 4.0
Black scabbardfish	*Aphanopus carbo*	65*	0.71±0.27	–	0.44±0.08	1.6
Blue ling	*Molva dypterygia*	79	–	0.72±0.060	0.38±0.010	2.0±0.1
Blue shark	*Prionace glauca*	10*	1.35±0.70	–	0.30±0.04	0.6
Blue whiting	*Micromesistius poutassou*	75	–	0.04±0.003	0.48±0.011	41.6±2.0
Bluemouth rockfish	*Helicolenus dactylopterus*	10*	0.74±0.35	–	0.36±0.05	1.2
Brown trout	*Salmo trutta*	20	–	0.3 ± 0.07	0.99 ± 0.17	26.1 ± 17.6
Catfish	*Pangasius hypophthalmus/ Clarias gariepinus*	8*	0.03	–	0.10±0.04	8.4
Chinook salmon	*Oncorhynchus tshawytscha*	9	–	0.02 ± 0.001	0.23 ± 0.04	27.2 ± 12.2
Chub mackerel	*Scomber colias*	2*	0.09±0.10	–	0.34±0.01	10
Cod	*Gadus spp.(Gadus morhua e Gadus macrocephalus)*	52*	0.10±0.08	–	0.28±0.08	7.4
Common dentex	*Dentex dentex*	2*	0.05±0.02	–	0.15±0.06	7.7
Common ling	*Molva molva*	294	–	0.22±0.014	0.41±0.005	7.7±0.3
Cutthroat trout	*Oncorhynchus clarkii*	6	–	0.1 ± 0.03	0.21 ± 0.05	7.2 ± 6.7
Eel	*Anguilla dieffenbachii*	5	–	0.21±0.11	0.508±0.139	6.1
European conger	*Conger conger*	1*	0.11±0.03	–	0.42	1.3
European eel	*Anguilla anguilla*	185	–	0.11±0.006	0.30±0.010	11.2±0.8
European hake	*Merluccius merluccius*	92	–	0.19±0.034	0.34±0.004	5.4±0.3
Gilthead seabream	*Sparus aurata*	37*	0.13±0.09	–	0.33±0.12	6.4
Greenland halibut	*Reinhardtiushippo glossoides*	546	–	0.14±0.004	0.42±0.009	10.2±0.3
Haddock	*Melanogrammus aeglefinus*	245	–	0.07±0.004	0.32±0.005	17.3±0.7
Hake	*Merluccius spp (Merluccius merluccius, Merluccius capensis e Merluccius gayi)*	107*	0.12±0.08	–	0.26±0.07	5.7
Hake	*Merluccius australis*	10	–	0.156±0.03	0.366±0.05	6
Hoki	*Macruronus novaezelandiae*	20	–	0.141±0.034	0.447±0.071	8.1
Horse mackerel	*Trachurus trachurus*	11*	0.06±0.04	–	0.35	14.6
Jack mackerel	*Trachurus novaezelandiae +Trachurus declivis*	20	–	0.385±0.097	0.602±0.072	4
Lemon sole	*Pelotretis flavilatus*	10	–	0.073±0.021	0.532±0.057	18.5
Ling	*Genypterus blacodes*	20	–	0.706±0.206	0.796±0.12	2.9
Mackerel	*Scomber Scombrus*	1042	–	0.04±0.001	0.55±0.003	43.3±0.7
Meagre	*Argyrosomus regius*	15*	0.12±0.05	–	0.27±0.05	5.7
Mountain whitefish	*Prosopium williamsoni*	20	–	0.1 ± 0.03	0.84 ± 0.15	10.7 ± 3.9

TABLE A1.1 **OCCURRENCE LEVELS OF MeHg, Hg AND Se AND Se:Hg/MeHg MOLAR RATIO IN FISH (continued)**

COMMON NAME	SCIENTIFIC NAME	N	MeHg (MG/KG)	Hg (MG/KG)	Se (MG/KG)	Se:Hg MOLAR RATIO
New Zealand sole	*Peltorhamphus novaezeelandiae*	10	–	0.083±0.066	0.265±0.046	8.1
Plaice	*Pleuronectes platessa*	198	–	0.06±0.004	0.38±0.009	23.2±0.9
Pollack	*Pollachius pollachius*	58	–	0.14±0.008	0.38±0.007	8.1±0.5
Rainbow trout	*Oncorhynchus mykiss*	12	–	0.1 ± 0.01	0.36 ± 0.04	11.3 ± 5.4
Ray	*Raja spp.*	10*	0.17±0.09	–	0.29±0.05	4.2
Red cod	*Pseduophycis bachus*	20	–	0.068±0.02	0.412±0.039	15.4
Redfish	*Sebastes spp.*	185	–	0.13±0.10	0.56±0.007	22.9±1.4
Saithe	*Pollacius virens*	439	–	0.07±0.003	0.29±0.002	16.9±0.5
Salmon	*Salmo salar/Oncorhynchus gorbuscha*	46*	0.02±0.02	–	0.23±0.07	24.3
Sardine	*Sardina pilchardus*	366*	0.02±0.02	–	0.46±0.46	58.4
Seabass	*Dicentrarchus labrax*	37*	0.11±0.03	–	0.32±0.16	7.5
Silver scabbardfish	*Lepidopus caudatus*	10*	0.40±0.26	–	0.37±0.07	2.4
Skate	*Amblyraja georgiana, Dipturus innominatus, Zearaja nasuta*	10		0.429±0.155	0.178±0.035	1.1
Smallmouth bass	*Micropterus dolomieu*	95	–	0.2 ± 0.02	0.39 ± 0.05	4.8 ± 2.9
Snapper	*Pagrus auratus*	20	–	0.149±0.048	0.47±0.087	8
Sole	*Solea solea*	8*	0.04±0.02	–	0.18±0.04	11.6
Swordfish	*Xiphias glaudius*	23*	1.21±0.80	–	0.44±0.06	0.9
Trevally	*Pseudocaranx dentex*	20	–	0.114±0.11	0.344±0.064	7.6
Trout	*Salmo trutta/Oncorhynchus mykiss*	7*	0.07±0.05	–	0.19±0.07	6.8
Tuna	*Thunnus spp.*	108*	0.37±0.21	–	0.55±0.15	3.8
Turbot	*Psetta maxima*	17*	0.06±0.02	–	0.37±0.10	15.6
Tusk	*Brosme brosme*	943	–	0.44±0.017	0.49±0.004	5.1±0.1
Walleye	*Sander vitreus*	10	–	0.3 ± 0.06	0.37 ± 0.04	3.8 ± 1.1
White sturgeon	*Acipenser transmontanus*	32	–	0.1 ± 0.01	0.30 ± 0.02	8.4 ± 3.2
Yellow perch	*Perca flavescens*	43	–	0.06 ± 0.01	0.43 ± 0.03	24.9 ± 14.6
Bocachico	*Prochilodus magdalenae*	17	–	0.049 ± 0.007	0.223 ± 0.021	11.56
Ratón / Piau	*Leporinus agassizii*	2	–	0.054 ± 0.024	0. 216 ± 0.045	10.16
Sábalo / Matrinchão	*Brycon melanopterus*	3	–	0.023 ± 0.0009	0.0283 ± 0.015	3.13
Suckermouth catfish	*Hypostomus plecostomus*	21	–	0.055 ± 0.010	0.131 ± 0.017	6.05
Granulated catfish	*Pterodoras granulosus*	5	–	0.095±0.003	0.0324±0.019	0.87
Cachegua / Matacaimán	*Centrochir crocodili*	3	–	0.140±0.037	0.298±0.064	5.41
Palometa	*Mylossoma duriventre*	8	–	0.046±0.008	0.0471±0.018	2.60
Atipa	*Hoplosternum littorale*	2	–	0.140±0.110	0.210±0.015	3.81
Mojarra	*Caquetaia kraussii*	2	–	0.490±0.200	0.344±0.056	1.78
Zamurito	*Calophysus macropterus*	2	–	0.360±0.084	0.423±0.115	2.98
Aimara	*Hoplerythrinus unitaeniatus*	10	–	0.120±0.020	0.252±0.025	5.33
Trahira	*Hoplias malabaricus*	5	–	0.120±0.020	0.305±0.061	6.46
Porthole shovelnose catfish	*Hemisorubim platyrhynchos*	2	–	0.630±0.047	0.251±0.094	1.01
Biara	*Rhaphiodon vulpinus*	9	–	0.880±0.130	0.197±0.025	0.57

TABLE A1.1 **OCCURRENCE LEVELS OF MeHg, Hg AND Se AND Se:Hg/MeHg MOLAR RATIO IN FISH (continued)**

COMMON NAME	SCIENTIFIC NAME	N	MeHg (MG/KG)	Hg (MG/KG)	Se (MG/KG)	Se:Hg MOLAR RATIO
Tiger sorubim	*Pseudoplatystoma tigrinum*	2	–	0.920 ± 0.087	0.102 ± 0.048	0.28
Kissing prochilodus	*Semaprochilodus insignis*	15	–	0.08 ± 0.02	0.27 ± 0.05	8.83 ± 3.01
Aracu	*Schizodon vittatus*	4	–	0.09 ± 0.01	0.27 ± 0.02	7.87 ± 0.89
Pacu	*Mylesinus schomburgkii*	4	–	0.04 ± 0.01	0.15 ± 0.05	10.2 ± 4.14
Threespot leporinus	*Leporinus friderici*	3	–	0.12 ± 0.02	0.28 ± 0.11	5.87 ± 1.01
Sardina	*Rhytiodus sp.*	3	–	0.18 ± 0.01	0.32 ± 0.09	4.59 ± 0.12
Elongate hatchetfish	*Triportheus elongatus*	5	–	0.05 ± 0.01	0.30 ± 0.01	15.1 ± 3.24
Acaratinga	*Geophagus proximus*	3	–	0.12 ± 0.02	0.19 ± 0.04	3.93 ± 0.91
Porthole shovelnose catfish	*Hemisorubim platyrhynchos*	3	–	0.49 ± 0.13	0.28 ± 0.13	1.47 ± 0.12
White piranha	*Serrasalmus calmoni*	3	–	0.40 ± 0.10	0.13 ± 0.10	0.82 ± 0.08
South American silver croaker	*Plagioscion squamosissimus*	3	–	1.51 ± 0.54	0.28 ± 0.01	0.47 ± 0.01
Tucunaré	*Cichla monoculus*	5	–	0.74 ± 0.14	0.18 ± 0.03	0.61 ± 0.01
Branquinha cascuda	*Psectrogaster rutiloides*	4	–	0.20 ± 0.14	0.28 ± 0.10	4.14 ± 1.61
Sailfin pimeloid	*Leiarius marmoratus*	6	–	0.11 ± 0.03	0.22 ± 0.12	5.27 ± 2.75
Mapará	*Hypophthalmus marginatus*	6	–	0.26 ± 0.03	0.27 ± 0.13	2.59 ± 0.93
South American silver croaker	*Plagioscion squamosissimus*	7	–	0.91 ± 0.18	0.21 ± 0.04	0.61 ± 0.16
Tucunaré	*Cichla monoculus*	7	–	0.61 ± 0.13	0.05 ± 0.04	0.18 ± 0.10
Tucunaré pleiozona	*Cichla pleiozona*	3	–	0.63 ± 0.11	3.47 ± 0.85	0.28 ± 0.05
Sábalo cola roja / Matrinxa	*Brycon cephalus*	4	–	0.37 ± 0.01	0.21 ± 0.03	1.43 ± 0.24
Black prochilodus	*Prochilodus nigricans*	4	–	0.19 ± 0.02	0.32 ± 0.02	4.33 ± 0.07
Highwaterman catfish	*Hypophthalmus edentatus*	4	–	0.34 ± 0.01	0.19 ± 0.01	1.45 ± 0.06
Sábalo cola roja / Matrinxa	*Brycon cephalus*	7	–	0.29 ± 0.07	0.17 ± 0.05	1.45 ± 0.21
Pirapitinga	*Piaractus brachypomus*	4	–	0.03 ± 0.01	0.19 ± 0.12	19.1 ± 17.3
Cachama	*Colossoma macropomum*	4	–	0.04 ± 0.01	0.05 ± 0.02	4.26 ± 3.18
Silver prochilodus	*Semaprochilodus taeniurus*	6	–	0.13 ± 0.03	0.16 ± 0.01	3.31 ± 0.89
Aracu	*Schizodon fasciatus*	8	–	0.11 ± 0.06	0.19 ± 0.07	5.46 ± 2.53
Barred sorubim	*Pseudoplatystoma fasciatum*	4	–	0.78 ± 0.05	0.41 ± 0.04	1.35 ± 0.21

Note: *As MeHg and Se were analysed in a different number of samples, the values shown correspond to the minimum number of fish samples that were analysed.
Source: Prepared by authors based on Hg/MeHg and Se content in: Afonso *et al.*, 2019; Azad *et al.*, 2019; Alcala-Orozco *et al.*, 2020; Lino *et al.*, 2018; WHO, n.d.

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JOINT FAO/WHO EXPERT CONSULTATION ON THE RISKS AND BENEFITS OF FISH CONSUMPTION

ROME, 9–13 OCTOBER 2023

MEETING REPORT

Evolving science and debate concerning the benefits and risks of consuming fish have resulted in confusion over the years, and national and international food safety agencies have recognized the need to provide useful, clear and relevant information in this regard to consumers. In October 2023, FAO and WHO held the second Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption to analyse new scientific evidence on the matter and draw relevant conclusions and recommendations. The overall conclusions of the exercise show that consuming fish provides energy, protein and a range of other nutrients important for health, and that there are benefits related to fish consumption during all life stages (pregnancy, childhood and adulthood). General population studies show that the benefits and individual effects of fish consumption vary depending on overall diet, the characteristics of consumers, and the fish that is consumed.

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