Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet

From the Scientific Committee of the Norwegian Scientific Committee for Food and Environment
From the Norwegian Scientific Committee for Food and Environment (VKM) 2020

Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet

The Steering Committee of the Norwegian Scientific Committee for Food and Environment 11.02.2020

ISBN: 978-82-8259-335-9
Norwegian Scientific Committee for Food and Environment (VKM)
Po 4404 Nydalen
N – 0403 Oslo
Norway

Phone: +47 21 62 28 00
Email: vkm@vkm.no

vkm.no
vkm.no/english

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Preparation of the opinion

A project group prepared this protocol for the risk-benefit assessment of fish in the Norwegian diet. The project group consisted of one VKM member from the Steering Committee/the Panel on Contaminants, three VKM members from the Panel on Nutrition, Dietetic Products, Novel Food and Allergy, two VKM members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics, seven external experts, and four employees of the VKM secretariat. The Steering Committee of the Norwegian Scientific Committee for Food and Environment evaluated and approved the protocol drafted by the project group.

Assessed and approved

The protocol was drafted by (in alphabetical order):

Lene Frost Andersen – Chair of the project group and vice-chair of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Affiliation: 1) VKM; 2) University of Oslo

Paula Berstad – Member of the project group. Affiliation: Cancer Registry of Norway

Monica Carlsen – Member of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) University of Oslo

Lisbeth Dahl – Member of the project group and member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Affiliation: 1) VKM; 2) Institute of Marine Research, Bergen

Anders Goksøyr – Member of the project group. Affiliation: University of Bergen

Helle Katrine Knutsen – Member of the project group, chair of the Panel on Contaminants, and member of the Steering Committee. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

Ingrid Kvestad – Member of the project group. Affiliation: NORCE Norwegian Research Centre AS

Inger Therese Laugsand Lillegaard – VKM secretariat and member of the project group. Affiliation: VKM

Bente Mangschou – VKM secretariat and member of the project group. Affiliation: VKM

Haakon E. Meyer – Member of the project group. Affiliation: Norwegian Institute of Public Health
Maarten Nauta – Member of the project group. Affiliation: Technical University of Denmark (DTU)

Kirsten E. Rakkestad – VKM secretariat and project leader. Affiliation: VKM

Josef Daniel Rasinger – Member of the project group and member of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Affiliation: 1) VKM; 2) Institute of Marine Research

Guri Skeie – Member of the project group. Affiliation: University of Tromsø – The Arctic University of Norway

Jostein Starrfelt – VKM secretariat and member of the project group. Affiliation: VKM

Sofie Thomsen – Member of the project group. Affiliation: Technical University of Denmark (DTU)

Stine Ulven – Member of the project group and member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy in VKM. Affiliation: 1) VKM; 2) University of Oslo, Department of Nutrition, Institute of Basic Medical sciences.

Members of the Steering Committee of the Norwegian Scientific Committee for Food and Environment that contributed to and approved the protocol:

In addition to Helle Katrine Knutsen, these were (in alphabetical order before chair/vice-chairs of the Committee):

Angelika Agdestein – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VK

Johanna Bodin – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health

Edel Elvevoll – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) University of Tromsø

Dag O. Hessen – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) University of Oslo

Trine Husøy – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health.

Åshild Krogdahl – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian University of Life Sciences

Asbjørn Magne Nilsen – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian University of Science and Technology

Taran Skjerdal – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian Veterinary Institute.
Inger-Lise Steffensen – Chair of the project group and member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian Institute of Public Health.

Tor A. Strand – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Centre for International Health, University of Bergen; 3) Innlandet Hospital Trust

Gaute Velle – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norce Norwegian Research Centre; 3) University of Bergen

Yngvild Wasteson – Member of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Norwegian University of Life Sciences

Jan Alexander – Chair of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Retired, former Norwegian Institute of Public Health; 3) Norwegian Veterinary Institute

Gro-Ingunn Hemre – Vice-chair of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) Institute of Marine Research

Vigdis Vandvik – Vice-chair of the Scientific Steering Committee in VKM. Affiliation: 1) VKM; 2) University of Bergen.

Acknowledgment

VKM would like to thank the librarians Trude Anine Muggerud and Ragnhild Agathe Tornes (Norwegian Institute of Public Health) for assistance with the literature search.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.
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Abbreviations and acronyms

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMSTAR</td>
<td>A MeaSurement Tool to Assess systematic Reviews</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylhydroxytolueen</td>
</tr>
<tr>
<td>bw</td>
<td>Body weight</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
</tr>
<tr>
<td>DHA</td>
<td>Docosahexaensyre</td>
</tr>
<tr>
<td>DRV</td>
<td>Dietary reference values</td>
</tr>
<tr>
<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EPA</td>
<td>Eikosapentaensyre</td>
</tr>
<tr>
<td>HBGV</td>
<td>Health based guidance value</td>
</tr>
<tr>
<td>IMR</td>
<td>Institute of Marine Research</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>KBS</td>
<td>Nutritional calculation software (kostberegningsystem)</td>
</tr>
<tr>
<td>LOD</td>
<td>Limit of detection</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
</tr>
<tr>
<td>MeHg</td>
<td>Methyl mercury</td>
</tr>
<tr>
<td>ML</td>
<td>maximum level</td>
</tr>
<tr>
<td>NAM</td>
<td>National Academy of Medicine</td>
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<tr>
<td>NDH</td>
<td>Norwegian Directorate of Health</td>
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<tr>
<td>NFSA</td>
<td>Norwegian Food Safety Authority</td>
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<tr>
<td>NIFES</td>
<td>National Institute of Nutrition and Seafood Research</td>
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<tr>
<td>NNR</td>
<td>Nordic Nutrition Recommendations</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>-------------</td>
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<tr>
<td>OHAT</td>
<td>Office of Health Assessment and Translation</td>
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<tr>
<td>OIM</td>
<td>Observed Individual Means</td>
</tr>
<tr>
<td>PCB</td>
<td>Polychlorinated biphenyl</td>
</tr>
<tr>
<td>PFAS</td>
<td>Perfluoroalkyl substances</td>
</tr>
<tr>
<td>PreventADALL</td>
<td>Preventing Atopic Dermatitis and ALLergies</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RA</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>RBA</td>
<td>Risk-benefit assessment</td>
</tr>
<tr>
<td>RBQ</td>
<td>Risk-benefit question</td>
</tr>
<tr>
<td>TEF</td>
<td>Toxic equivalency factor</td>
</tr>
<tr>
<td>ToR</td>
<td>Terms of reference</td>
</tr>
<tr>
<td>VKM</td>
<td>Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø)</td>
</tr>
<tr>
<td>WoE</td>
<td>Weight of evidence</td>
</tr>
<tr>
<td>WCRF</td>
<td>World Cancer Research Fund</td>
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Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet
1 The request from the Norwegian Food Safety Authority

1.1 Background

Fish contain nutrients that are positive for our health. At the same time, it contains varying levels of undesirable substances that can have a negative effect on health. Undesirable substances can be found in different levels in most types of food. A risk-benefit assessment assesses both the nutrients and the undesirable substances and evaluate if it in total gives a more positive effect to eat certain foodstuff than not, and possibly how much one should eat to achieve optimal use of the positive health effects.

A risk-benefit assessment of fish has been conducted two times earlier by the Norwegian Scientific Committee for Food and Environment (VKM). The reports were published in 2006 and 2014. In 2006 VKM pointed out that consumption of fish had positive effects on public health, especially because of the content of polyunsaturated fatty acids and vitamin D. VKM also found that mainly mercury, dioxins and dioxin-like-PCBs posed a potential risk when consuming fish in Norway. In 2014, VKM concluded that the health benefits by eating fish clearly outweighed the risk of negative health effects from the exposure to undesirable substances from fish (VKM, 2014). According to the committee, it was well documented that fish protect against cardiovascular disease. Further on, in the assessment VKM concluded that fish contribute to a positive development of the neural system in the foetus and in breastfed infants, and that they can miss out on these effects if the mother does not eat enough fish (i.e. less than one dinner portion per week).

The role of the Norwegian Food Safety Authority (NFSA) is to warn the population against foods that can contain too high levels of substances that can give negative health effects. In addition, the NFSA contributes in the work to develop regulations and maximum levels (MLs) for contaminants in foodstuffs, which also is a means to protect the population. The Norwegian Directorate of Health (NDH) gives advice on diet that describes what one should eat to get the best possible health effects from our diet.

After 2014, several new data relevant for a risk-benefit assessment of fish, has become available. The Institute of Marine Research (IMR) has on commission from NFSA and others collected occurrence data for undesirable substances and nutrients in fish species that we did not have sufficient data on in earlier assessments. The Department of Nutrition at the University of Oslo has, in collaboration with the Norwegian Institute of Public Health (NIPH), NDH and NFSA, completed diet studies of children and adolescents (4-, 9-, and 13-year-olds) in 2015-2016. In addition to more data available, the general knowledge has also increased. Several tolerable weekly intakes (TWIs) for undesirable substances have been revised by EFSA. The most important ones were published in 2018 and are summarised below:
In November 2018, EFSA published a new risk assessment of the substance group dioxins and dioxin-like-PCBs in food and feed (EFSA et al., 2018b). In this assessment, EFSA concluded that the tolerable weekly intake level for this substance group should be lowered from 14 to 2 pg/kg body weight/week. The new tolerable intake protects against reduced sperm concentration. In the assessment EFSA also suggested that the WHO-TEF-value (which describes the relative toxicity of the substances in the group compared with the most toxic substance of dioxins, 2,3,7,8-TCDD) for PCB-126 probably is too high and should be revised. A revision will probably take at least one year. It is therefore important that the risk-benefit assessment in fish can adjust to possible new WHO-TEF-values.

In December 2018, EFSA published a risk assessment of the perfluoroalkylated substances, PFOS and PFOA in food (EFSA et al., 2018a). Also, in this assessment EFSA concluded that the health-based guidance values should be lowered for both substances. For PFOS the TWI level was lowered from 1050 to 13 ng/kg body weight/week. The new TWI protects against risk of increased cholesterol in adults, and reduced effect of vaccines in children. For PFOA, the TWI was reduced from 10500 to 6 ng/kg body weight/week. The new tolerable intake protects against increased cholesterol. The conclusions in the assessment are provisional until a second assessment of other PFAS is ready. It is therefore important that the risk-benefit assessment of fish in the Norwegian diet can be adjusted to possible changes in the PFAS TWI when the second assessment is published.

With regard to the new knowledge available, NFSA suggest that there is a need for a new risk-benefit assessment of fish in the Norwegian diet.

1.2 Terms of reference (ToR)

The Norwegian Food Safety Authority (NFSA) asks the Norwegian Scientific Committee for Food and Environment (VKM) to conduct a risk-benefit assessment for fish consumption in the Norwegian diet. In the assignment we ask VKM to answer the following questions:

Which health consequences will it have for the Norwegian population if they:

- Continue with the same consumption levels as of today
- Increase the consumption of fish to match the recommendations given by the Norwegian Directorate of Health (NDH)¹

¹ “Eat fish for dinner two to three times a week. Use also fish as a bread spread. The advice equals 300-450 grams of fish filets each week. A minimum of 200 grams should be fatty fish like salmon, trout, mackerel or herring. Six portions of fish used as bread spread equals approximately one dinner portion.” Matportalen.no 09.04.19
- Reduces the consumption of fish and replaces parts or all of it with other foods in the diet

VKM decides which substances and scenarios that should be included to conduct a relevant risk-benefit assessment of fish consumption. The decisions need to be justified in the assessment. The assessment of dioxins and dioxin-like-PCBs must be done in a manner that allow for later adjustments if/when the toxic equivalency factor (TEF) values is revised. Perfluoroalkylated substances (PFAS) should also be assessed in a manner that makes it possible to adjust the assessment to new health-based guidance values (tolerable intakes\(^2\)).

Data gaps and insufficient data (e.g. too high limit of quantification, LOQ) should be made visible in the assessment; this information will be useful for planning future data collection.

### 1.3 Scope of the protocol

This protocol will describe how the project group intends to answer the two first questions of the ToR. How the project group intends to answer the 3rd question of the ToR, related to substitution of fish with other foods in the diet, will not be covered in this protocol. The reason for this limitation is merely the time frame of the project. The project group has not had time to discuss how to approach the substitution of fish with other foods in the diet, and prioritised to get started with the first part of the ToR.

The protocol has been developed with the aim of being open and transparent about the risk-benefit assessment (RBA) process, the choices that are made, and the limitations and restrictions that are set.

This is done by defining the strategy for data collection (i.e. which data to use for the assessment, and how to identify and select them), and presenting the criteria that will be applied for inclusion or exclusion of compounds and health effects in the assessment. In addition, some compounds that are pre-decided to be included are listed here, together with the reasoning for their inclusion.

Due to the limited time available, the project group has already performed a literature search for fish consumption and a defined set of health outcomes. How the search was performed, as well as how we have identified and chosen health outcomes, is thoroughly described in this protocol.

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\(^2\) Tolerable intake (which is a health-based guidance value) describes the maximum intake of substances in food, such as nutrients or contaminants, that can be consumed daily or weekly over a lifetime without risking adverse health effects.
How we intend to appraise the relevant evidence, and to analyse and integrate the evidence in order to draw conclusions that will form the basis for the Scientific Opinion, are described in brief.
2 Problem formulation

2.1 Objectives

The overall aim is to weigh the risks and benefits associated with fish consumption. See Figure 2.1-1 for a schematic view of the process. The sub-objectives will be to:

1. Identify and characterise adverse and beneficial health effects related to eating fish, i.e;
   a. Identify relevant adverse and beneficial health effects associated with consumption of fish as such
      i. Evaluate the quality of scientific evidence for the associations through a systematic literature search, and a weight of evidence (WoE) approach
      ii. Characterise the adverse and beneficial effects, if possible describe dose-response relationships
   b. Identify relevant contaminants where fish is an important contributor to the total dietary exposure
      i. Identify relevant adverse health effects associated with exposure to the relevant contaminants from fish and fish products
      ii. Evaluate the quality of scientific evidence for the associations
      iii. Characterise the adverse effects, if possible describe dose-response relationships
   c. Identify relevant micro- and macronutrients where fish is an important contributor to the total dietary exposure
      i. Identify relevant beneficial health effects associated with intake of the nutrients from fish and fish products
      ii. Evaluate the quality of scientific evidence for the associations
      iii. Characterise the beneficial effects, if possible describe dose-response relationships
      iv. 
   
2. Calculate fish consumption and exposure to contaminants and nutrients identified in sub-objective 1.b and 1.c, using the various scenarios;
   a. The Norwegian population continue with the same fish consumption levels as of today
   b. The Norwegian population increase the consumption of fish to match the recommendations given by the Norwegian Directorate of Health (NDH)\(^3\)

3. Perform a risk characterisation
4. Perform a benefit characterisation
5. Perform a risk-benefit comparison/integration
6. Identify and describe uncertainties and knowledge gaps

\(^3\) “Eat fish for dinner two to three times a week. Use also fish as a bread spread. The advice equals 300-450 grams of fish filets each week. A minimum of 200 grams should be fatty fish like salmon, trout, mackerel or herring. Six portions of fish used as bread spread equals approximately one dinner portion”. Matportalen.no, 09.04.19.
2.2 Target population

The target population is the general Norwegian population, both sexes, including children, adolescents, and adults.

2.3 Limitations

The risk-benefit assessment of fish will be based on the intake estimates of fish as such, including all intake of fish, from fish filet and fish products (like fish cakes, fish fingers, fish gratin etc), and in addition the exposures of selected contaminants and nutrients found in fish. The assessment will *not* cover the consumption of other seafood, fish oils or other marine oils.

Levels of both nutrients and contaminants in fish vary between fat and lean fish, between species, and there may be geographical differences. Geographical differences will not be
specifically addressed⁴, whereas type and species of fish will be taken into consideration. Foodborne pathogens will not be covered in the risk assessment.

⁴ NFSA provide specific warnings for fish from areas with high levels of contaminants
3 Identification and characterisation of health effects

To make a risk-benefit assessment of fish in the Norwegian diet, the adverse and beneficial health effects related to eating fish, and selected nutrient and contaminants from fish (see above), needs to be identified and characterised.

The following sections describe how VKM plan to identify and characterise health effects associated with fish consumption, how to select nutrients and contaminants, and how to identify health effects from the selected nutrients and contaminants.

3.1 Identification and characterisation of health effects associated with fish consumption

Fish consumption is linked to a variety of different health effects. The health outcomes from fish consumption to be included in this RBA have already been identified in a separate step, as described below, before a systematic literature search for associations and effect estimates were performed. An evaluation of the quality of the scientific evidence for associations and effect estimates will be performed using a WoE approach. The included health effects will be characterised, and if possible, dose-response relationships will be identified.

In the following the process is described in more detail.

3.1.1 Identification of relevant health outcomes to include in the search

The project group discussed if it was possible to perform an open search for all health outcomes and fish intake, but concluded that this would be too comprehensive since the literature search would be overwhelming. The project group therefore proceeded to identifying relevant health outcomes to include in the search. These are:

- The most widespread non-communicable diseases in the Norwegian population
- Health outcomes with a well-established association to fish intake
- Health outcomes with a well-established association to compounds, both contaminants and nutrients, found in fish

World Cancer Research Fund (WCRF) did a high quality updated report on fish consumption and all type of cancers in 2018 (see Appendix 1), and it was decided by the project group that we will use information from this report in the RBA, and not include cancer as an outcome in our search (WCRF/AICR, 2018).
Health outcomes with a well-established association to fish were identified from published systematic reviews and meta-analyses, as well as previously published national and international risk-benefit assessments of fish (from VKM and EFSA).

Health outcomes associated with contaminants in fish were identified from relevant national and international science based assessments that had performed systematic literature searches (risk assessments from EFSA). Health outcomes associated with nutrients were identified from published systematic reviews and meta-analyses. The inclusion and exclusion of compounds and related health outcomes are further described in Chapter 3.2 and 3.3.

To check if there were any systematic literature reviews available that were thorough enough to replace our own search for fish consumption and the chosen outcomes, a search for ‘fish consumption’ and ‘systematic reviews’ or ‘meta-analyses’ was performed in Medline and Embase. This search was performed on November 25, 2019. It was limited in time to the years 2015-2019. This search for reviews and meta-analyses resulted in 246 hits. None of these were considered “fit for purpose”, and hence a new search was performed as planned.

3.1.2 Systematic literature search

Librarians at the NIPH performed a first literature search on November 25, 2019. This search was performed in the Medline, Embase, and PsychInfo databases, and resulted in 21,857 unique hits. Updated and/or additional searches may be performed later if needed.

To identify search terms and text words for the relevant health outcomes, VKM used the project group’s expertise, and when needed, counselled other experts.

A systematic approach is used for the selection of papers/studies from the literature search. Screening of titles and abstracts are performed in a pairwise blinded manner using Rayyan (Ouzzani et al., 2016). The screening is performed against pre-defined inclusion/exclusion criteria. These criteria are given in Table 3.1.2-1 below.

After the first round of screening, the blinding is removed, and the reviewers can discuss conflicting decisions. If the two reviewers are unable to reach an agreement, the paper in question shall be included. If two articles are published from the same cohort data, but in different follow-up durations, the article with the longest follow-up study shall be used.

The potentially relevant papers selected via the screening procedure based on title and abstract will be reviewed in full text.
### Criteria for Inclusion

- Studies investigating fish intake in relation to one or more health outcomes that was included in the systematic search
- **Study designs:**
  - Prospective observational studies, such as: Cohort studies, Case-cohort studies, Nested case-control studies, Case-control studies
  - Experimental studies, such as: Randomised Controlled Trials (RCTs), Controlled clinical trials (CCTs), Controlled before-and-after studies (CBAs)
- **Population:** general population, all age groups. Including the following patient groups:
  - Diabetes type 2
  - Obesity
  - Musculoskeletal disorders
- **Publication type:** original papers
- **Other:** fish intake needs to be measured at individual level, effect estimates must be given. Studies on secondary prevention should be included

### Criteria for Exclusion

- Studies investigating fish intake without any relation to the specific health outcomes included in the search
- Studies investigating exposure to supplements (omega 3/fish oil/vitamin D)
- **Dietary pattern-studies**
- **Publication types:**
  - reviews
  - case histories
  - letters to editors
  - book chapters
  - posters
  - abstracts
- **Population:** specific patient groups (see include for exceptions)
- **Study designs:**
  - Cross sectional studies
  - Animal model studies
  - In vitro-studies
3.1.3 Quality assessment/assessment of internal validity (risk of bias)

All the included full text papers/studies will be graded in a three-category rating system considering quality and internal validity. The rating system will be based on an existing, well recognised tool, i.e. either the tool developed for Nordic Nutrition Recommendations (NNR) or the OHAT tool (Nordiska ministerrådet, 2014; NTP, 2015). The chosen tool will be adjusted, optimised and fitted for our purpose.

The review of the full text papers and the methodological quality assessment will be conducted independently by two reviewers. Disagreement on the final quality rating of a paper will be resolved by consensus.

Only papers graded in one of the two upper categories in the quality assessment will be included in the further process. Papers graded in the lowest category will be excluded from this RBA.

3.1.4 Data extraction

For the papers that pass the quality assessment, a systematic data extraction will be done.

The exact parameters to extract will be agreed by the project group in connection with the data extraction. Extracted data will typically include several aspects related to

i) study characteristics (e.g. country, type of study, number of cases and controls or number of cohorts, year study ended, etc.)

ii) study population (e.g. ethnicity-, gender- and age composition, proportion smokers, proportion response rate/loss-to-follow-up, etc.)

iii) exposure (see also chapter 4 below for more details on exposure assessment)

iv) outcome ( e.g. determination of outcome – self-report, registry, medical records, mean/median, covariates adjusted, precision of the effect estimate, etc.)

3.1.5 Weight of Evidence (WoE) assessment

After the quality assessment, and the extraction of data, an overall assessment of the weight of evidence for the associations between fish intake and a health effects will be performed.

The weighing of the evidence will follow either the guidelines described by WCRF or the OHAT guideline (NTP, 2019; WCRF/AICR, 2018). The chosen WoE-process will be adjusted, optimised and fitted for our purpose.
The overall grading following the WCRF-protocol are summarised in: 1) convincing (strong), 2) probable (strong), 3) limited suggestive, 4) limited no conclusion, or 5) substantial effect on risk unlikely (strong evidence). This system, and how it was used for cancer, is shown in Appendix I. The equivalent overall grading following OHAT is 1) high level of evidence, 2) moderate level of evidence, 3) low level of evidence, 4) inadequate evidence, or 5) evidence of no health effect. For a description of the OHAT, see NTP, 2019.

Only effects for which the total body of evidence (across studies) is rated in one of the first categories will be included in a refined RBA. It will be attempted to establish dose-response curves for these effects, see Chapter 6 for further description of the process.

3.1.6 Characterisation of the adverse and beneficial health effects

Dose-response relationships for selected adverse and beneficial health effects from fish consumption will be derived, when possible. If dose-response relationships can not be derived, reference points for toxicity or nutritional sufficiency will be described.

3.2 Identification of relevant contaminants

The project group has defined general inclusion/exclusion criteria of contaminants that may be included in the RBA. These criteria are given in Table 3.2-1

<table>
<thead>
<tr>
<th>Criteria for inclusion</th>
<th>Criteria for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fish is an important source for exposure AND</td>
<td>• Fish is not an important source for exposure</td>
</tr>
<tr>
<td>• Exposure in Norway may be above health based guidance values as described in previous risk assessments</td>
<td>• Exposure is clearly below health based guidance values</td>
</tr>
<tr>
<td>• Given in the mandate</td>
<td>• Insufficient data (hazard and/or exposure) to conclude on risk</td>
</tr>
</tbody>
</table>

Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet
Contaminants will be considered for inclusion, based on a decision process outlined in Figure 3.2-1. The final list of compounds to be included will be presented in the final opinion. All other contaminants that are considered for inclusion, but are excluded, will be listed with a given reasoning for exclusion in the final opinion.

**Figure 3.2-1** Flow chart describing decision process for inclusion or exclusion of candidate contaminants for the risk-benefit assessment (RBA) of fish in the Norwegian diet. HBGV: health based guidance value, MOE: margin of exposure.

Three contaminants that are to be included have already been identified. These are listed in Table 3.2-2 with the reasons for inclusion.
Table 3.2-2  Contaminants that will be included in the assessment, and the reasons for including them.

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Reasons for inclusion</th>
<th>Reference(s)</th>
</tr>
</thead>
</table>
| Dioxins and dl-PCB| • Given in the mandate  
• Fish is an important source for exposure  
• New health-based guidance values (tolerable intakes) from EFSA, and exposure in Norway may be above the new health based guidance value (HBGV) | (EFSA et al., 2018b)              |
| PFAS              | • Given in the mandate  
• Fish is an important source for exposure  
• New health-based guidance values (tolerable intakes) from EFSA*, and exposure in Norway may be above the new HBGV | (EFSA et al., 2018a)              |
| MeHg              | • Fish is an important source for exposure  
• Exposure in Norway may be above health based guidance values as described in previous risk assessments                                                                                                     | (EFSA, 2012; EFSA, 2015; VKM, 2014; VKM et al., 2019) |

*) Preliminary TWI for PFOS and PFOA, awaiting final PFAS report

### 3.2.1 Identification of health effects associated with the included contaminants

The purpose of identification of health effects related to the included contaminants was, in step one; to identify relevant search terms and text words for the search strategy for fish consumption (see section 3.1.1). In step two; the effects to include in the RBA will be characterised, and dose-response relationships identified where possible.

Table 3.2.1-1 shows criteria for inclusion/exclusion of health effects related to the included contaminants.
Table 3.2.1-1 Criteria for inclusion or exclusion of health effects for the contaminants.

<table>
<thead>
<tr>
<th>Criteria for inclusion of health effects</th>
<th>Criteria for exclusion of health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Health effect considered causal or critical in previous risk assessment</td>
<td>• Effect not likely/described for doses relevant for fish consumption (i.e. effect occurs at higher doses)</td>
</tr>
<tr>
<td>• Intermediate endpoints are included only if evidence is good and consistent both for association between compound and intermediate endpoint as well as for an association between intermediate endpoint and disease</td>
<td>• Intermediate endpoints are excluded if consistent evidence is lacking either for association between compound and intermediate endpoint or for an association between intermediate endpoint and disease</td>
</tr>
</tbody>
</table>

Health effects from contaminants for step one were identified from relevant national and international science based assessments that had performed systematic literature searches (Risk assessments from EFSA). The same approach will be used for step two. Hence, VKM will not perform their own literature searches, unless previous risk assessments are clearly outdated.

3.3 Identification of relevant micro- and macronutrients

The project group has defined general inclusion/exclusion criteria for nutrients that may be included in the RBA. These criteria are given in Table 3.3-1. Evidence for beneficial health effects will be based on previous risk-benefit assessments, and updated systematic reviews and meta-analyses. The final list of nutrients to be included will be presented in the final opinion. All other nutrients that are considered for inclusion according to the criteria in Table 3.3-1, but are excluded, will be listed with a given reasoning for exclusion in the final opinion.

Table 3.3-1 Criteria for inclusion or exclusion of nutrients.

<table>
<thead>
<tr>
<th>Criteria for inclusion</th>
<th>Criteria for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fish is an important source for exposure AND • Good and consistent evidence exists for a beneficial health effect</td>
<td>• Fish is not an important source for exposure • Lack of evidence for beneficial health effect and/or exposure</td>
</tr>
</tbody>
</table>

Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet
Two nutrients have already been identified that are to be included. These are listed in Table 3.3-2 with the reasons for inclusion.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Reasons for inclusion</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA/EPA</td>
<td>Fish is one of the most important sources for exposure</td>
<td>(Totland et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Alexander et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Good and consistent evidence exists for several health effects: CHD, preterm birth and birth weight</td>
<td>(Balk et al., 2016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Wan et al., 2017)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Aung et al., 2018)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Middleton et al., 2018)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Fish is one of the most important sources for exposure</td>
<td>(Totland et al., 2012)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NNR, 2012)</td>
</tr>
<tr>
<td></td>
<td>Good and consistent evidence exists for several health effects: bone health, mortality</td>
<td>(IOM, 2011)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Yao et al., 2019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Bjelakovic et al., 2014)</td>
</tr>
</tbody>
</table>

### 3.3.1 Identification of health effects associated with included nutrients

The purpose of identification of health effects related to the included nutrients was, as for the contaminants, in step one; to identify relevant search terms and text words for use in the search strategy for fish consumption (see section 3.1.1). In step two; the project group will characterise the effects, and identify dose-response relationships where possible, to include in the RBA.

Table 3.3.1-1 shows criteria for inclusion/exclusion of health effects related to the included nutrients.
Health effects associated with the selected nutrients are identified from published systematic reviews or meta-analyses. VKM will not perform a systematic search on each nutrient.

For step one, to identify relevant outcomes for use in the search strategy for fish consumption, it was essential to include all potentially important health outcomes. Therefore, both outcomes with less consistent evidence and good and consistent evidence were included in this step.

For step two, to identify health outcomes to include in the RBA, with good and consistent evidence for associations to the relevant nutrients, the project group will search for, and only include, high quality systematic reviews/meta-analysis. For some intermediate endpoints (see Table 3.3.1-1), Clinical Trials (ClinicalTrials.gov) may also be a source for good and consistent evidence. Data from Clinical Trials will be considered when relevant. The quality of the reviews/meta-analysis will be judged using AMSTAR 2 (Shea et al., 2017).

The overall grade of evidence will decide which health effects to include in the present RBA. I.e., only health effects where the overall evidence is graded as convincing or probable will be included. For the grading we will use either the guidelines described by WCRF or the OHAT guideline.

Table 3.3.1-1 Criteria for inclusion or exclusion of health effects for the included nutrients.

<table>
<thead>
<tr>
<th>Criteria for inclusion of health effects</th>
<th>Criteria for exclusion of health effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evidence for an effect between nutrient and health outcome is good and consistent</td>
<td>• Evidence for an association/effect is limited or inconsistent</td>
</tr>
<tr>
<td>• Source of evidence: Systematic reviews or meta-analyses published in one of the following (or equivalent): Cochrane Database, NNR, IOM/NAM; OR assessment published by EFSA or VKM</td>
<td>• Association/Effect not likely/described for doses relevant for fish consumption (i.e. effect occurs only at higher doses)</td>
</tr>
<tr>
<td>• Intermediate endpoints are included only if evidence is good and consistent both for association between compound and intermediate endpoint as well as for an association between intermediate endpoint and disease</td>
<td>• Intermediate endpoints are excluded if consistent evidence is lacking either for association between compound and intermediate endpoint or for an association between intermediate endpoint and disease</td>
</tr>
</tbody>
</table>
4 Exposure assessment

Occurrence data and consumption data are needed to calculate the exposure, both for the risks and the benefits.

The exposure estimations will be performed for chronic exposure only. For the occurrence, mean values will be used (more details below Table 4.1-1). The consumption estimates will be made using the Observed Individual Means method (OIM; semi-deterministic), and custom-made scripts in R (probabilistic). Probabilistic estimates rely on distributions as inputs in place of single values for key parameters. This results in a distribution of possible exposure estimates and greater ability to characterise variability and uncertainty.

Person-specific body weights will be used where possible; otherwise Norwegian age- and gender-specific body weights will be used.

4.1 Occurrence data

Table 4.1-1. Occurrence data that will be used in the exposure calculations.

<table>
<thead>
<tr>
<th>Compound(s)</th>
<th>Occurrence data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioxins and dioxin-like PCBs</td>
<td>Data on different fish species analysed by the Institute of Marine Research (IMR)</td>
</tr>
<tr>
<td>PFAS</td>
<td>Data on sushi analysed by the National Institute of Nutrition and Seafood Research (NIFES), now IMR.</td>
</tr>
<tr>
<td>MeHg</td>
<td>Data available in the EFSA (2018) assessment «Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food» (EFSA et al., 2018b)</td>
</tr>
<tr>
<td></td>
<td>Data available in the EFSA (2018) assessment «Risk to human health related to the presence of perfluorococtane sulfonic acid and perfluorooctanoic acid in food» (EFSA et al., 2018a).</td>
</tr>
<tr>
<td></td>
<td>If newer data are made available from coming EFSA opinions in the timeframe of this opinion, these will be taken into consideration.</td>
</tr>
<tr>
<td>Fatty acids (DHA/EPA)</td>
<td>The KBS (nutritional calculation software) database contain values for fatty acids, vitamin D and iodine.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td></td>
</tr>
<tr>
<td>Iodine</td>
<td></td>
</tr>
</tbody>
</table>
The KBS database contain nutrient values for DHA/EPA, vitamin D, and iodine. Data on fatty acids and iodine were newly updated in 2014 and 2018.

Norwegian occurrence data for foods most likely eaten in Norway, will be preferred over pooled European data from EFSA.

Occurrence data of contaminants will be given in lower and upper bound values. Lower bound estimates will be calculated by substituting values below the limit of detection (LOD) or limit of quantification (LOQ) for an analytical method with zero. Upper bound estimates will be calculated by substituting values below the LOQ, or LOD if LOQ is missing, with values set to equal to the LOD or LOQ.

How to handle any lack of occurrence data (e.g. use the most comparable value, or set the occurrence to 0) cannot be clarified until a complete overview of all available data has been created.

4.2 Intake data for exposure calculation

To get the best possible picture of the intake of fish, and the whole diet for different population groups, intake data from several types of dietary surveys and studies will be used. The surveys/studies using short term recall/record methods like 24-hour recalls and 4 days food records give detailed information of food intake over a few days, whereas food frequency methods give less detailed information but for a longer period, like a month or a year.

The Norwegian national food consumption surveys will be used as the basis for the exposure calculations. These include:

- Norkost 3 (Totland et al., 2012)
- Ungkost 3 (Hansen et al., 2016)
- Småbarnkost 3 (datacollection 2019, data ready for use 2019/2020)

Norkost 3 and Ungkost 3 are surveys that give detailed information of food intake on an individual level. The dietary methods used are 24-hour recalls and 4-days web record, respectively. For Småbarnskost 3 and Spedkost 3 the dietary assessment method used are food frequency questionnaires.

Data from other surveys and studies, all addressing food frequency, will also be considered used for the exposure calculations or as supporting data for fish intake, and intake of rarely eaten foods:

- Tromsø 7; The seventh survey of the Tromsø Study was carried out in 2015-16. The questionnaires includes data on diet
• Hunt4; The HUNT study. The latest data gathering started in 2017. The HUNT Study includes data from questionnaires (including food habits)
• HUSK; Part of the Hordaland Health Studies and was conducted in 1997/99 as a joint project between the University of Bergen, the Norwegian Health Screening Service (now part of the National Institute of Public Health) and the Municipal Health Service in Hordaland
• The Norwegian Mother, Father and Child Cohort (MoBa)- the 13-year-olds study
• PreventADALL (Preventing Atopic Dermatitis and ALLergies)
5 Risk and benefit characterisations

The risk and benefit characterisations will be based on the identified and characterised adverse and beneficial health effects, respectively, as described in Chapter 3, and the estimated exposure from the given scenarios, derived as described in Chapter 4.
6 Risk and benefit integration

The weighing of the benefits against the risks will need to take into account the timeframe for the effects to become apparent and their severity/magnitude.

EFSA’s guidance on human health risk-benefit assessment of foods (EFSA, 2010) lays out three distinct steps; 1) Initial assessment, 2) Refined assessment and 3) Assessment using a composite metric. The guidance recommends that initial assessment is sufficient when benefits clearly outweigh risks (or vice versa), whilst step 2, refined assessments are needed when the risks and benefits do not clearly outweigh each other. Such a refined risk-benefit assessment aims to provide, depending on the availability of data, semi-quantitative or quantitative estimates of risk and benefits at relevant exposures. A semi-quantitative assessment contains comparisons of relevant exposures to health-based guidance values (HBGV; for contaminants), dietary reference values (DRV; for nutrients), and risks and benefits are summarised as probabilities of exceeding these reference values. Step 3, a more quantitative approach aims to link the exposure to explicit health effects, and report outcomes, where possible, using common metrics, such as incidence or mortality.

Information on dose-response relationship, i.e. the relationship between intake of a substance and the size of its health effects, is crucial in order to be able to estimate the size of the health impact associated with a change in diet.

EFSA recommends, if possible, to perform the assessment using a composite metric; i.e. to use weights for various health outcomes (typically Disability-adjusted life year (DALY), Quality-adjusted life year (QALY) or other), to quantify the impacts of scenarios on a common scale of measurement. A quantitative methodology has the advantage that it allows for a comparison of risks and benefits on the same scale, and provides a quantitative expression of the overall health impact of a given change in diet.

From Chapter 1.1 (Background) and 1.2 (Terms of reference) in this protocol, it is clear that the benefits do not clearly outweigh the risks with regard to (more or less) fish consumption, and VKM will perform a refined assessment (Step 2). For health effect/impacts that have sufficient data available to quantify the increase/decrease in incidence and mortality a quantitative assessment will be performed, whereas for compounds for which less data are available, a semi-quantitative approach will be used (i.e. comparison with HBGVs and DRVs).

The transformation of incidence of different health outcomes, including mortality, onto a composite metric (e.g. by using DALY-weights, Step 3) is neither a trivial task, nor an unchallenged scientifically sound approach. The project group will discuss the possibility of performing a full-scale risk-benefit assessment using DALYs, critically evaluate the necessary assumptions for such an approach and consider the potential impact and bias arising from the availability of underlying data, to decide if this option will be used. This will be done in close dialogue with the NFSA.
6.1 Weighing risks and benefits that are assessed by quantitative and qualitative methodology

If different risks and benefits, to be compared in the RBA, are obtained by different methods (quantitative and qualitative), a comparative diagram/table will be constructed to get a complete overview of the risk-benefit assessment.
7 Uncertainty

Factors introducing uncertainty in the various steps of the assessments will be identified and described. VKM will strive to quantify and indicate the direction of the uncertainty where possible.
8 References


Protocol and description of literature search for the risk-benefit assessment of fish in the Norwegian diet


IOM (Institute of Medicine, 2011) Dietary Reference Intakes for Calcium and Vitamin D, The National Academies Press, Washington, DC.


Appendix I

WCRF Grading of evidence


Convincing (strong evidence)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error, and selection bias.
- Presence of a plausible biological gradient (‘dose-response’) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

Probable (strong evidence)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer. All the following criteria are generally required:

- Evidence from at least two independent cohort studies, or at least five case-control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

Limited — suggestive

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but
shows a generally consistent direction of effect. This judgement is broad, and includes associations where the evidence falls only slightly below that required to infer a probably causal association through those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer, any exceptions to this require special, explicit justification. All the following criteria are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

Limited — no conclusion

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded ‘limited — no conclusion’ for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders), or by any combination of these factors.

When an exposure is graded ‘limited — no conclusion’, this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged ‘substantial effect of risk unlikely’

Substantial effect on risk unlikely (strong evidence)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to cancer outcomes. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates. All the following criteria are generally required:

- Evidence from more than one study type
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high versus low exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power,
imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.

- Absence of a demonstrable biological gradient (‘dose-response’).
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Special upgrading factors

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a ‘limited-suggestive’ causal factor in the absence, for example, of a biological gradient, might be upgraded to ‘probable’ if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated. Factors may include the following:

- Presence of a plausible biological gradient (‘dose-response’) in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomized trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanism actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.