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Risks and Benefits of Fish Consumption

A Risk-Benefit Analysis Based on the Occurrence of Dioxin/PCB, Methyl Mercury, n-3 Fatty Acids and Vitamin D in Fish

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Abbreviations/Glossary

Term	Detail
AA	Arachidonic acid, 20:4 n-6
Atopy	Inherited tendency to develop e.g. allergic conjunctivitis, hay fever, allergic asthma and dry itchy eczema
Benchmark-method	Approach that involves fitting a model to dose-response data. A reference point for risk assessment is derived from the model that also takes into account the uncertainties in the data
CNS	Central nervous system, the brain
DDT	1,1,1-trichloro-2,3-bis(4-chlorophenyl)ethylene
DHA	Docosahexaenoic acid, 22:6 n-3
DPA	Docosapentaenoic acid, 22:5 n-3
Dioxins	(In common parlance) polychlorinated dibenzo-p-dioxins and dibenzofurans (=PCDD/PCDF)
DL-PCB	Dioxin-like PCB congeners
EPA	Eicosapentaenoic acid, 20:5 n-3
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
Hg	Chemical symbol for mercury
JECFA	WHO/FAO scientific expert committee: Joint FAO/WHO Expert Committee on Food Additives and Contaminants
Cognitive development	A child's intellectual development. Cognitive functions include perception, conceptualisation, memory, reasoning, problem solving, concentration
LOAEL	Lowest Observed Adverse Effect Level
MeHg	Methyl mercury, the chemical form of mercury found in fish
NO(A)EL	No Observed (Adverse) Effect Level
n-3 fatty acids	Fatty acids in the n-3 series
n-6 fatty acids	Fatty acids in the n-6 series
PCB	Polychlorinated biphenyls
PCB- congeners	Various types of PCB compounds
PCDD/PCDF	Polychlorinated dibenzo-p-dioxins and dibenzofurans
PTWI	Provisionally tolerable weekly intake. The amount of a substance on a body weight basis that an individual can be exposed to, at population level, during a lifetime without perceptible risk of negative effects. Term used by the WHO/FAO scientific committee in risk assessment of substances that have effects upon chronic exposure.
Reference dose	A estimation (with an uncertainty of around one order of magnitude) of daily intake in the population, including all vulnerable groups, that probably does not lead to any harmful effects during a lifetime. Used by e.g. the US authorities.

Term	Detail
TEQ	Toxic equivalents. 17 congeners of dibenzodioxins/ dibenzofurans and 12 congeners of dioxin-like PCB have been allocated so-called TEF (toxic equivalency factors), which means that their toxicity has been evaluated in relation to the most toxic congener, 2,3,7,8-tetrachlorodiobenzo-p-dioxin (TCDD), which has a TEF factor of 1. The TEF for an individual congener is multiplied by the actual measured concentration (in e.g. pg/g), which results in a TEQ value. The TEQ values of the congeners analysed are added together to give a combined TEQ value that shows the toxicity-weighted content of dioxins in the actual sample. Depending on whether the dioxins (PCDD/PCDF) or dioxin-like PCB have been analysed, a PCDD/DF-TEQ or PCB-TEQ is obtained. If analytical data on both dioxins and dioxin-like PCB are available these can be added to give the total-TEQ.
TDI	Tolerable daily intake. The amount of a substance on a body weight basis that an individual can be exposed to, on a population level, during a lifetime without any perceptible risk of negative effects. Term used by the WHO/FAO scientific committee in risk assessment of substances that have effects upon acute exposure
TMI	Tolerable monthly intake. See TDI (not applicable for acute exposure)
TWI	Tolerable weekly intake. See TDI (not applicable for acute exposure)
Total-TEQ	TEQ content comprising both PCDD/PCDF and DL-PCB, see TEQ
WHO-TEQ	TEQ contents based on TEF data agreed at the WHO expert meeting on 1998 (van den Berg et al., Environ Health Perspect 1998;106:775-92). Newly published reviews of TEF values will over time give rise to certain changes (van den Berg et al., Toxicol Sci 2006;93:223-241)

Preface

The project Risks and Benefits of Fish Consumption was initiated in 2004 with the aim of studying various methods for assessing the risks and benefits associated with the consumption of fish. The National Food Administration's advice on fish consumption to date has been based separately on either nutritional advantages or toxicological risk assessments. The project studied methods for risk-benefit assessment and nutritional evaluation that considered the health effects associated with certain organic environmental pollutants (dioxins/dioxin-like PCBs) and methyl mercury, and certain nutrients.

The working group reviewed the scientific literature and reports regarding methods for risk-benefit assessments and the health effects of fish, with the focus on n-3 fatty acids and the abovementioned environmental pollutants. In May 2004, a seminar was organised within the framework of the project on the risks and benefits of fish, with invited representatives from the authorities in Finland and the United Kingdom, in order to exchange experiences and obtain a broader base for the work.

Within the framework of the project, intake calculations for dioxins/PCB from 2002 have been updated using new analytical data. The results have been published in a separate report from the National Food Administration (25/2005). Furthermore, intake calculations for dioxins/PCB and mercury have been made for children using results from the National Food Administration's investigations on children in 2003. Model calculations have also been made taking into account both environmental pollutants and nutrients in various scenarios.

The results of the project will be used as part of the underlying material for the review of dietary advice on fish taking place during 2007.

The project group consisted of Wulf Becker (Nutrition Department), Rickard Bjerselius (Toxicology Unit), Per Ola Darnerud (Toxicology Unit), Kierstin Petersson Grawé (Toxicology Unit), Marie Aune (Chemistry Unit 2), and Maj Olausson (Communications Unit). Emma Ankarberg (Toxicology Unit) worked on updating the dioxin calculations. Gabriela Concha (Toxicology Unit) was responsible for the intake calculations based on the investigation in children. Anders Glynn (Toxicology Unit) wrote the section on complex mixtures in Appendix 1. Professor Staffan Skerfving, Occupational and Environmental Medicine Clinic in Lund, also external scientific advisor to the National Food Administration, contributed data for the section on the interaction between methyl mercury and cardiovascular disease in Appendix 1. A reference group consisted of Annica Sohlström (Nutrition Department), Anders Glynn (Toxicology Unit), Östen Andersson (Legal Department), Roland Lindqvist (Microbiology Unit), Arne Andersson (Supervisory Department) and Helene Håkansson (Institute of Environmental Medicine, Karolinska Institute).

Summary

In the project Risks and Benefits of Fish Consumption, toxicological and nutritional aspects of fish consumption were highlighted. Evaluation of the risks and benefits associated with fish consumption were limited to certain nutritional compounds (long-chain n-3-fatty acids and vitamin D) and certain environmental pollutants (dioxins/dioxin-like PCBs and methyl mercury, MeHg). Balanced intake calculations were made based on consumption data from Riksmaten [National Diet] 1997-1998 and actual data on concentrations of the compounds studied. The project group reviewed the scientific literature and reports, with the focus on methods for assessing and comparing the health effects of fish consumption.

Overall conclusions

- An increase in fish consumption in accordance with current dietary advice (2-3 times per week) would probably result in a decreased incidence of cardiovascular disease in the population, particularly in those who eat little or no fish and in those with an increased risk of cardiovascular disease. A considerable proportion of the population aged 50 or over has at least one risk factor for an increased risk of cardiovascular disease.

- Increased fish consumption by women of childbearing age who eat little or no fish would probably be positive. n-3 fatty acids are required for normal development of children during the gestation period and early infancy. Fish consumption 2-3 times a week, with 1 portion consisting of fatty fish, provides a satisfactory intake of long-chain n-3 fatty acids for the majority of the population.

- Intake of vitamin D is low in relation to nutritional recommendations for a large proportion of the population. Increased consumption of fish by those who eat little or no fish would considerably improve the intake of vitamin D. Increased intake of vitamin D contributes to improved vitamin D status and thereby decreases the risk of osteoporosis and fractures.

- Regular consumption of certain types of fish (e.g. fatty Baltic fish and freshwater fish) with increased concentrations of environmental toxins can lead to the so-called tolerable intake levels regarding dioxins/dioxin-like PCBs and methyl mercury being exceeded. This primarily concerns children and women of childbearing age as regards dioxins/dioxin-like PCBs, and pregnant and lactating women and children as regards methyl mercury. However, consumption of these types of fish is low for most individuals.

- An estimated 5% of women in the ages 17-40 years have a dioxin intake that exceeds TDI of 2 pg/kg body weight/day, but many of these eat oily Baltic fish more often than the Administration's current advice of at most once a month. For a woman who eats fish in accordance with the general advice (lean sea fish/freshwater fish 2 times per week and oily fish, e.g. farmed salmon, 1 time per week) and who otherwise eats a diet in accordance with nutritional recommendations, TDI is not exceeded. However, the proportion that exceeds TDI can be around 35% in the following scenario: Total consumption of fish 3 times per week, of which oily Baltic fish 1 time per month (i.e. corresponding to the current dietary advice) and other oily fish (e.g. farmed salmon) 3 times per month. It is therefore not advisable to generally recommend an increase in consumption of oily Baltic fish, since the scope for increased consumption is highly limited for certain groups. However there is no reason to completely advise against consumption of oily Baltic fish.

- It should be emphasised that PCB and dioxins are accumulated in the body over a long time and that it is the total body load of these compounds, and not the actual intake, that is critical from a risk perspective. Exceeding the tolerable intake thus does not mean that health effects immediately arise, but that the safety margin decreases.

- Consumption of freshwater fish is low in the population and intake of methyl mercury does not exceed the JECFA's provisional tolerable weekly intake (PTWI) of 1.6 µg/kg. Limited consumption of fish with up to 1 mg/kg methyl mercury (at most once per month) is estimated to give a small risk of the tolerable intake being exceeded. However, regular consumption of freshwater fish with higher concentrations can lead to the tolerable intake being exceeded. Pregnant women are the group in the population that is most sensitive to methyl mercury due to the greater sensitivity of effects on the foetus.

- In a large proportion of the population there is scope to increase fish consumption without any fear of the tolerable intake levels of environmental pollutants being exceeded. Consumption of the commonest fish species 2-3 times a week, with a mixture of lean and oily fish species, carries a small risk of exceeding tolerable intake levels. The model calculations carried out demonstrate that increased consumption of fish provides health advantages in the form of improved nutrient intake. However, the scope for oily Baltic fish and fish containing high concentrations of MeHg is limited for certain groups.

- In some examples, balanced quantitative risk parameters such as QALYs (Quality Adjusted Life Years) have been applied to fish consumption and the health effects of n-3 fatty acids and methyl mercury have been

compared. The net result in the form of positive or negative health effects is dependent on whether the entire population is studied or whether different groups are studied separately.

- In some examples, DALYs (Disability Adjusted Life Years) have been applied to nutritional, microbiological and toxicological food-related aspects in order to estimate the consequences for public health at present and after desirable changes in dietary patterns, incl. increased consumption of fish. The results indicate that an increase in fish consumption would provide health benefits expressed as DALY.

- The scientific basis at present does not allow balanced quantitative risk/benefit assessments of all the health effects associated with fish consumption. However from a consumer perspective it is an advantage for experts from different disciplines to jointly draw up a complete picture that illustrates both risk and benefit aspects. This area is being developed and should be actively monitored by the National Food Administration.

Consumption of fish in Sweden

According to the latest national dietary investigation (Riksmaten, 1997-98) consumption of fish and shellfish among adults was on average 30-35 g/day. Between 20 and 30% ate fish more seldom that once per week. Cod and similar fish and fish products (fish fingers, fish balls) were consumed most, followed by other sea fish, shellfish and processed fish. Older people mainly eat more oily fish such as processed herring, salmon and salmonids, while younger people prefer lean fish and fish products such as fish fingers and fish balls. Investigations in pregnant and lactating women indicate lower fish consumption than for adults in general. Results from investigations of the dietary habits of 4-year-olds and children in school years 2 and 5 (Riksmaten – barn, 2003) showed that intake of fish and fish products was on average 17-19 g/day, with small variations between these groups. Between 35 and 45% of the children did not eat fish during the recording period (4 days). The commonest fish meals consisted of fish fingers, fish balls, farmed salmon/rainbow trout and lean sea fish.

Investigations of consumption among 'high consumers' (mainly professional fishers and anglers and their families) show that consumption among these groups is up to several-fold greater than consumption in the adult population in general.

Content of nutrients and environmental pollutants

Fish is generally a good source of several nutrients and contributes on average one-quarter of the intake of vitamin D, B_{12} and selenium. Fish represents one-fifth

of total intake of n-3 fatty acids and 80% of the long-chain n-3 fatty acids in the diet. High consumption of fish is associated with higher intake of e.g. vitamin D and selenium. Low fish consumption generally means that intake of long-chain n-3 fatty acids and vitamin D is too low.

Persistent organic pollutants (POPs) are fat-soluble and are therefore found in oily fish such as North Sea herring and salmonids, but are also present in other foods of animal origin. Intake calculations have shown that around half of the dioxin intake in adults is estimated to come from fish and fish products, with other animal products being responsible for the remaining half. For the fish species commonly consumed in Sweden, the concentrations of dioxins/dioxin-like PCBs are usually under the EU limits for fish by a good margin, but there are exceptions. The highest concentrations are found in oily fish caught in the wild in the Baltic, Bay of Bothnia and Lakes Vänern and Vättern, e.g. salmon, salmon trout, Baltic herring and eel. Median intake of dioxins/dioxin-like PCBs in Swedish consumers is estimated to be around half the tolerable intake. Due to great variation in dioxin intake, at the same time around 5% of women of childbearing age have an intake above the tolerable intake. Dioxin intake, expressed on a body weight basis, is also age-dependent and decreases from infancy to adulthood, before increasing slightly again for people in their thirties and older. The higher intake is children is due to a higher body weight-based nutrient intake, and the reason for the higher intake in older people is probably higher consumption of fish. The highest intake of dioxins is observed in breastfeeding babies, since breast milk contains relatively high dioxin concentrations.

Methyl mercury is present in fish and the concentrations vary depending on fish species and capture site. For those fish that are usually consumed in Sweden methyl mercury concentrations are low as a rule, but there are exceptions. Elevated concentrations are found in predatory fish such as pike, pike-perch, perch, halibut, some tuna and swordfish. For predatory fish captured in inland waters the variation in methyl mercury concentration is very large as a result of several factors. Swedish intake calculations and exposure studies have shown that the vast majority of consumers do not exceed the tolerable intake of methyl mercury, but there are exceptions. Very high fish consumption regardless of fish type, or regular consumption of fish with elevated methyl mercury levels can lead to the tolerable intake being reached or exceeded.

Quantitative risk-benefit assessments

Various methods have been used to quantitatively assess and evaluate the risks and benefits of consumption of different types of food. DALY (disability adjusted life years) and QALY (quality adjusted life years) are different measures of the health status in a population. These measures have been used in recent years to assess the effects of food consumption. A few calculations have been published that include fish, where the content of n-3 fatty acids and methyl mercury has been

considered. The results of these calculations show that the health effects of increased fish consumption are dependent on factors such as the concentration of environmental pollutants in the fish and the target group. With the entire population as the target group, the positive health effects (decreased risk of cardiovascular disease due to n-3 fatty acids) exceeded the negative effects (impaired foetal development due to methyl mercury). When the target group was women of childbearing age, the negative effects were able to dominate due to the content of mercury in the fish consumed, since the risk of suffering from cardiovascular disease is small in this group.

Model calculations using Swedish data

The project group concluded that it was not possible to carry out a balanced quantitative risk-benefit assessment. The reasons include the supporting data not consistently specifying quantification in terms of dose-response for exposure or incidence values for health effects on humans. However, the risks can be quantified in the form of exceedance of tolerable intake expressed as TDI or PTWI and compared with beneficial effects in terms of how intake of nutrients, e.g. n-3 fatty acids and vitamin D, fulfil actual recommendations. This was done in so-called model calculations using dietary data from Riksmaten 1997-98.

The model calculations for women of childbearing age show that the risk of intake of dioxin-TEQ exceeding the tolerable weekly intake of 14 pg/kg body weight (TWI) is low for consumption of Baltic herring up to around 1 portion per month if consumption of other fish remains unchanged. With this level of consumption, intake of long-chain n-3 fatty acids in around a third of the women is under the suggested desirable level of 0.2 g/day. If the calculations are instead based on consumption of e.g. farmed salmon, then 1 portion per month, together with the current intake of other fish, would give an intake of marine n-3 fatty acids of around 0.2 g/day in the majority of the women. However, if the women were to increase their total consumption of fish in accordance with the general dietary advice, the proportion exceeding the TDI would be around 35% for the following scenario: total consumption of fish 3 times per week, of which oily Baltic fish 1 time per month (i.e. corresponding to the current dietary advice) and other oily fish (e.g. farmed salmon) 3 times per month.

Corresponding calculations were made for intake of vitamin D and methyl mercury in relation to consumption of freshwater fish with varying concentrations of methyl mercury. The results for methyl mercury show that none of the women exceed the provisional tolerable weekly intake (PTWI) of 1.6 µg/kg body weight at a consumption of freshwater fish with a concentration of 0.5 mg/kg up to 2 times per month. At a concentration of 1 mg/kg, the PTWI is reached by around 1% of the women at a consumption of 2 times per month. The average intake of vitamin D also increases, even though the recommended intake is not completely achieved.

Calculations based on the National Food Administration's food-based dietary advice (SNO, Swedish Nutrition Recommendations Objectified) show that increasing fish consumption in accordance with the current nutrient-based recommendations to 2-3 portions a week would means intake of long-chain n-3 fatty acids increasing from an average of just over 0.2 g/d to 0.4-0.5 g/d in adults, i.e. being doubled. In addition, intake of other nutrients such as vitamin D and selenium would increase to the recommended levels. Exposure to dioxin/PCBs and methyl mercury was also calculated for an adult woman. If the dietary advice (for fish 2-3 times per week) is followed and if they eat the most commonly occurring commercial fish types such as cod, saithe, haddock, farmed salmon, and fish products such as fish balls, the risk of the tolerable intake being exceeded is small. However, if they regularly eat fish with elevated levels of persistent organic pollutants or methyl mercury, the tolerable intake levels can be exceeded.

Expertise requirements for risk-benefit assessments

If the National Food Administration is to expand its risk assessment work to also include the beneficial aspects, current methods would need to be complemented with others that can evaluate and grade both the risks and benefits. This area is still under development internationally and there is currently no accepted methodology available for use. The National Food Administration should therefore actively monitor progress here. New methods for risk assessments are increasingly being based on the so-called benchmark method. Expertise in understanding and the ability to use these methods is required by the National Food Administration. Methods for intake calculations need to be developed and complemented with e.g. probability-based calculation models, both for acute and long-term exposure, in order to provide a better estimations of uncertainty and variation in exposure. Experience of working with probability models exists in the Microbiology and Toxicology Units and could be utilised for exposure analyses within other areas in the National Food Administration. The fundamental expertise required is mainly of a mathematical, statistical character and the majority of the work consists of analysis and description of data and application of probability models. It is important that such expertise be incorporated into the base organisation.

Work with DALY calculations or similar within the National Food Administration's areas of activity would require increased expertise in epidemiology and access to empirical models. The project group concluded that it is not a primary objective for the National Food Administration to carry out its own DALY calculations. Resources should instead be devoted to improving the underlying support regarding e.g. concentrations of environmental pollutants and nutrients, consumption data, exposure calculations, health effects and dose-response relationships in humans. Such data can be of benefit in e.g. DALY

calculations or other types of risk-benefit assessments, in collaboration with external experts.

This pilot project demonstrates the advantages of experts from different disciplines meeting in a joint process to provide as complete a picture as possible of the consequences as regards risks and benefits on a population level, so that the choice of risk management measures is optimal from a public health perspective. The most probable scenario in any future risk-benefit assessments is that the potential to quantify both the risks and benefits is generally limited due to lack of quantitative data regarding exposure and effects. Even though there are difficulties in performing quantitative risk-benefit assessments, there are still great advantages in making as balanced an assessment as possible of both risks and benefits in order to provide the consumer with a complete picture. Such an assessment would then be semi-quantitative or qualitative, which is probably preferable to a one-sided risk or benefit assessment.

Summary of Appendix 1. Health Effects

Long-chain n-3 fatty acid supplements during pregnancy can increase the length of pregnancy (1.6 days), but the dose-response relationships are unclear. Increased supply of long-chain n-3 fatty acids can probably be beneficial if the n-3 status before pregnancy is low. Some studies indicate that intake of around 15-20 g fish per day, corresponding to 0.15-0.2 g marine n-3 fatty acids, can be sufficient.

A number of studies indicate that supplying mainly long-chain n-3 fatty acids during the foetal stage and in the early years is related to certain cognitive functions in child. The doses have generally been considerably larger than the intake that can normally be achieved via the diet. The supporting data are not sufficient to reliably establish the optimal level of intake of various n-3 fatty acids. Intake of DHA in the order of magnitude of 0.1-0.3 g/d via the diet has been suggested to be adequate during pregnancy. This corresponds to fish consumption 2-3 times per week, with one portion of oily fish.

The importance of intake of fish and n-3 fatty acids for the risk of developing allergies and other inflammatory conditions is still unclear. However there are studies showing beneficial effects of supplying large doses of long-chain n-3 fatty acids in the form of fish oil for certain conditions, e.g. rheumatoid arthritis, while such supplementation has had no clear effects asthma, cystic fibrosis or inflammatory diseases of the intestine.

Lower blood levels of n-3 fatty acids have been demonstrated for various neurological complaints. The importance of intake via the diet for the emergence of such complaints is unclear, but there are epidemiological data indicating that low intake or tissue levels of long-chain n-3 fatty acids can be important for the

development of certain complaints, e.g. dementia. However, results from controlled studies in which supplements containing e.g. n-3 fatty acids were provided have not shown any clear positive effects.

Regular consumption of fish can contribute to decreasing the risk of cardiac mortality. The evidence is strongest for individuals with an increased risk. Cohort studies also indicate that relatively moderate consumption can decrease the risk in the general population. The estimates of dose-response relationships that have been made are based on cohort studies and give variable results, which can be due e.g. to uncertainties in the dietary data, which are usually based on frequency methods. In a meta-analysis of cohort studies, a reduced risk was observed for fish consumption 1 time per week or more often.

The importance of fish consumption and intake of long-chain n-3 fatty acids for the incidence of various forms of cancer is unclear. Reviews of the results from epidemiological studies show little or no effects.

Dioxins and PCB are absorbed reasonably well from the gastro-intestinal tract, with calculations from a generally used degree of absorption of 50% up to an assumed absorption of 90% in some studies. The half-life in the body is considered to be 7-8 years for the most toxic dioxin compound (2,3,7,8-TCDD), but a range from 2 to 16 years has been calculated for the group dibenzodioxins/-furans.

In epidemiological studies, certain effects on gender ratio, length and regularity of the menstruation cycle and sperm status have been reported in populations where dioxin exposure in the acute phase has been very high. However, it is unclear what these observations mean for reproductive ability. In experimental studies on monkeys and rats, reproductive ability was affected (abortions and incomplete gestations), and in rodents there were also foetal abnormalities after dioxin exposure.

A number of human studies have indicated negative effects on child development after exposure to dioxins and PCBs during the foetal and breastfeeding stage. The effects on children born to mothers with high exposure include low birth weight, delayed development during childhood, with e.g. behavioural changes, changes/ malformations of the genital organs, changes in dentition and effects on the immune system. In populations with moderately higher exposure to dioxins and PCB, as in Sweden, it is more difficult to draw conclusions on causal relationships between exposure and effects. Certain studies indicate impaired cognitive and psychomotor development and immunological effects, while other studies have not shown corresponding effects. The effects reported in humans in epidemiological studies are supported by findings in animal studies.

High occupational TCDD exposure has been related to changes in markers for immune system function, but it has not been possible to establish that these

changes are significant for health. In children exposed to background levels, a correlation was observed between dioxin/PCB exposure and changes in the amount of white blood cells, antibodies and in certain cases also an increased risk of ear infections. However the relationship between asthma/allergies and dioxin exposure is difficult to interpret. In animal trials too, an effect on immune status has been seen, e.g. in the form of downregulation of the immune response in rats.

The carcinogenic characteristics of dioxins have been described in animal trials, where higher doses have been used. In occupationally-exposed cohorts, a correlation has been observed between dioxin exposure and increased frequency of certain forms of cancer. IARC has classified TCDD as a human carcinogen (group 1), while other dioxin/furan-congeners are unclassified (group 3). It is difficult to use epidemiological data to quantify the cancer risk in humans. There are many failings in the epidemiological studies as regards e.g. treatment of confounding problems and multiexposure. In addition, the exposure analysis is often faulty in many cases. It should also be emphasised that the non-occupationally exposed population is exposed to TCDD levels that are two to three orders lower than the estimated potential lifetime doses in occupationally-exposed groups, i.e. in those cohorts for which a risk increase has been demonstrated.

The effects on the nervous system of exposure to methyl mercury during the foetal stage have been studied in a number of populations with elevated chronic exposure. The two most significant studies have reported contradictory results. In a study from the Seychelles, no correlation was reported between prenatal exposure to methyl mercury and negative effects up to 9 years of age, while a study from the Faroe Islands reported a significant correlation between prenatal exposure to methyl mercury and child development, particularly as regards alertness, language and memory at 7 years of age.

Epidemiological data indicate that there is a correlation between high MeHg-exposure and an increased risk of acute heart attack, but the conclusions on the shape of the dose-response curve are partly unclear. In the Swedish studies that have been carried out no such correlation has been found, and this can probably be explained by the exposure to MeHg having been considerably lower than in e.g. Finnish studies. In fact, in the Swedish studies there has been a positive correlation between exposure to MeHg and decreased risk of heart attack. This can be interpreted as the protective effects of the n-3 fatty acids (and perhaps also selenium) dominating up to a certain intake level at which the MeHg-induced negative effects begin to dominate. However, there are some minor Swedish studies of individuals who eat a lot of fish with elevated MeHg concentrations showing that this exposure can be of the same level as that reported in the Finnish studies. Therefore the possibility cannot be ruled out that within the Swedish population there are groups that have such a high intake of MeHg that the risk of cardiovascular disease in these groups can be elevated. There is no basis for determining the magnitude of this proportion, but it is probably small and limited

to individuals who eat self-caught fish with elevated MeHg concentrations very regularly.

The few studies on rodents that have been reported show that MeHg has the potential to influence the immune response in adults and foetuses. However, these studies do not give a clear answer as regards what the most sensitive immunological parameters are, or in what direction MeHg affects the individual parameters. It is unclear to what extent MeHg exerts effects on the immune response at low exposure levels and also what is the highest exposure level that does not give rise to effects.

Summary of Appendix 2. Risk Management

Appendix 2 describes national and international risk management measures, such as limit values and dietary advice. Dietary advice in all cases involves recommending regular fish consumption, with variations between lean and oily fish types, to the population in general. At the same time, the advice given to sensitive groups involves limiting or completely avoiding consumption of certain fish species.

Background

The work of the National Food Administration is aimed at decreasing the health risks of food and at promoting good dietary habits. This means that it is essential to assess both the risks and benefits of consumption of particular foods. The work on these issues is to be based on the risk analysis model developed at the Administration. For fish, there are general recommendations on increased fish consumption and detailed dietary advice on limiting consumption of specific types of fish in order to avoid high exposure to methyl mercury and persistent organic pollutants. In addition to dietary advice, there are also limit values for the highest permissible concentrations of mercury and dioxins in commercial fish.

The current general advice is that from a health perspective most people should eat more fish, both lean and oily. This advice is based on data from clinical and epidemiological studies showing that regular consumption of fish can decrease the risk of e.g. cardiovascular disease. Fish is also an important source of several vitamins and minerals, e.g. vitamin D, iodine and selenium. Increased consumption is desirable to increase intake of vitamin D, selenium and n-3 fatty acids in particular, and to decrease intake of other less beneficial foods. The dietary limiting advice is primarily directed at the risk groups pregnant women, women of childbearing age and girls, but also at high consumers of fish (see Appendix 2). The advice is based on both animal studies and epidemiological investigations. The studies show that high exposure to methyl mercury and organochloride compounds can have health effects in foetuses and infants.

Dioxins and PCB are groups of environmental pollutants that are broken down very slowly in the environment and that accumulate in fat-rich matrices. These properties mean that the compounds are taken up in the fat fraction in organisms at various levels in the food chain and accumulated at increasing concentrations with increasing distance up the food chain. This so-called biomagnification is particularly efficient in the aquatic environment, which means that animals higher up in the food chain such as ospreys, sea eagles, otters and seals, risk having very high concentrations of dioxins and PCB in their body fat. People who eat fish and other animal-based foods also risk having relatively high body loads and a diet with a small proportion of animal fat can thus decrease exposure to these compounds. Humans also live to a greater age than most other animals, which leads to a relatively high body load since the concentration of these long-life organic compounds in the body increases with age.

Mercury (Hg) can be spread long distances via the atmosphere and is converted in natural processes into methyl mercury (MeHg). MeHg passes easily across the cell membrane and uptake of MeHg in organisms is therefore high. In the ecosystem there is a biomagnification, which means that the muscle tissue of edible fish such

as pike and other predatory fish can contain relatively high concentrations of MeHg. Similarly, predatory fish in the marine environment, e.g. tuna, halibut and swordfish, have higher concentrations of MeHg than fish species further down in the food chain. However, MeHg is present in all fish, even in important food fish – but in considerably lower concentrations. Fish is the clearly dominant source of MeHg exposure in humans.

Aims and Scope

The aim of the present project was to examine the methods and data support used for risk-benefit assessments of fish consumption, i.e. methods that simultaneously take into account and evaluate both negative and positive health effects, and to carry out a risk-benefit assessment of fish consumption based on Swedish conditions. The analyses were restricted to certain nutrients (n-3 fatty acids, vitamin D) and environmental pollutants (dioxins, dioxin-like PCB, MeHg) that the project group deemed to be the most important, and for which data regarding intake and health effects were also available.

The project group carried out an inventory of risk-benefit assessments in which quantitative estimations had been made of the health outcome of fish consumption in terms of e.g. DALY (Disability Adjusted Life Years) or QALY (Disability Adjusted Life Years) based on the content of e.g. n-3 fatty acids and environmental pollutants. The health effects used in these assessments mainly comprise cardiovascular disease and neurological effects during early development. In addition, calculations were made of how varying intake of fish affects the risk of exceeding the current TWI (tolerable weekly intake) for dioxins/PCBs or the PTWI (provisional TWI) for MeHg as the sole parameter in the risk-benefit assessment. It should be pointed out that exceeding the tolerable intake levels does not mean that health effects arise, but that the safety margin is less. Benefit assessments were based on how recommendations for intake of n-3 fatty acids and vitamin D are fulfilled in relation to actual recommendations, including the Swedish nutritional recommendations.

The results of the project will form part of the underlying support for the revision of dietary advice on fish that will take place during 2006-2007. The report can also be used as support for continuing work on risk-benefit assessments at the National Food Administration.

Consumption of fish in Sweden

Statistics on consumption of fish and fish products (excl. angling) are produced by the Swedish Board of Agriculture (SJV, 2005). Since 2000, no details are reported on the total consumption of fish, but rather on certain fish products (SJV, 2005). Catch statistics are reported by the Swedish Board of Fisheries (Fiskeriverket, 2005). Statistics on household spending on fish and fish products are collected in the Central Statistics Bureau investigations of household spending (HUT) (SCB, 2005). Data on consumption of fish are also collected in investigations of dietary habits and in epidemiological studies. The results from some national and targeted dietary investigations are reported here.

Adults

According to the latest dietary survey Riksmaten 1997-98, consumption of fish and shellfish among adults is on average up to 30-35 g/d (Becker & Pearson, 2002). These figures are based on results from 7-day records (menu diaries) of food intake. Consumption is highest among older people, see Figure 1. On average, fish and shellfish were consumed 6.5 times per month.

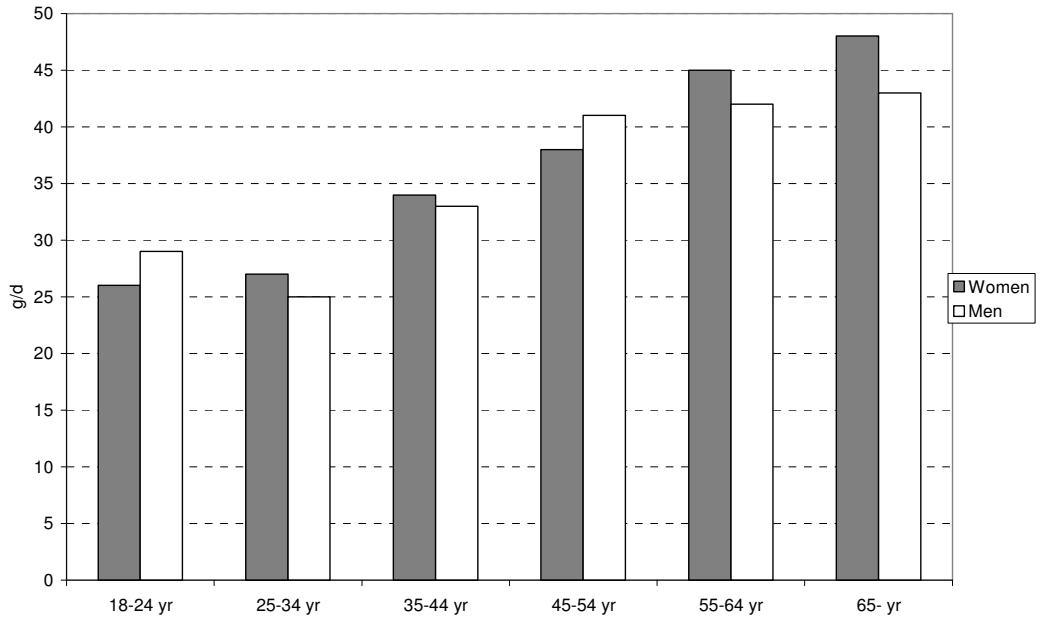

Fig. 1. Average consumption per day of fish and shellfish in Riksmaten 1997-98 according to age and gender. Data from 7-day menu diaries.

Consumption frequencies for different types of fish and fish products were also collected in Riksmaten with the help of questionnaires. For people in the age range 17-49 years, around 2% stated that they did not eat fish at all, while approx. 8% never ate oily fish. In the older group, 50-74 years, the corresponding figures were 2% and 4%. Only 2% of the younger group stated that they ate fish more seldom than once a month, while the corresponding figure for oily fish was 44%. In the older group, 1% of individuals reported that they ate fish more seldom than once a month, while 21% ate oily fish to the same limited extent. At least one fish dish per week was reported by 73% of the younger group and by 81% of the older group.

The majority of the adult population stated that they ate herring and salmon from the Baltic a few times per year or never. Fifteen percent stated that they ate Baltic herring 1-3 times per month, while 2% stated 1 time per week. One percent reported that they ate Baltic salmon 1-3 times per month and 1% one time per week. Half the individuals stated that they generally did not eat freshwater fish (pike, pike-perch, perch, burbot), 39% ate freshwater fish a few times per month and 6% ate freshwater fish 1-3 times per month.

To estimate the amounts consumed, the consumption frequencies were combined with standard portions for the different alternatives. Table 1 shows consumption of different types of fish and fish products. Estimates of total fish consumption from questionnaire data agree well with data from the menu diaries. However, comparisons with catch statistics for Baltic salmon showed that the questionnaire responses gave a large overestimation of consumption (Ankarberg & Petersson Grawé, 2005). This indicates that consumers probably have difficulty in distinguishing between farmed salmon and wild Baltic salmon. Estimates of consumption from the questionnaire responses have therefore been adjusted on the basis of catch statistics (Table 1).

Table 1. Consumption of fish types (g/d) according to a questionnaire in the dietary habits survey Riksmaten 1997-98 (n=1211). Mean values (mv) and 50 and 95 percentiles (50p, 95p)

	Fraction that ate	Consumers			All		
	%	mv	50p	95p	mv	50p	95p
Cod etc.	93	9.1	8.3	16.7	8.4	8.3	16.7
Plaice etc.	79	4.2	1.0	16.2	3.4	1.0	8.3
Pickled herring	85	2.0	0.4	6.7	1.7	0.4	6.7
Fish preserves	82	3.0	0.6	10.0	2.5	0.6	10.0
Fish fingers	58	4.8	1.0	16.7	2.7	1.0	8.3
Fish balls	55	4.5	1.3	10.0	2.5	1.3	10.0
Baltic herring	58	3.6	1.0	8.3	2.1	1.0	8.3
Smoked Baltic herring	33	1.1	0.8	0.8	0.4	0.0	0.8
Smoked North Sea herring	14	1.5	0.8	0.8	0.2	0.0	0.8
Pacific salmon	47	2.0	1.0	8.3	0.9	1.0	8.3
Baltic salmon	10	0.8	0.4	3.3	< 0.1	0.0	0.4
Other salmonids (farmed salmon, rainbow trout, char, sea trout, whitefish)	76	3.5	1.0	9.4	2.6	1.0	9.4
Freshwater fish (pike, pike-perch, perch, burbot)	43	2.1	1.0	8.3	0.9	0.0	4.7
Eel	19	1.2	0.8	0.8	0.2	0.0	0.8
Caviar	79	1.0	0.7	3.6	0.7	0.1	3.6
Shellfish	89	4.4	6.0	12.0	3.9	0.8	12.0
Liver	3	2.0	0.4	1.3	0.1	0.0	0.0
Total, all	98				33		

Cod and similar fish and products made from these (fish fingers, fish balls) were consumed most, followed by other saltwater fish, shellfish and fish preserves. Older people mainly eat more oily fish, such as herring products, salmon and salmonids, while younger people prefer lean fish and fish products, e.g. fish fingers and fish balls (Figure 2).

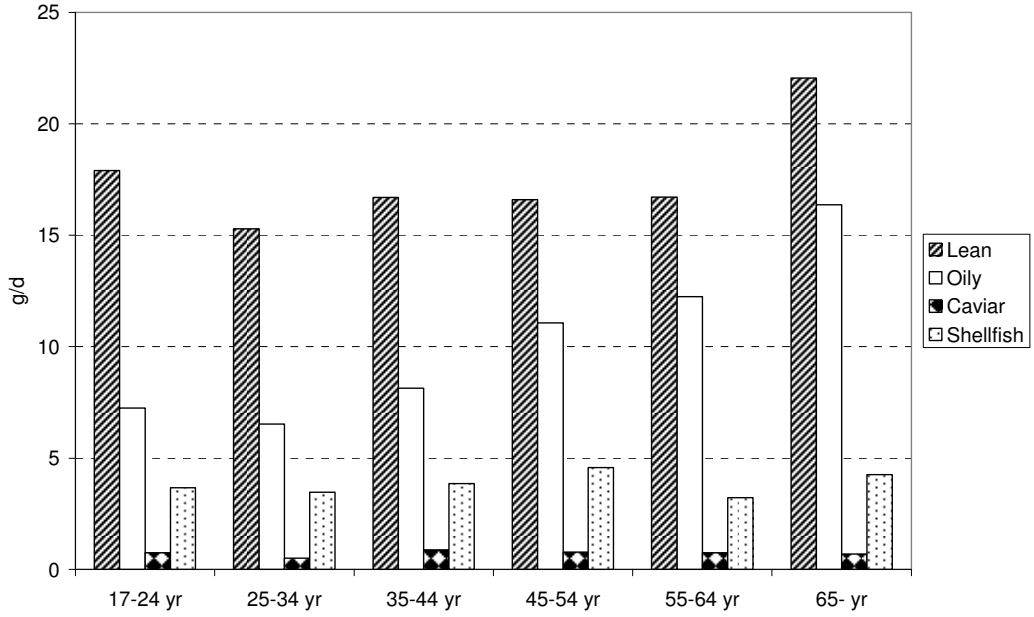

Fig. 2. Consumption of fish and shellfish according to a questionnaire in the dietary habits survey Riksmaten 1997-98, sub-divided according to age. Mean values (g/day).

Consumption frequencies for fish and shellfish according to various studies are shown in Table 2. In a questionnaire study on dietary habits among the adult population of Sweden in 2002, fish and shellfish were consumed on average 7 times per month, of which over 5 consisted of fish (Becker, 2002). In this study too, consumption among older people was higher than among younger. Around 75% of people reported that they ate fish, including shellfish, more than once a week or more, which agrees well with the results in Riksmaten, despite there being 4-5 years between the two studies. Around 10% reported that they fish once a month or less, which is more than was reported in Riksmaten.

Table 2. Consumption frequencies (times/month) for fish in different Swedish populations

Study	n	Category	Total, mv	Of which: Oily	Lean	Shell-fish
Svensson et al., 1995b	150	Prof. fishermen, east coast	11	5	6	-
Svensson et al., 1995b	100	Prof. fishermen, west coast	12	4	8	-
Svensson et al., 1995b	248	Reference population	7	3	4	-
Rylander et al., 1995	38	Fishermen's wives, east coast	6.9	2.1	3.3	1.3
Rylander et al., 1995	38	Ref. population, east coast	5.4	0.9	1.3	1.1
Rylander et al., 1995	31	Fishermen's wives, west coast	10.4	2.7	5.7	2.4
Rylander et al., 1995	31	Ref. population, west coast	7.1	0.7	2.7	1.8
Rylander&Hagmar, 1995	100	Fishermen's wives, east coast	9.6	3.8	5	1
Rylander&Hagmar, 1995	100	Ref. population, east coast	7.2	2.7	3.5	1.1
Rylander&Hagmar, 1995	100	Fishermen's wives, west coast	12.6	4	7.9	2.3
Rylander&Hagmar, 1995	100	Ref. population, west coast	8.2	2.4	4.6	1.6
Helmfrid et al., 2003	37	Women 37-87 yrs, fishing family, Lake Vättern	5	3	2	-
Björnberg et al., 2005	127	High consumers, women	8*[x], 13[xx]	-	-	-
Rödström et al., 2004	99	Pregnant women, W. Sweden	<4*	-	-	-
Gerhardsson et al., 2005	104	Pregnant women, Scania	4*	-	-	-
Glynn et al. , 2006	249	Primogravida, Uppsala co.**	5.8	1.4	4.3	-
Bergdahl et al., 2006	96	Pregnant women, Västerbotten	<4*	-	-	-
Bárány et al., 2003	245	17-year-olds	4.4	-	-	-
Becker & Pearson, 2002	1211	*Riksmaten 1997-98*, Adults 18-74 yrs	6.5	3.6	2.9	1.3
Becker, 2003	1000	Norbagreen 2002, Adults 16-80 yrs	7#	-	-	-

Incl. shellfish
*Median
**Consumption in the year prior to pregnancy
[x] General fish consumption
[xx] Detailed survey of consumption of specific types of fish

Other studies mainly include high consumers of fish, but also reference groups of the general population and pregnant and breastfeeding women. Within the framework of the Environmental Protection Agency's health-related environmental monitoring, a number of studies have been carried out on exposure to environmental pollutants in pregnant women, where fish consumption has also been reported (Rödström et al., 2004; Gerhardsson et al., 2005; Glynn et al., 2006; Bergdahl et al., 2006). In all cases, selection was random and representative of this population group, with a certain reservation that women born abroad may have been under-represented. Mean or median consumption of fish in all studies of

pregnant women lies in the range <4-5.8 times per month and is lower than that reported for other groups in the population and in Riksmaten (6.5 times/month).

High consumers

A number of investigations on high consumers of fish have been carried out in Sweden. A study of 127 female high consumers of fish was carried out in 2001 to investigate exposure to environmental pollutants (Björnberg et al., 2005a). According to a survey that included questions on consumption of individual fish species, the median value for combined fish consumption was 4.3 meals per week, with large variation. The responses to a general question about how often fish was consumed gave a lower frequency, a median value of 2 meals per week with a variation of 0.5-7 meals.

Women living in the vicinity of Lake Vättern reported that they ate fish 5 times per month (Helmfrid et al., 2003). Sporting anglers are a group that can be expected to have higher consumption of fish than other groups. Among sporting anglers in Hagfors (Lake Vänern), one-third ate freshwater fish (pike and pike-perch) at least once a week (Johnsson et al., 2004). A smaller study from the same area comprised 20 older men and of these, 6 ate freshwater fish at least once a week, 8 ate freshwater fish a few times per month, and 6 did not eat freshwater fish (Johnsson et al., 2005).

Professional fishermen are another group that has been shown to have high fish consumption. Surveys of fish consumption among fishermen on the east and west coast showed that fish consumption was approx. double that in the normal population (Hagmar et al., 1992; Svensson et al., 1995b). In the group fishermen's wives, which can constitute a particular risk group if the women are of childbearing age, fish intake was also approx. double that in the corresponding section of the general population (Rylander & Hagmar, 1995). Fishermen's wives ate on average 3-4 meals of oily fish per month, but the variation in intake of oily fish and in total amount of fish was considerable.

A study has been carried out on fish consumers in Sweden and Latvia, where intake of oily Baltic fish, mainly wild salmon and herring, was recorded (Sjödin et al., 2000). High consumers from Sweden reported that they ate oily east coast fish in 16 meals per month (median), with a maximum intake of 20 meals per month.

The results from these studies show that consumption among high consumers is up to several-fold as much as in the general adult population, see example in Table 2.

Children

The National Food Administration's diet investigation Riksmaten – barn 2003, described the dietary habits of 4-year-olds and children in school years 2 and 5 (aged 8 and 11). The study included a questionnaire on consumption frequencies for different types of fish and fish products (Becker & Enghardt Barbieri, 2004). Table 3 shows the proportion of children that ate these types of fish more frequently than once per month and once per week. The children's food intake was also recorded for four days in a food diary. Intake of fish and fish products was on average 17-19 g/day, with small variations between the ages (Enghardt Barbieri et al., 2006). Between 35 and 45% of the children did not eat fish during the recording period (4 days). The commonest fish dishes consisted of fish fingers, fish balls, lean sea fish and farmed salmon/rainbow trout. Less than 0.5% of the children responded that they ate freshwater fish more often than once a week. In a study of teenagers carried out in 1996, consumption of fish was 4.4 times per month (Bárány et al., 2003).

Table 3a. Percentage of children eating different types of fish more often than once per month

	4-year-olds	Yr 2	Yr 5
Fish fingers, fish balls	70	65	64
Farmed salmon/rainbow trout	19	20	20
Sea trout, wild Baltic salmon	3	3	4
Perch, pike, pike-perch, burbot	1	2	4
Lean sea fish (cod, saithe, haddock)	63	53	46
Flatfish (plaice, flounder, turbot)	15	14	14
Tuna, swordfish, giant halibut, shark	1	1	2
Tuna, tinned	9	12	14
North Sea herring, mackerel	8	9	11
Baltic herring, smoked herring	2	3	2
Anchovies, sardines	1	2	2
Eel	0.2	0.5	1
Roe, caviar	46	37	36
Shellfish	16	18	23

Table 3b. Percentage of children eating different types of fish more often than once per week

	4-year-olds	Yr 2	Yr 5
Fish fingers, fish balls	25	23	24
Farmed salmon/rainbow trout	3	4	5
Sea salmon-trout, wild Baltic salmon	1	1	2
Perch, pike, pike-perch, burbot	0.3	0.3	1
Lean sea fish (cod, saithe, haddock)	22	18	15
Flatfish (plaice, flounder, turbot)	3	2	3
Tuna, swordfish, giant halibut, shark	0	0.1	1
Tuna, tinned	2	3	4
North Sea herring, mackerel	3	2	3
Baltic herring, smoked herring	1	0.5	1
Anchovies, sardines	0	0.5	1
Eel	0	0.1	0.4
Roe, caviar	27	21	20
Shellfish	2	2	4

Content of nutrients and environmental pollutants

Nutrients

By tradition, fish has been an important part of the Swedish diet. Nutritionally, fish contributes a range of vitamins and minerals, particularly vitamin D, vitamin B_{12}, selenium, iodine and tocopherols (vitamin E). Fish oil is characterised by a high proportion of polyunsaturated n-3 fatty acids (omega-3 series). Examples of the nutrient content in some types of fish are shown in Table 4. The vitamin D content is generally high in oily fish, but a number of lean fish species, such as whitefish, pike-perch and pike, can have equally high or higher concentrations. The iodine content is generally high in fish from salt water, but can also be relatively high in fish from the Baltic Sea and in certain freshwater fish, e.g. salmon-trout and burbot. A 100-150 gram portion of fish provides a large proportion of the recommended daily intake of e.g. vitamin D, vitamin E, iodine and selenium.

Table 4. Content of certain nutrients and environmental pollutants in different fish species (per 100 g edible part). The values shown are means or weighted values (Livsmedelsdatabasen, 2004; Ankarberg & Petersson Grawé, 2005)

	Oils	n-3 fatty acids	Vit D	α-Toco-pherol	Selen-ium	Iodine	Dioxin[1]	Hg
	g	g	µg	mg	µg	µg	pg TEQ	µg
Perch	0.6	0.2	21.4	0.7	44	8	(130)[2]	24-32[3]
Pike	0.2	0.1	5.3	0.5	20	12	130	22-46[3]
Pike-perch	0.2	0.1	29	0.5	23	23	(130)	11-23[3]
Farmed Norwegian fjord salmon	13.4	3.0	11.3	2.2	19	45	210	2
Swedish river salmon steak	3.1	0.8	14.3	0.4	28	8	1040	8
Pink/humpback/'Pacific' salmon	5.2	1.7	1.3	2.2	26	-	-	-
Farmed rainbow trout	10.0	2.0	4.4	1.8	26	25	(210)	3
Mackerel	15.1	2.9	12.8	0.3	37	90	155	3
Tinned sardines in oil	21.1	3.9	15	1.7	35	25	(99)	-
North Sea herring	18.5	3.1	12	1.1	18	60	153	3
Baltic herring	9.3	1.7	9.2	2.0	18	30	1040	3
Tinned tuna in oil, drained	11.0	0.8	5.8	6.3	42	25	(31)	6
Cod	0.7	0.2	1	1.0	27	55	47	5
Eel	33.0	4.7	30	8.0	57	60	465	10
Recommended daily intake, SNR 2005[4]	-	-	7.5	8-10	40-50	150		

[1] PCDD/DF (Σ17) + dioxin-like PCB (Σ10)
[2] Values within brackets are extrapolated from concentrations in other fish species
[3] Examples of mean values, considerably higher concentrations can be observed in certain areas
[4] Swedish Nutrition Recommendations

Environmental pollutants

Organic environmental pollutants

Many targeted investigations of organic environmental pollutants in fish consumed in Sweden have been carried out over the years. The investigations carried out in the period 1985-1995 have been compiled in a report (Andersson et al., 1997). This report presents the concentrations in fish of PCBs, dioxins (PCDD/PCDFs) and a range of chloro-pesticides (DDT, HCB, HCHs, dieldrin, chlordanes, toxaphen). The concentrations of organic environmental pollutants (PCB, dioxins and other compounds) in fish are also reported in a national database within the framework of environmental monitoring (IVL, 2005).

In conjunction with the establishment of common EU limits for dioxins in commercial fish, a comprehensive investigation of dioxins and PCBs in commercial fish was carried out by the National Food Administration in collaboration with other authorities. Around 140 analyses were carried out in the period 2000-2003 of, in the first instance, oily east coast fish (incl. Baltic herring, wild salmon and sea trout, char), but also certain other fish species and shellfish. The results of the dioxin analyses are reported on the National Food Administration website (SLV, 2005). A number of cases of concentrations above the current limit for dioxins in fish (see Appendix 2) were recorded in herring and wild salmon from the Baltic Sea and the Bay of Bothnia. Particularly high dioxin concentrations were observed in Baltic herring caught off the Gästrike and Hälsingland coast (Bålsön, Västra Banken), while Baltic herring caught in the Bay of Bothnia and the southern Baltic Sea have considerably lower concentrations. In a 2005 study, dioxins and dioxin-like PCBs were analysed in Baltic herring from the Bay of Bothnia and the north of the actual Baltic Sea (Bignert et al., 2005). This study showed season-, age- and size-related differences in dioxin concentrations in fish, with Baltic herring caught in spring generally containing considerably higher concentrations than autumn-caught, including on a fresh weight basis. This means that spring-caught Baltic herring in this area in many cases exceed the limit for dioxins, and for dioxins + dioxin-like PCBs.

Dioxin-like PCBs also contribute to total-TEQ. Measurements show that dioxin-like PCBs in fish generally make up 40-60% of total-TEQ. In certain fish species, e.g. eel, dioxin-like PCBs make up 80% of total-TEQ (SLV, 2005).

Temporal trends in environmental pollutants in environmental matrices have been studied for long periods by the Swedish Museum of Natural History. The studies on fish include e.g. Baltic herring and North Sea herring and in these samples a number of organic environmental pollutants, including PCB and dioxins, have been analysed. The concentrations of most of these compounds have displayed a declining trend from the 1970s on. In the case of dioxins, however, the concentrations declined from the 1970s until to about 1990 but since then they have remained at about the same level (Bignert et al., 2005). The reasons for the

halt in the decline are unknown, but it could be due to continuing emissions of dioxins.

Methyl mercury

Mercury in fish occurs predominantly as methyl mercury (MeHg) (Westöö & Rydälv, 1969; Lasorsa & Allen-Gil, 1995; Storelli et al., 2003). The total concentration of mercury (total-Hg) in fish muscle in usually reported and calculations of exposure to MeHg often assume that 100% of the total-Hg in fish is made up of MeHg. For the fish species that are particularly interesting for calculation of mercury exposure in humans, the mercury concentration can vary greatly depending on the capture site (Andersson et al., 1987). Fish in nutrient-poor forest lakes have a higher mercury content than fish in nutrient-rich plains lakes. Other factors affecting the mercury content include the amount of mercury in circulation and a range of chemical, physical and biological factors in the water area. In Scania for example, the mercury content in pike is reported to vary at least tenfold between lakes, from <0.1 mg/kg to over 1 mg/kg in one-kilo pike (Meili et al., 2004). Predatory fish have higher Hg concentrations than other species, but the concentration also increases with size of the individual fish. The mean concentrations for the most commonly consumed marine fish species are <0.05 mg/kg. Certain marine fish species can contain high concentrations of MeHg, e.g. halibut, certain species of tuna, swordfish, shark and ray, for which mean concentrations have been reported to be in the range 0.7-1.8 mg/kg, but can be even higher (Ohlin, 1993; Storelli et al., 2003; Forsyth et al., 2004). In Swedish waters, it is pike, pike-perch, perch, burbot and eel that can particularly accumulate MeHg, but other species can also have elevated Hg concentrations depending on capture site, e.g. salmonids caught in Lakes Vänern and Vättern (Lindeström & Grotell, 1998; Sundström et al., 2004). Local emissions of Hg affect the Hg concentrations in fish to a great extent, as can be seen e.g. in the north of Lake Vänern (Lindeström, 2001). Coastal pike in areas without local impacts can have relatively low MeHg concentrations (Greyerz et al., 2000).

As a basis for dietary advice and maximum levels, the National Food Administration in collaboration with the Swedish Board of Fisheries and the Environmental Protection Agency has mapped Hg concentrations in consumption fish. Sampling within the framework of the National Food Administration's monitoring activities is not carried out at national level, but rather at municipal level. Only a few samples were taken in retail outlets on behalf of the National Food Administration in this mapping project. For details of actual concentrations, see Table 4. Investigations of the Hg concentration in fish have also been carried out by other actors, often within the framework of national and regional environmental monitoring. From an environmental status perspective, however, it is samples other than those from commercial fish that are of interest. It is therefore not always possible to use data from environmental monitoring to calculate exposure in humans. IVL Swedish Environmental Research Institute Ltd. is the database host for reporting of the investigations, incl. Hg in biota, that are carried

out within the framework of national and regional environmental monitoring (IVL, 2005).

No general continuous temporal trend monitoring as regards mercury content in consumption fish has been carried out. In the Environmental Protection Agency's programme for environmental monitoring of freshwater, there are temporal trend data on mercury concentrations in pike from one lake, Storvindeln, perch from Skärgölen and Bälgsjön and salmon-trout from Abiskojaure. The concentration in pike-perch from Skärgölen has increased by 5% annually, while no trends can be observed in fish from the other lakes (Bignert, 2002).

Intake of nutrients and environmental pollutants from fish

Nutrients

Adults

Dietary data from Riksmaten 1997-98 (Becker & Pearson, 2002) show that fish contribute on average one-quarter of the intake of vitamin D, B_{12} and selenium (Figure 3). Fish make up around one-fifth of the total intake of n-3 fatty acids and 80% of the long-chain n-3 fatty acids in the diet. In addition, fish contribute 5-10% of intake of protein, α-tocopherol and niacin. Previous studies showed that intake of e.g. vitamin D and selenium was higher among individuals who often consumed fish and fish products than among those who consumed fish once a week or never (Becker, 1995). Among high consumers of fish, the mean intake of both vitamin D and selenium was on the level of the recommended intake according to SNR (Swedish Nutritional Recommendations), while those who seldom or never ate fish had a low intake.

Children

According to the National Food Administration's dietary survey Riksmaten – barn 2003, fish contributed 12-13% of selenium intake, around 10% of vitamin D intake, 52-56% of long-chain n-3 fatty acid intake and 4% of α-tocopherol intake, thus generally a smaller proportion than for adults (Enghardt Barbieri et al., 2006).

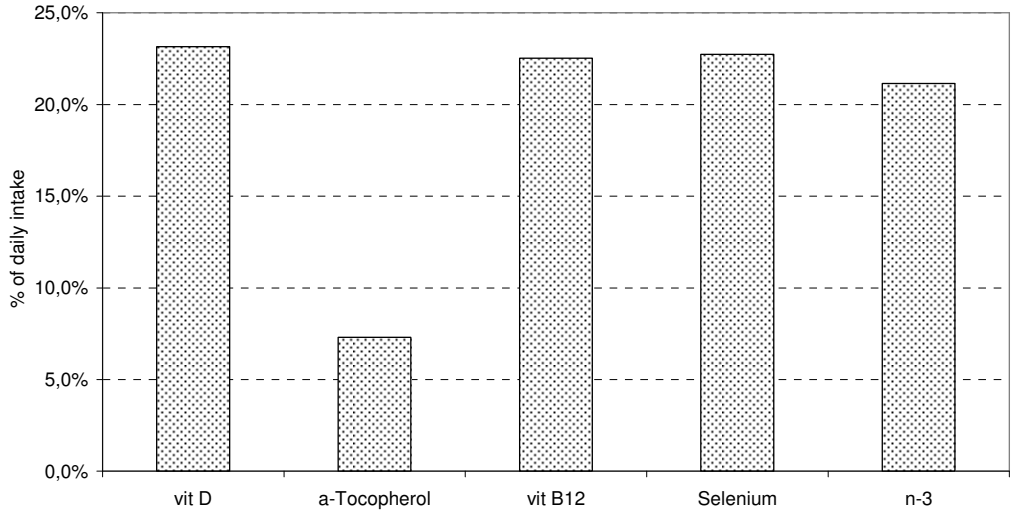

Fig. 3. Mean percentage contribution of certain nutrients from fish and shellfish in *Riksmaten 1997-98*.

Dioxins and PCB

Adults

Intake of environmental pollutants in adults via the diet has been monitored in a number of investigations from the National Food Administration. In the case of organic environmental pollutants, such as PCBs and dioxins, intake estimates of these compounds were made in conjunction with the latest revision of dietary advice on oily Baltic fish (Darnerud et al., 1995; Wicklund Glynn et al., 1996). Data on concentrations used for these estimates were from the beginning of the 1990s and consumption data consisted of the Swedish Board of Agriculture's per capita statistics for food. In 2002, new intake estimates based on the dietary survey Riksmaten 1997-98 were published (Becker & Pearson, 2002), where samples for concentration data were mainly collected in the period 1998-99 (Lind et al., 2002). The estimated intake of PCBs and dioxins in the latter study was considerably lower, only 20-30% of the values produced in the 1995 study. One explanation may be the decline in concentrations of these compounds that has taken place in the environment during the past decade. For example, a decline in the concentration of PCBs, but also of other organic environmental pollutants, could be observed between 1991 and 1997 in Swedish beef and pork (Wicklund Glynn et al., 2000). However, better analytical methods and changes in consumption patterns may also have played a part.

An updated calculation of dioxin intake was made during 2005. It included new concentration data obtained in targeted investigations and within the framework of

the National Food Administration's monitoring programme (Ankarberg & Petersson Grawé, 2005). In addition to new concentration data being available, the concentrations in Baltic herring have been weighted on the basis of actual catch data from the Swedish Board of Fisheries, so that dioxin concentrations in various parts of the Baltic Sea are matched against the catch volumes of Baltic herring for the corresponding area of the sea. In the case of salmon, new estimates for consumption of farmed versus wild salmon have been made, which are based on the volumes imported from Norway and the volumes landed at Swedish ports respectively. The national median intake for all consumers is calculated at 1.1 pg total-TEQ/kg body weight/day, and the 95 percentile occurs at 2.9 pg/kg body weight/day. Dioxin intake for women of childbearing age (17-40 years) is somewhat less, 93 pg total-TEQ/kg body weight/day, and in this case the 95 percentile occurs at 2.0 pg total-TEQ/kg body weight/day. Around half the dioxin intake is calculated to come from fish and fish products, with other animal products making up the remainder. This new calculation also includes theoretical regional intake, which assumes that the Baltic herring consumed comes from neighbouring fishing grounds in the Baltic Sea. Overall, this new estimate of the national intake involves no major changes compared with the 2002 estimate, but certain regional differences have been observed.

In certain groups of consumers with particular dietary habits, intake of organic environmental pollutants can be considerably greater, e.g. as a result of higher fish consumption. Intake of organic environmental pollutants has thus been shown to be higher in east coast fishermen than in west coast fishermen or in the general population, since east coast fishermen eat more oily east coast fish, which have higher concentrations of organic environmental chemicals than other fish. It was also found that east coast fishermen had higher concentrations of these compounds in their blood (Asplund et al., 1994). In a study of male high consumers of fish from Sweden and Latvia, the concentration of organic environmental pollutants in blood, including a number of PCB-congeners, was correlated with intake of oily Baltic fish (Sjödin et al., 2000).

Children

Data from the 1989 dietary survey HULK (Household food purchasing and dietary habits; Becker, 1994) have been used for calculations of dioxin intake among children and young people aged 1-17 years (Appelgren et al., 2002). Overall, these calculations show that exposure to dioxins (PCDD/DF + DL-PCB) on a body weight basis decreased with increasing age from the ages 1-3 to 19-24 years. The younger age groups (1-10 years) had a mean daily exposure that exceeded 2 pg TEQ/kg body weight/day. Boys had a higher exposure than girls, regardless of whether the basis for calculations was per kg body weight or per person. Dairy products represented the largest proportion of total exposure, ~30%, followed by meat products (20-25%), fish (15-20%), fats (7-12%), other fatty foods (7-12%) and eggs (3-7%). In this calculation, PCDD/DF made up around 70% and DL-PCB around 30% of the total-TEQ exposure. It should be noted that the above-mentioned results reflect the dietary patterns of children and young people during

the 1980s, which may differ from those prevailing at the present time, and that the concentration data were mainly collected during 1998-99.

Intake of dioxins and dioxin-like PCB has also been calculated on the basis of consumption data from Riksmaten – barn 2003 and data on actual concentrations in animal foods (Becker & Enghardt Barbieri, 2004; Enghardt Barbieri et al., 2006; Concha et al., 2006). Preliminary results showed that median intake of dioxins/dioxin-like PCBs (total-TEQ) in 4-year-olds was 2.3-2.4 pg/kg kg body weight/day, in 7-8-year olds 1.8-1.9 pg/kg body weight/day, and in 11-12-year olds 1.2-1.3 pg/kg body weight/day. Based on median intake, fish, meat and dairy products were approximately equally significant for the total intake of dioxins in children in these ages. Compared with the dietary study HULK (see above), intake of dioxins and dioxin-like PCBs appears to have decreased for the corresponding age groups (Concha et al., 2006).

Methyl mercury

Adults

A calculated intake for mercury has been produced based on Riksmaten 1997-98 (Ankarberg & Petersson Grawé, 2005). A number of scenarios were included with different assumptions about Hg concentrations. The median value for exposure in women of childbearing age varied between 0.1 and 0.2 µg/kg body weight/week depending on scenario. The highest exposure was found in the worst-case scenario where pike was assumed to have a mercury content of 1.0 mg/kg (i.e. corresponding to the upper limit) and salmon a mercury content of 0.33 mg/kg, corresponding to concentrations measured in salmonids from Lakes Vänern and Vättern. For the women in this age group that represent the 95th percentile, intake varied between 0.3 and 0.8 µg/kg body weight/week depending on scenario.

A number of studies of exposure to MeHg in pregnant women and high consumers of fish in Sweden have been reported. The median MeHg concentration in the blood of pregnant women has been reported to be 1.3 µg/L in umbilical cord blood (Björnberg et al., 2003). Lower median concentrations have been measured in the blood of pregnant women, e.g. 0.7 µg/L (Rödström et al., 2004), 0.3 µg/L (Gerhardsson et al., 2005), and 0.5 µg/L (Bergdahl et al., 2005). In professional fishermen, high consumers of fish and individuals who eat a lot of fish from contaminated waters, higher mean Hg loads have been reported. In women who reported high consumption of fish, the median MeHg concentration in the blood was 1.7 µg/L (Björnberg et al., 2005), while in women with high consumption of fish from Lake Vättern the blood concentration was 7.9 µg/L (Helmfrid et al., 2003) and in older male anglers with high consumption of fish it was 8.6 µg/L (Johnsson et al., 2005). The concentration in the hair of sporting anglers' families was 0.9 mg/kg (median), while the median hair concentration in those who reported consumption of freshwater fish at least once a week was 1.8 mg/kg

(Johnsson et al., 2004). Mean Hg concentration in fish in the area was 0.7 mg/kg. The concentration of Hg in the hair of individuals with high consumption of freshwater fish in a study from 1985 was on average 3.2 ± 2.3 mg/kg (min-max 0.3-10.8 mg/kg) (Oskarsson et al., 1990), while the concentration measured in the hair of pregnant women during the period 1989-1991 was up to 0.27 mg/kg (min-max 0.07-0.96 mg/kg) (Oskarsson et al., 1994).

Children

A estimate of MeHg intake in Swedish children has been made based on the National Food Administration's study Riksmaten – barn 2003 (Becker & Enghardt Barbieri, 2004; Concha et al., 2006). Four-year-olds and children in school years 2 and 5 (approx. 8 and 11 years old) responded to a survey comprising questions on how often they ate a number of specific fish species. Exposure to MeHg was calculated with the aid of the survey responses and data on representative MeHg concentrations in fish. Median intake was calculated at 0.2, 0.2 and 0.1 µg MeHg/kg body weight/week for 4-, 8- and 11-year-olds (Concha et al., 2006). In those with high exposure (95th percentile) the estimated intake of MeHg varied between 0.35-0.62 µg/kg body weight and week in the different age groups, while the highest intake varied between 0.84-3.1 µg/kg body weight and week. The greatest contributor to intake of MeHg was lean sea fish (24-42%), while consumption of pike, perch, pike-perch and burbot contributed 10-36%, despite consumption of these fish species being very limited.

Assessments of benefits and risks

A range of different methods are used to estimate the health effects of dietary habits, both positive and negative. Within epidemiology, measures such as relative risk, odds ratio and etiological fraction are used. The results of this type of calculation are dependent on a range of factors, of which risk gradation and assumptions on exposure, effects and dose-response relationships are some. Knowledge of dose-response relationships is particularly important in low dose areas. All assumptions and estimates include uncertainty in the outcome and the magnitude of the uncertainty is often unknown. In those cases where the risk assessment is based on animal trials, e.g. for dioxins, there is an additional uncertainty in extrapolating from animal to human and in handling the unknown variation in sensitivity and kinetics in humans. This is dealt with through the use of uncertainty factors. The magnitude of these uncertainty factors is affected by whether the supporting data are regarded as weak and by the type of health effect. In many cases there are indications of effects but no quantitative data, which makes it difficult to determine a reliable exposure level. Differences in sensitivity and exposure between different groups in the population must also be considered. In those cases where uncertainty factors are used, the risk of effect in the population is not actually described, but it is rather a question of a reliability assessment, in which an exposure level that is considered to be reliable is established.

Assessment of benefits of fish consumption

The most well-documented health effect of eating fish is the decreased risk of cardiovascular disease. A range of clinical and prospective epidemiological studies have revealed a correlation between consumption of fish or fish oil and a decreased risk of dying from cardiovascular disease. The degree of dose-response, i.e. the intake levels at which this correlation applies, is not as well documented, mainly due to uncertainty in estimates of intake of fish and n-3 fatty acids. Meta-analyses of prospective population studies among the healthy normal population have shown that the risk of dying from cardiovascular disease among individuals who eat fish a few times per month or more often is lower than for individuals who eat fish more seldom than once per month (He et al., 2004a; Whelton et al., 2004). In the study by He et al., the risk decreased with increased fish consumption, and the risk decreased by 7% for each 20 g/d increase in fish consumption within the range 0 to $\geq$ 105 grams per day (assuming a portion size of 105 g). Other assessments indicate a progressively decreasing risk of cardiovascular disease in high risk groups, e.g. those who have previously suffered a heart attack, at intake of up to 40-60 grams of mainly oily fish per day (2-3

portions per week), corresponding to 0.6-0.9 g long-chain n-3 fatty acids per day (Marckmann & Grønbæk, 1999). Meta-analyses of controlled intervention studies provide no estimates of the dose-response relationship (Studer et al., 2005; Hooper et al., 2006; Wang et al., 2006).

An estimate made by the Danish Nutrition Council shows that if individuals with an elevated risk of ischaemic heart disease who do not eat fish were to begin to eat fish, around 25% of deaths from such diseases could be prevented (Ernæringsrådet, 2000). These calculations refer to the so-called etiological fraction, which is a measure of how the proportion of total morbidity in a population (expressed as a percentage) would be altered by a given change in consumption. The calculations are based on knowledge of consumption patterns or distribution of intake in the actual population and dose-response data for the relationship between changes in the actual dietary factors and morbidity or mortality.

The proportion of individuals with an elevated risk of cardiovascular disease in Sweden is difficult to estimate, but a considerable proportion of the population aged 50 and over has at least one of the risk factors high LDL cholesterol, overweight or high blood pressure (Socialstyrelsen, 1997). This group in the population would benefit most from regular fish consumption, based on the available epidemiological studies. Heart attack is the single greatest cause of death in Sweden, with more than 50 000 people suffering from heart attack or severe angina annually. In 2002, cardiovascular disease was responsible for around 45% of total mortality in Sweden (Socialstyrelsen, 2005).

Risk assessments

Dioxins and PCB

Assessment of the toxicity of dioxins has recently been tightened up, since new effect studies have shown effects at lower doses. The WHO's previous tolerable daily intake (TDI) for dioxins from 1990, 10 pg TEQ/kg body weight and day, was based on cancer effects in rodents (Ahlborg et al., 1992). At around the same time (1988), a Nordic expert group proposed a TWI of 35 pg TEQ/kg body weight (=TDI 5 pg TEQ/kg), based on similar effects (reproductive and tumour effects in monkeys and rats) (Ahlborg et al., 1988). In the risk assessments carried out since then, more sensitive effects have been identified and at present it is the effects on the progeny (morphology and function of reproductive organs in rats) that are considered to be the most sensitive. As a consequence of this, the tolerable intake has been lowered and is now the equivalent of TDI of approx. 2 pg TEQ/kg body weight and day (WHO: 1-4 pg TEQ/kg body weight and day; EU-SCF 14 pg TEQ/kg body weight and week; JECFA 70 pg TEQ/kg body weight and month; all tolerable intake data include both PCDD/PCDF and DL-PCBs) (van Leeuwen & Younes, 2000; SCF, 2000 and 2001; JECFA, 2002). The uncertainty factor in the

SCF assessment is based on a LOAEL in animal trials (effect on male reproduction parameters in rats), which converted to 'estimated daily human intake' for dioxins becomes 20 pg/kg body weight. To compensate for differences in sensitivity between individuals, a factor 3.2 (WHO recommendation) was used, while to take into account the use of LOAEL instead of NO(A)EL, a factor 3 was used. The combined uncertainty factor is thus 9.6 (3 x 3.2) and gives rise to a TDI of 2 pg TEQ/kg body weight (=TWI: 14 pg TEQ/kg).

In the UK, the advice on fish consumption was revised in 2004 (SACN/COT, 2004). In conjunction with this, a toxicological assessment was made of the intake of dioxins that could be tolerated by consumer groups other than women of childbearing age and girls, i.e. a risk assessment based on critical effects other than those affecting the foetus/offspring. The Kociba cancer study on rats was used (Kociba et al., 1978) and, converted to body weight and with an uncertainty factor of 9.6 (× 3.2 in order to compensate for differences in accumulation of various dioxin-like compounds, and ×3 because LOAEL was used instead of NO(A)EL), resulted in a tolerable intake, or reference intake, of 8 pg TEQ/kg body weight/day, thus 4 times higher than the EU's current TDI.

A Swedish risk assessment has recently been carried out that in the same way as the British example above attempted to calculate the risk of dioxin exposure for groups other than girls and women of childbearing age. In this case too, cancer was used as the most sensitive effect when *in utero* effects were excluded. Based on quantitative benchmark-modulated data from animal trials and knowledge of the effects of dioxins in epidemiological studies, the authors consider the exposure range 2-10 pg TEQ/kg body weight/day to represent the range where the cancer risk in humans is very low or non-existent (Hanberg et al., 2007).

There is currently no internationally accepted TDI for non-dioxin-like PCBs due to the fact that this is a very complex group of chemicals with many different congeners with different degrees of toxicity, and where commercial preparations can contain more or less of various types of environmental pollutants (including chlorinated dibenzofurans). However within the framework of the Inter-Organisation Programme for Chemical Safety (IPCS), a document has been produced that, based on a range of effects, suggests a TDI, or reference dose, concerning a technical PCB mixture (Aroclor 1254) (CICAD, 2000). This reference dose has been calculated to be 20 ng/kg body weight/day, and has been produced with the use of an uncertainty factor of 300.

In the EFSA's assessment of non-dioxin-like PCBs (EFSA, 2005), the option taken was to not establish any health-based reference value/TDI, since interpretation of the results from epidemiological and toxicological studies is complicated by mixed exposure to both dioxin-like and non-dioxin-like PCB, and in many cases also other compounds. However reference is made to data indicating that exposure to non-dioxin-like PCB, or these compounds in combination with others, during early stages of development can lead to impaired

development of, for example, the central nervous system at a body load that is only slightly higher than that which could be expected in the average European consumer. However, certain individuals are exposed to intake that is considerably higher than the mean intake and the document therefore calls for continued efforts to decrease the PCB content in food.

MeHg

Up until 2003, the provisional tolerable weekly intake (PTWI) was set at 3.3 µg/kg body weight and week by the WHO/FAO's scientific expert committee the Joint FAO/WHO Expert Committee on Food Additives and Contaminants (JECFA) (WHO, 2000). The assessment was based on neurotoxic effects in adults, but it was decided that the PTWI was not intended to protect pregnant women (i.e. the foetus) from effects. Based on new epidemiological studies from the Faroe Islands and the Seychelles on effects on child development, the JECFA has revised its risk assessment and now specifies a PTWI of 1.6 µg/kg body weight and week (WHO, 2004). At this exposure level, pregnant women and their foetuses are considered not to risk neurotoxic effects. In 2000, the American National Research Council (NRC) carried out an assessment of the risk of effects from exposure during the prenatal stage based on the study from the Faroe Islands (NRC, 2000) that resulted in a reference dose of 0.1 µg/body weight/day, which corresponds to 0.7 µg/kg body weight and week. The respective assessments by NRC and JECFA thus resulted in a highest tolerable exposure level of 0.7 and 1.6 µg/kg body weight and week, which corresponds to a mercury level in hair of 1.2 and 2.2 mg/kg respectively. That these two assessments arrived at different conclusions is mainly due to the fact that they used different sizes of uncertainty factors. The NRC added an extra uncertainty factor to take account of indications of cardiovascular-related and immunotoxicological effects. During 2006, the JECFA investigated whether the current PTWI should include others in the population in addition to pregnant women, e.g. children and the elderly. For adult individuals it is concluded that exposure can be of a magnitude of approx. twice as high as the PTWI, except for women of childbearing age, without any need to fear health effects (WHO, 2006). For children up to around 17 years of age, it is assumed that the sensitivity is not greater than in the foetus, but the possibility cannot be excluded that the sensitivity is greater than in adults, so the PTWI is also recommended for this age group.

The JECFA's PTWI has been calculated from the exposure levels at which no effects were observed in the Seychelles and Faroe Islands studies. On the Seychelles, no effects were observed in children at a hair concentration of 15.3 mg/kg in the mother during pregnancy, while the study from the Faroe Islands reports a so-called benchmark dose of 12 mg/kg. The mean value for these two studies is 14 mg/kg, which has been used in the calculation of PTWI (WHO, 2004).

Risk characterisation

Low fish consumption

In epidemiological studies, low fish consumption has been associated with an increased risk of cardiovascular disease. However, the dose-response relationships have not been fully clarified. The meta-analysis by He et al. (2004a) showed a decreased risk for intake one time per week or more often compared with more seldom than one time per month. In addition, a 20g/d increase in fish intake was found to be associated with a risk decrease of 7%.

The results from Riksmaten indicate that 2% of the adult population never eat fish and that approx. 2% eat fish more seldom than one time per month, while approx. 70-80% eat at least one fish meal per week (Becker & Pearson, 2002).

A Nordic-Baltic investigation from 2002 (Norbagreen; Becker, 2002) showed that around one-fifth of the adult population in Sweden eat fish and shellfish more seldom than one time per week (Table 5). The proportion is higher (27-30%) among individuals under 45 years of age. The proportion that meets the general dietary advice on eating fish 2-3 times per week is 44% and is lower among younger people than among older. The results from interview studies carried out in autumn 2005 and 2006 show that around one-third of the adult population eat fish *as a main course* 2 times per week or more often, while one-fifth responded that they eat fish more seldom than 1 time per week (Becker, 2007).

Table 5. Consumption frequencies (%) for fish and shellfish among adults, 2002 (Becker, 2002)

	All	Gender		Age			
Frequency		Women	Men	16-24 yrs	25-44 yrs	45-65 yrs	65+
< 1 time/mon	5	4	6	12	5	2	5
1 time/mon < 1time/wk	15	14	17	18	22	12	10
1 time/wk	36	38	33	33	34	38	36
≥ 2 times/wk	44	44	44	37	39	48	49
Times per month, mean	6.7	6.7	6.7	5.8	6.1	7.3	7.6

Against the background of the nutrition recommendations, 50-60% of the adult population should increase their fish consumption to 2-3 times/week. On the basis of epidemiological studies (He et al., 2004a), 20-30% of the adult population should increase their fish consumption to at least 1 time per week in order to decrease the risk of dying from cardiovascular disease.

Increasing fish consumption in accordance with the nutrition-based recommendations (Enghardt Barbieri & Lindvall, 2003) to 2-3 portions per week means that the estimated intake of long-chain n-3 fatty acids increases from an average of 0.2-0.25 g/d to 0.4-0.5 g/d among adults, i.e. is almost doubled. The importance of this for public health is difficult to estimate, but it could probably

contribute to a decrease in deaths from cardiovascular disease (Ernæringsrådet, 2000; van Kreijl et al., 2006).

Low intake of DHA in pregnancy

A supply of DHA during pregnancy and nursing is essential for normal child development during the prenatal stage and in infancy. Studies indicate a link between increased intake of DHA and the outcome of pregnancy and development of the nervous system in the foetus. DHA can be formed from α-linolenic acid but the intake required to ensure an adequate supply to the foetus and child is unclear. SNR 2005 recommends an intake of n-3 fatty acids of 1 energy percent (E%), but no specific recommendations are given for long-chain n-3 fatty acids. Some expert groups recommend 0.1-0.3 g DHA per day via the diet during pregnancy (SACN, 2004, Akabas & Deckelbaum, 2006). Data from Riksmaten show that average intake among women of childbearing age is 0.15 g/d and that around 50% have an intake below 0.1 g/d. An increased intake of n-3 fatty acids from fish can probably be beneficial for the baby during pregnancy and early development, particularly as regards women with a low intake of n-3 fatty acids. Based on SNO (Enghardt Barbieri & Lindvall, 2003), consumption of fish corresponding to the general dietary advice of 2-3 times per week with variation between lean and oily fish would give an intake of around 0.2-0.25 g/d.

Intake of vitamin D

According to Riksmaten 1997-98, average intake of vitamin D was 5 µg/d for women and 6 µg/d for men. Intake was higher among the elderly (> 65 years) than among younger people (< 35 years). The recommended intake of vitamin D was raised in the latest edition of NNR and SNR from 5 µg/d to 7.5 µg/d for adults and children over 2 years of age. It is difficult to estimate the proportion of the population lying in the risk zone for low vitamin D status (i.e. low serum concentrations of 25-hydroxy-vitamin D) on the basis of dietary data alone, and there is a lack of actual Swedish data for serum levels of 25-OHD, which is a marker of status. However, the results from studies on young people and the elderly in e.g. Finland and Denmark indicate that 25-OHD levels are low in a considerable proportion of these groups in the population (Andersen et al., 2005). In Finland, enrichment of milk with vitamin D has been shown to decrease the proportion of young men with low vitamin D status by 50% (Laaksi et al., 2006).

An intake of fish corresponding to the general dietary advice of 2-3 times per week would mean an average increase in vitamin D intake of 7 µg/d among women and 9 µg/d among men, which should lead to improved vitamin D-status. The long-term significance of increased intake is difficult to estimate. Supplementary vitamin D in the order of magnitude of 10-20 µg/d in combination with calcium supplementation has been shown to decrease the risk of fractures in post-menopausal women and in men over the age of 65 (Avenell et al., 2006).

From a nutritional perspective, consumption of fish should therefore increase in the Swedish population, especially among individuals with low consumption.

Dioxins/PCB

Median intake of dioxins/dioxin-like PCBs (WHO-TEQ) in Swedish adults is calculated to be half the relevant TDI (Table 6), but due to the great variation in dioxin intake it is also estimated that 14% of the population has an intake above the TDI (2 pg TEQ/kg body weight; EU-SCF). However, it should be noted that TDI is based on *in utero* effects in research animals, and thus primarily concerns the risks of effects in the offspring of women of childbearing age. In women of childbearing age (17-40 years) the proportion that exceeded the TDI was 5%. In the women in this age group that had a dioxin intake higher than TDI, this higher exposure was due in part to higher consumption of oily east coast fish compared with the dietary advice, but consumption of other oily fish can also play a certain role.

Table 6. Number (proportion) of individuals adhering to the dietary advice on oily Baltic fish and number (proportion) with total-TEQ intake exceeding TDI for dioxin/PCB* (Ankarberg & Petersson Grawé, 2005)

	Women < 40 years	Women > 40 years	Men
Total number, n	271	347	567
Eat more fish than advised	9 (3.3%)	10 (2.9%)	9 (1.6%)
Total-TEQ intake > TDI (%)	15 (5.5%)	90 (26%)	78 (14%)
>TDI, > advised	9/15 (60%)	10/90 (11%)	9/78 (12%)
> TDI, < advised	6/15 (40%)	80/90 (89%)	69/78 (88%)

*NB: The dietary advice for women of childbearing age is stricter than for other consumers.

According to recently published intake calculations for Swedish children (Concha et al., 2006), median intake for 4-year-olds is 2.3-2.4 pg TEQ/kg body weight/day, for children in school yr 2 (8-9-year-olds) it is 1.8-1.9 pg TEQ/kg/day, and for children in school yr 5 (11-12-year-olds) it is 1.2-1.3 pg TEQ/kg/day. These intake calculations show that 65% of 4-year-olds, 41% of children in yr 2 and 14% of children in yr 5 have a daily TEQ intake that exceeds the EU-SCF recommended TDI of 2 pg TEQ/kg body weight (=TWI: 14 pg TEQ/kg).

MeHg

The most sensitive group in the population is pregnant women, due to the greater sensitivity of effects on the foetus. In the latest investigations of exposure in a random selection of pregnant women in Sweden, the JECFA's PTWI value of 1.6 µg/kg body weight/week was not exceeded, while 0-4% exceeded the American reference dose of 0.7 µg/week. When this is translated to the entire Swedish population, according to calculations it can mean that 2400-8500 pregnant women

per year exceed the reference dose somewhat (Rödström et al., 2004). Calculations of intake indicate that the JECFA's PTWI value can also be exceeded by pregnant women with high consumption of fish with elevated concentrations of MeHg (Ankarberg & Petersson Grawé, 2005).

With the knowledge that exists today, it is unlikely that any negative health effects will arise in the foetus at the actual exposure levels, but the safety margin is smaller for those with higher MeHg exposure.

For men and older women, the PTWI can be exceeded by a factor of 2 according to the JECFA assessment. In targeted investigations of exposure in high consumers of fish, the average exposure has been under such a level, but the individual variation is very great and cases of it being exceeded have also been reported. For the vast majority of men and older women, MeHg-exposure is at a safe level. However there are some minor Swedish studies of individuals who eat a lot of fish with elevated MeHg concentrations (Helmfrid et al., 2003; Johnsson et al. 2004, 2005) showing that exposure in certain cases can be on a par with that reported in Finnish studies that indicate a link between high exposure to MeHg and cardiovascular disease. The possibility cannot be excluded that within the Swedish population there are groups that have such a high intake of MeHg that the risk of cardiovascular disease in these groups can be elevated. There is no basis available for determining what proportion of the population is involved but it is probably small and limited to individuals who eat self-caught fish with elevated MeHg concentrations very regularly.

Calculations based on the National Food Administration's 2003 investigation on children indicated that 0.1-2.6% of 4-year-olds and children in school years 2 and 5 exceeded the American reference dose or the JECFA's PTWI. These levels were observed to be exceeded in children who ate fish in the order of 50-100 grams daily. In many cases, consumption involved pike or similar. With regular consumption of fish with high Hg concentrations, the tolerable intake was exceeded in some cases at a total fish consumption of approx. 25-35 grams per day. The American reference dose was exceeded by children who consumed 20-160 grams of fish daily. In most cases, these children regularly consumed fish species with elevated Hg concentrations (Concha et al., 2006).

Against the background of the studies and calculations that have been carried out on MeHg exposure, it can be concluded that there is a potential for elevated intake of MeHg if consumption patterns are altered in favour of fish with elevated concentrations of MeHg.

Conclusions

Consuming fish 2-3 times/week provides good conditions for fulfilling the nutritional recommendations, especially as regards vitamin D and selenium. This

means that 50-60% of the adult population should increase their fish consumption. On the main basis of epidemiological studies, 20-30% of the adult population should increase their consumption of oily fish in particular to at least 1 time/week in order to decrease the risk of contracting cardiovascular disease.

With high consumption of fish with elevated concentrations of environmental toxins, there is a risk of the tolerable intake being exceeded. For both persistent organic compounds and MeHg, exceeding the tolerable intake to a limited extent does not mean that health effects arise, but that the safety margin is smaller. In rare cases the tolerable intake for MeHg can be exceeded to a greater magnitude. This applies to individuals who very often eat self-caught fish with elevated concentrations of MeHg. The exposure can even be so high that there is an increased risk of MeHg-induced effects in the form of cardiovascular disease.

Methods for comparing risks and benefits

A balanced quantitative assessment of the positive and negative health effects of food consumption requires that the supporting data in their entirety are comparable and that there are data that are applicable to different groups in the population. One difference between studies dealing with nutritional aspects and risk aspects is that the former give an estimate of the dose-response in relevant dose areas, while in the risk-based studies the dose-response relationship is often reported for dose ranges that are considerably higher than those relevant for most population groups. Assessments of the magnitude of the risk of toxicological effects in a population is therefore generally expressed as the proportion exceeding the intake level considered to be safe, e.g. JECFA's PTWI. Exposure above such a level is regarded as unacceptable. In order to carry out a balanced quantitative assessment of risks and benefits, there is also a need for a common scale for the degree of effect for the toxicological and nutritional aspects. DALYs (disability adjusted life years) and QALYs (quality adjusted life years) are two measures of public health that have been used in some risk-benefit assessments that include fish consumption, and these are described more fully below.

DALYs and QALYs

DALYs and QALYs are different measures of the health status in a population (Peterson et al., 1998; Moradi et al., 2006; Allebeck et al., 2006). DALY is the total number of healthy years lost due to death (years of life lost, YLL) and impaired function (years lived with disability, YLD). DALY gives the contribution from different groups of diagnoses and can be used to evaluate the magnitude of the different risk factors contributing to the total DALY value. QALY is a measure of the total number of years with full health in a population.

The DALY value is calculated on the basis of age-specific and gender-specific data on mortality and morbidity in a population and a weighting factor that is an assessment of the degree of disability caused by different diseases. Data are also required on life expectancy depending on age, gender and disease. Weighting factors have been produced at international level and are based on combined assessments carried out by various groups of experts (Gold et al., 2002). Weighting factors are available for a range of ailments, both psychiatric and somatic. A Swedish DALY calculation published in 1998 based on statistics on morbidity and mortality due to different ailments (Diderichsen et al., 1998) showed that cardiovascular disease, various mental illnesses and cancer made the

largest contribution to the total DALY value. The results from more recent calculations give similar results (Allebeck et al., 2006; Moradi et al., 2006). In recent years DALY and QALY have also begun to be applied in order to assess the effects of food consumption on the health outcome in the population in a standardised and quantitative way (WHO, 2002). Calculations have been made of the contribution of various dietary factors and diet-related risk factors to DALY, including on an international level by WHO (WHO, 2002) and on a national level by the Nederlands (van Kreijl et al., 2006).

The Dutch DALY calculations are based on the estimated decrease in the incidence of cardiovascular disease as a result of increasing fish consumption by one or two portions per week (van Kreijl et al., 2006). This decreased incidence value was then used to calculate the health benefit expressed in DALY. The total health benefit of increasing fish consumption from the current 2-3 times to 4-8 times per month is estimated to be around 20% of the total food-related DALYs. However, fish consumption in the Nederlands is lower than in Sweden. The Dutch report includes no calculations of the health consequences of mercury or dioxins, but considers the contribution from these compounds in terms of DALY to be low.

A comprehensive quantitative analysis of the risk and benefit aspects of fish consumption based on American conditions and QALYs has been published by a group at the Harvard Risk Analysis Center in the USA. Cohen and co-workers (2005a) carried out a risk-benefit assessment based on the risk of impaired development of the nervous system (decreased IQ) induced by exposure to MeHg (Cohen et al., 2005b) and nutritional benefits in the form of decreased risk of stroke and cardiovascular disease (Bouzan et al., 2005; König et al., 2005) and of increased IQ in children due to n-3 fatty acids (Cohen et al., 2005c). The analysis by Cohen et al. (2005a) is based on five scenarios constructed around consumption advice directed at different groups and assumptions on how consumption of fish is altered in all or parts of the population. Scenario one represents the ideal situation; women of childbearing age avoid eating fish with moderately elevated or high Hg concentrations, while eating the same amount of fish as previously (i.e. they eat fish with concentrations <0.14 mg/kg). Scenario two is based on women of childbearing age reducing their fish consumption, regardless of fish species, by 17%, which was the actual outcome when the American FDA presented its dietary advice in 2001 (Oken et al., 2003). The third scenario assumes that the entire population decreases its fish consumption by 17%. Scenario four shows the outcome of men and older women increasing their consumption of fish by 50%, while in scenario five women of childbearing age also increase their fish consumption by 50%.

Using QALY as a quantitative measure of the population's health, it was found that the greatest benefits on a population basis were achieved if the entire population, except women of childbearing age, increased its fish consumption by 50%. The net gain calculated in QALYs would then be 120 000 due to a decreased risk of cardiovascular disease and stroke. Were women of childbearing age to also

increase their fish consumption, the net gain would instead be 90,000 QALY, due to decreased IQ as a result of MeHg giving rise to a loss of QALY. The worst alternative of the scenarios studied was if the entire population decreased its fish consumption by 17%, which would result in a net loss of 41,000 QALY, mainly caused by an increase in morbidity in cardiovascular disease and stroke. If women of childbearing age avoided consumption of fish containing MeHg concentrations in excess of 0.13 mg/kg, this would result in a gain of 49,000 QALY.

Estimates of changes in IQ in children are also reported. These are marginal in all scenarios, in the order of magnitude of 0.02-0.1 IQ unit per child. If fish consumption were to increase by 50% in the entire population, it would result in a net loss of 0.07 IQ units per child. In the third scenario, the individual risk of dying from cardiovascular disease increases in older men (75-84 years) by 2 per 10 000 annually due to the decreased consumption of fish. With a 50% increase in fish consumption in the entire population according to scenario four, the risk of older men dying from cardiovascular disease decreases by 5 per 10,000. The uncertainty in the estimates arising from the assumptions made regarding positive and negative effects is also presented and shows that the end result expressed in QALY can be altered depending on the assumptions made. The authors emphasise the importance of clarity in the formulation of dietary advice directed at women of childbearing age in order to avoid secondary effects in the form of a general decrease in fish consumption, which according to the calculations on a population basis leads to a net loss of QALY. Dietary advice should therefore be preceded by thorough investigations of how the population might react to it and alter its dietary habits.

In an earlier study (Ponce et al., 2000), QALYs were also used to estimate the health effects of fish consumption. The measures of effects were the decreased risk of dying from a heart attack with increased fish consumption due to increased intake of n-3 fatty acids; and the increased risk of delayed speech in children (only begin speaking after 24 months) due to increased exposure to mercury during pregnancy. The latter estimates were based on a study of children born to mothers who consumed mercury-treated grain (Marsh et al., 1987). The authors took as their starting point various assumptions on the magnitude of the weighting factors and tested the method on the entire population or only on women of childbearing age. Similarly to Cohen et al., they found that the outcome was strongly dependent on whether the effects were investigated in the entire population or only in the women of childbearing age group. In the former case the benefit outweighed the risk, while the risk outweighed the benefit in the latter case. They also tried varying the size of the various weighting factors and found that this had the greatest impact on the outcome. In a later study (Ponce et al., 2001), the analysis was further extended to also include what was referred to as 'discounting', i.e. that a healthy year at a young age weighs heavier than a healthy year at a high age. Since heart attacks generally occur at older age this had greater importance, with the benefits of fish consumption having less impact in the calculation of QALY. They also examined the impact of births on the outcome, i.e. the incidence of

babies born that can suffer from delayed development. The authors found the method to be information-intensive and to require a range of assumptions in addition to those used in risk assessment. Despite this, the authors considered QALY or other methods for comparing health effects with each other to be a good tool for supporting strategic environmental health work.

Other risk-benefit assessments of fish consumption

A number of risk-benefit assessments of fish consumption have been published in recent years. A common feature of most of these assessments as regards fish consumption is that they have been of a descriptive or qualitative character due to lack of quantitative data. Searches in the databases PubMed and DialogSelect (+) on the key words risk, benefit, fish, consumption or mercury produced 44 references, but only a small proportion dealt with simultaneous analysis of both risks and benefits (Ponce et al., 2000; Wong et al., 2003; Hites et al., 2004; Tuomisto et al., 2004; Sakamoto et al., 2004; Foran et al., 2005; Cohen et al., 2005a; Gochfeld & Burger, 2005; Hansen & Gilman, 2005). It is mainly against the background of the latest risk assessments of MeHg and POPs and the increasingly clear correlation between fish consumption and decreased risk of cardiovascular disease that risk-benefit assessments have been initiated.

A detailed description of an innovative theoretical model for quantification of risks and benefits has been presented by Anderson et al. (2002). As their model, they selected fish consumption and weighed the negative effects of methyl mercury and the pesticide chlordan and the positive effects in the form of decreased risk of stroke, arterial disease and arthritis. However, they emphasise that theirs was not a complete evaluation based on all the existing literature, but should be seen as a description of a conceptual method of weighing benefits and risks. Their starting point was information on the relative probability of beneficial effects for certain ranges of fish consumption, and classification of the value of these benefits, a type of qualitative estimate of the health-promoting effects on a scale of zero to three. A similar process was carried out for the risks. In contrast to most other attempts to carry out risk-benefit assessments, the study not only used a cut-off value (e.g. PTWI or reference dose) to weigh the risk aspects but also dose-response data for exposure, both under and over the cut-off value. They then developed algorithms for calculating risk and benefit that make it possible to add a number of benefit and risk aspects. By adding the sum of risks and benefits, a fish consumption index was produced. It is shown through examples how the method can be used to calculate a net value for risk/benefit for different groups in the population and it is suggested that other aspects, such as cultural or even risk perception, could be weighed into the total calculation. Based on the work presented, the authors suggest a range of areas that need to be strengthened in order to improve this type of evaluation. For example, they identify weaknesses in the classification of seriousness and in knowledge of beneficial aspects, both in

the entire population and in certain groups within the population. As regards the risks, they ask for more information on the risks at exposure higher than the cut-off values.

An attempt at a combined response curve for risk and benefit effects has been presented (Gochfeld & Burger, 2005). This used the meta-analyses of He et al. (2003, 2004), who investigated the relationship between fish consumption and the risk of cardiovascular disease, and produced a threshold value of 15 g fish per day for beneficial effects to be achieved, primarily based on decreased risk of cardiovascular disease. A report on length of pregnancy and low birth weight also indicates a threshold value around 15 grams of fish per day for a beneficial effect (Olsen & Secher, 2002). This threshold value has been set in relation to the American reference dose (US EPA) of 0.1 µg Hg/kg body weight and day to ensure absence of damage in the foetus. The calculations showed that the threshold value for negative effects of MeHg exposure, i.e. the reference dose, was achieved at a daily consumption of around 30 grams of fish with an average concentration of 0.23 mg Hg/kg. At a lower average mercury concentration in fish (0.10 mg/kg), 60 grams of fish per day could be consumed without the reference dose being exceeded. Thus in both cases, the threshold value for the beneficial aspects was reached without the reference dose for MeHg being exceeded. Gochfeld & Burger (2005) did not evaluate the risks and benefits separately for different groups in the population, but rather assumed that the risks and benefits applied for both older population groups and women of childbearing age.

Tuomisto et al. (2004) calculated the positive and negative effects of limiting consumption of farmed salmon to one time per month. Based on the American EPA assessment of the cancer risk (EPA, 2000) Tuomisto et al. concluded that at most 40 deaths within the EU could be prevented by more restrictive dietary advice for farmed salmon, but that at the same time there would be increased mortality from cardiovascular disease (based on data from Harper & Jacobson, 2001; Din et al., 2004). The net effect of such restriction of salmon consumption would be 5200 more deaths in total within the EU.

The UK, Denmark and Norway have recently presented national reports where the nutritional and toxicological aspects of fish consumption are examined (Fødevaredirektoratet, 2003; SACN/COT, 2004; VKM, 2005; EFSA, 2005). In all cases, the risk-benefit assessments are of a qualitative character. The investigations have resulted in dietary advice with the main messages that fish is healthy, that consumption of oily fish is encouraged and that children, women of childbearing age, pregnant women and breastfeeding mothers should avoid or limit their consumption of certain fish species. This dietary advice is described in more detail in Appendix 2.

Conclusions

There are relatively few reports that have presented quantitative estimates of both the risks and benefits of consumption. Application of DALY or QALY has mainly been based on effects on cardiovascular disease (n-3 fatty acids) and cognitive development (n-3 fatty acids and MeHg). The results show that the net effect on population level is dependent on the boundaries set. If the entire population is included in the calculations, the net effect of high fish consumption is a health gain expressed in QALY, mainly because a large proportion of the population includes individuals who lie in the risk zone for contracting cardiovascular disease. Calculations that only include women of childbearing age (15-44 years) result in a negative net effect expressed in QALY because of predicted impairment of IQ or speech in their offspring due to exposure to MeHg. Calculations are based on estimates of dose-response relationships between intake of fish and the risk of heart attack, and between intake of n-3 fatty acids or MeHg and mental development (IQ). It should also be pointed out that a range of assumptions have been made, e.g. as regards the shape of the dose-response curve in the low dose area. Sensitivity analyses show that the magnitude of the effect calculated in QALY can vary considerably.

Calculations of beneficial health effects of fish are based on e.g. cardiovascular diseases in prospective cohort studies, where fish consumption is estimated using frequency questionnaires. Differences in portion estimates, frequency intervals and dietary pattern (e.g. as regards fish consumption in population) give rise to uncertainty in dose-response. For effects on pregnancy and development, there are unclarities as regards dose-response, which can be due e.g. to differences in dietary pattern and n-3 status in the groups studied.

For MeHg there are human data available, but the dose-response relationship is unclear at low exposure levels. Furthermore, there is currently a lack of internationally agreed weighting factors for effects that can arise, which are necessary for calculating DALY or QALY, although it may be possible to make extrapolations. This applies particularly if the risk assessment is based on animal data, as is the case for dioxins and PCBs. In the case of dioxin from e.g. fish, the supporting data for quantifying the risk of health effects in humans at relevant exposure levels is relatively weak and incidence data are therefore lacking. It is thus not possible to carry out a quantitative assessment on the basis of the actual exposure situation with regard to POPs.

Model calculations of intake of nutrients and environmental pollutants using Swedish data

n-3 fatty acids and dioxin/PCB

One way to indirectly assess whether consumption of oily Baltic fish can carry overall benefits or risks is to calculate the consumption level at which the majority of the population (95%) have an intake below TDI for dioxin (2 µg/kg body weight), while at the same time keeping intake of n-3 fatty acids above a desirable level for the majority (95%). The example uses consumption data from Riksmaten for women of childbearing age, 17-40 years. The value used for desirable intake of long-chain n-3 fatty acids is 0.2 g/day, which has been proposed in e.g. the Eurodiet project (Eurodiet Core Report, 2000).

The calculations are based on the actual base intake of n-3 fatty acids and dioxins from fish other than Baltic herring and Baltic salmon. Intake of n-3 fatty acids and dioxin-TEQ for each individual was then calculated at increasing consumption of Baltic herring or farmed salmon in the range 50-350 g/month. In the scenario with Baltic herring, intake of dioxin-TEQ from other animal products was added.

Figure 4a shows that the risk of TDI being exceeded by 5% of women (95th percentile for intake) is achieved at lower consumption of Baltic herring than the consumption required in order for intake of n-3 fatty acids among the majority ($\geq$ 95%) of women to be at least 0.2 g/day (5th percentile). In this example, the content of dioxins is limiting for consumption. If however farmed salmon is chosen instead of Baltic herring, the majority of women will achieve the desirable intake of n-3 fatty acids at a lower consumption level, while the risk of TDI being exceeded by any of the women is small (Figure 4b). This is because the actual value for n-3 fatty acids is higher in farmed salmon than in Baltic herring and because the weighted mean value for dioxin in farmed salmon is around one-fifth of the content in Baltic herring (Table 4).

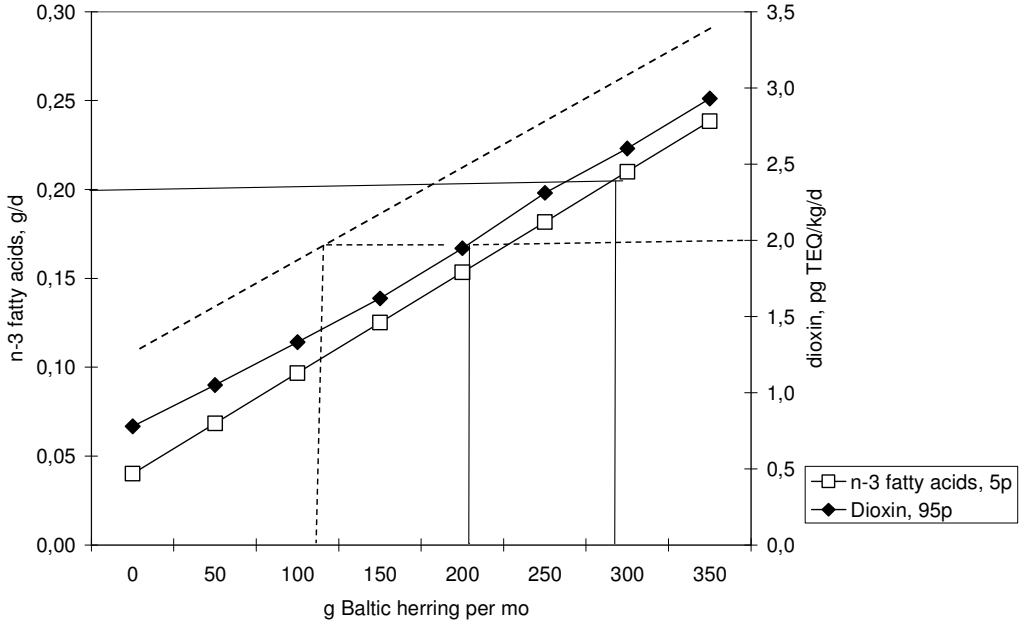

Fig. 4a. Relationship between monthly consumption of Baltic herring among women (17-40 years) and intake of dioxin and n-3 fatty acids. The vertical lines show the herring consumption at which at least 5% of the women reach the TDI for dioxins (2 pg/kg and day), i.e. the 95th percentile, and 95% of the women achieve an intake of 0.2 g/d of n-3 fatty acids, i.e. the 5th percentile. The dashed curve shows the 95th percentile for dioxin from fish and other animal products. For concentration data for dioxins and n-3 fatty acids, see Table 4.

This example only includes intake of dioxin and n-3 fatty acids from fish. The contribution of dioxin-TEQ from other animal products (milk, cheese, meat, eggs) give on average 0.5 pg/kg body weight. This means that the scope for consuming Baltic herring is less than the 200-250 g/month shown in Figure 4a. As the figure shows (solid line), and for a consumption in the order of 1 portion per month (100-150 g/month; dashed line) there is a small risk of TDI being exceeded in the majority of the women. The same result is achieved if Baltic salmon is used in the calculations, since the dioxin-TEQ content is comparable to that in Baltic herring. In the example with farmed salmon, consumption of around 1 portion per month gives a total intake of long-chain n-3 fatty acids of approx. 0.2 g/day in the majority of the women (Figure 4b). In these calculations, only the consumption of oily Baltic fish has been varied, while consumption of other fish remained unchanged, i.e. as in Riksmaten. However, if the women were to increase their total consumption of fish in accordance with the general dietary advice, the proportion exceeding TDI would be around 35% in the following scenario: Total consumption of fish 3 times per week, of which oily Baltic fish 1 time per month (i.e. corresponding to the current dietary advice) and other oily fish (e.g. farmed salmon) 3 times per month (Ankarberg et al., 2007).

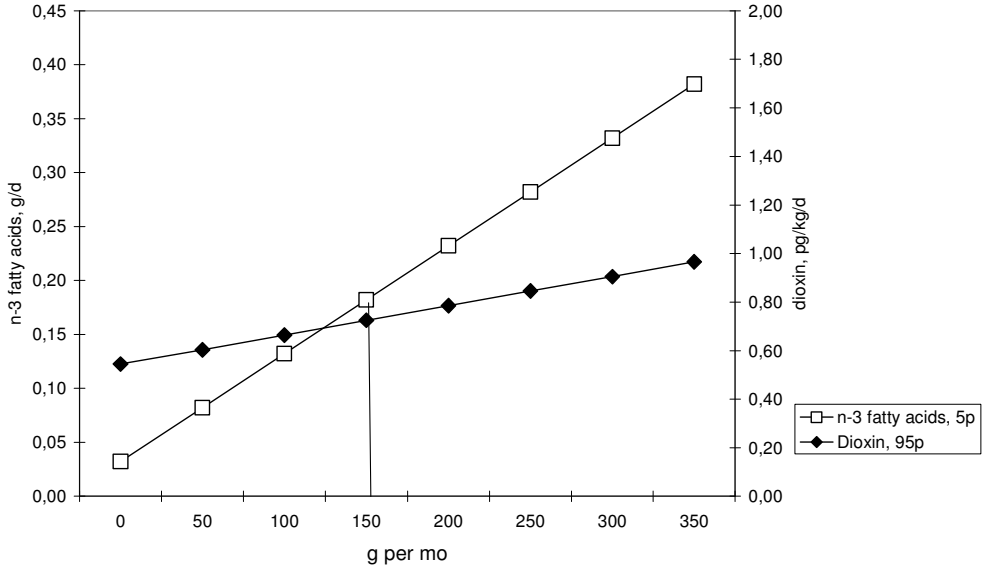

Fig. 4b. Relationship between monthly consumption of farmed salmon among women (17-40 year) and intake of dioxins and n-3 fatty acids. The vertical line shows the consumption at which 95% of the women achieve an intake of 0.2 g/d of n-3 fatty acids, i.e. the 5th percentile. For concentration data for dioxins and n-3 fatty acids, see Table 4.

Vitamin D and MeHg

Data from Riksmaten were also used to calculate intake of mercury at different intakes of freshwater fish. The mercury intake from other fish was used as background intake. The contribution of mercury from freshwater fish was then calculated at increasing intake of freshwater fish from 50 g/month to 350 g/month. Two different Hg concentrations in fish were used, 0.5 mg/kg, which is the limit for most fish, and 1.0 mg/kg, which is the limit for pike. A portion size of 150 grams was used.

Intake of mercury among women of childbearing age (set as 17-40 years) and for women older than 40 years is shown in Table 7. The distribution of intake in the younger women at consumption of freshwater fish with different Hg concentrations is shown in Figure 5. Table 7 and Figure 5 show that none of the younger group reach the tolerable intake of 1.6 µg/kg body weight per week if fish consumption is increased to 2 times per month and if the MeHg concentration in the additional fish is under 0.5 mg/kg. At a concentration in fish of 1 mg/kg, the 99th percentile lies at the tolerable weekly intake at a consumption of 2 times per month. The latter means that increasing consumption of fish with a mercury content of 0.5 mg/kg at most 1 time per week would carry little risk of exceeding the tolerable weekly intake of 1.6 µg/kg body weight and week. Set in relation to the American reference dose, 0.7 µg/kg body weight per week, fish consumption can increase from the level in Riksmaten by approx. 1 portion per month of fish

with a concentration of 0.5 mg/kg, without the reference dose being exceeded. For an increase in consumption of 1 portion per month of fish with a concentration of 1 mg/kg, the reference dose is exceeded by 50% of women of childbearing age.

The calculations thus show that there is scope for increasing fish consumption at population level without the tolerable intake for MeHg being exceeded. However, it should be noted that the calculations in Figure 5 are based on everyone, including those who already eat a lot of fish, increasing their fish consumption by the same amount. A scenario in which those who eat little fish increase their fish consumption, while those who already eat a lot of fish do not alter their diet, would of course produce different results.

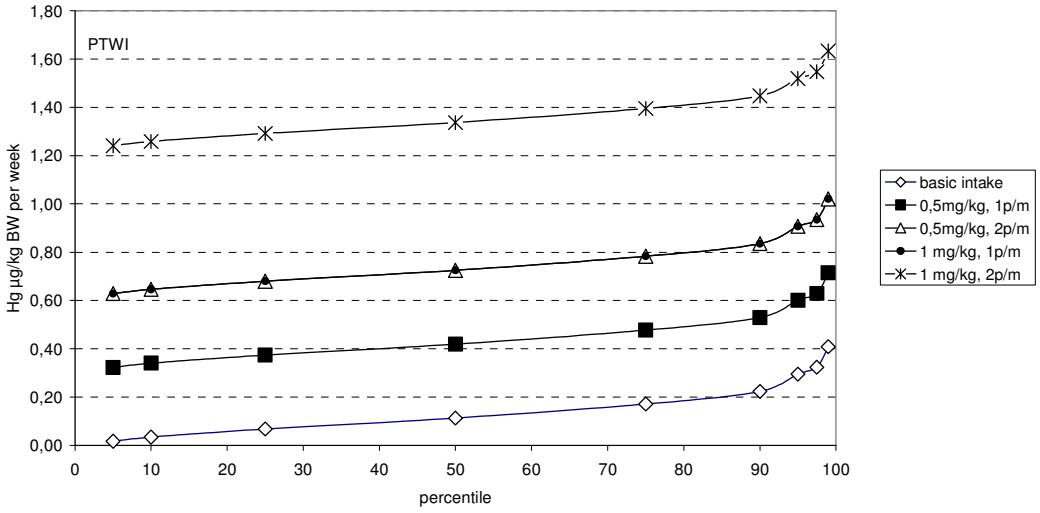

Fig. 5. Intake of mercury in relation to consumption of fish with different MeHg concentrations among women aged 18-40 years from Riksmaten (Becker & Pearson, 2002). The base intake comprises the fish consumption that the women in the study reported, excluding consumption of pike, perch, pike-perch and burbot.

Table 7. Intake of Hg (µg/kg/week) from fish at different levels of consumption of freshwater fish

	Base intake*	1 port/mon	2 port/mon	2 port/mon
		0.5 mg/kg	0.5 mg/kg	1 mg/kg
Women < 40 years				
Mean	0.13	0.43	0.74	1.35
SD	0.09	0.09	0.09	0.09
50p	0.11	0.42	0.73	1.34
90p	0.22	0.53	0.84	1.45
95p	0.29	0.60	0.91	1.52
97.5p	0.32	0.63	0.94	1.55
99p	0.41	0.72	1.02	1.63
Max	0.62	0.93	1.23	1.85
Women > 40 years				
Mean	0.10	0.36	0.62	1.14
SD	0.09	0.09	0.09	0.09
50p	0.08	0.34	0.60	1.13
90p	0.19	0.45	0.71	1.23
95p	0.26	0.52	0.78	1.30
97.5p	0.34	0.60	0.86	1.38
99p	0.39	0.65	0.91	1.44
Max	1.12	1.38	1.64	2.16

Table 8. Intake of vitamin D at different levels of consumption of freshwater fish

	Base intake*	1 port/mon	2 port/mon
Women < 40 years			
Mean	4.4	5.4	6.3
SD	1.7	1.7	1.7
50p	4.2	5.2	6.1
90p	6.6	7.6	8.5
95p	7.4	8.4	9.3
97.5p	8.3	9.2	10.1
99p	9.3	10.3	11.2
Max	10.9	11.8	12.7
Women > 40 years			
Mean	5.3	6.3	7.2
SD	2.1	2.1	2.1
50p	5.1	6.0	6.9
90p	8.1	9.0	9.9
95p	9.3	10.2	11.2
97.5p	10.3	11.2	12.1
99p	11.4	12.3	13.3
Max	12.4	13.3	14.3

* Intake from other foods

The 'benefit factor' used was vitamin D. The recommended daily intake is 7.5 µg/day (SNR, 2005). The vitamin D content is high in the freshwater fish in question, especially in perch and pike-perch (Table 4). A weighted mean value of 18.6 µg/100 g was used in the calculations, which were carried out in the same way as for mercury. Intake of vitamin D increased from an average of 4.4 µg/d to 6.3 µg/d in the younger women and from an average of 5.3 µg/d to 7.2 µg/d in the older women at a consumption of 2 portions a month (Table 8).

Figure 6 illustrates how the 95th percentile for intake of MeHg and median intake of vitamin D changes in relation to consumption of freshwater fish with different Hg concentrations. With consumption of fish with an average content of 0.5 mg Hg/kg 2-3 times per month in addition to consumption of other fish, the risk of PTWI being exceeded is small. If the concentration is on average 1 mg/kg, around 5% of the women risk having an intake that exceeds PTWI at consumption of around 2 times per month, if fish consumption is otherwise unchanged. With consumption of freshwater fish around 2 times per month the calculated median intake of vitamin D increases from 4.2 to 6.1 µg/d among the younger women and from 5.1 to 6.9 µg/d among the older women. This should be compared with the recommended intake of 7.5 µg/d according to SNR (2005). An increase in fish consumption in those consumers who eat little or no fish would considerably improve vitamin D intake.

These model calculations exemplify the fact that increased consumption of certain types of fish can be associated with both health-related risks and benefits. The risk of high intake of environmental pollutants is dependent on the concentration of these pollutants and under a certain level the benefits of eating fish, e.g. as a source of n-3 fatty acids and vitamin D, outweigh the risks.

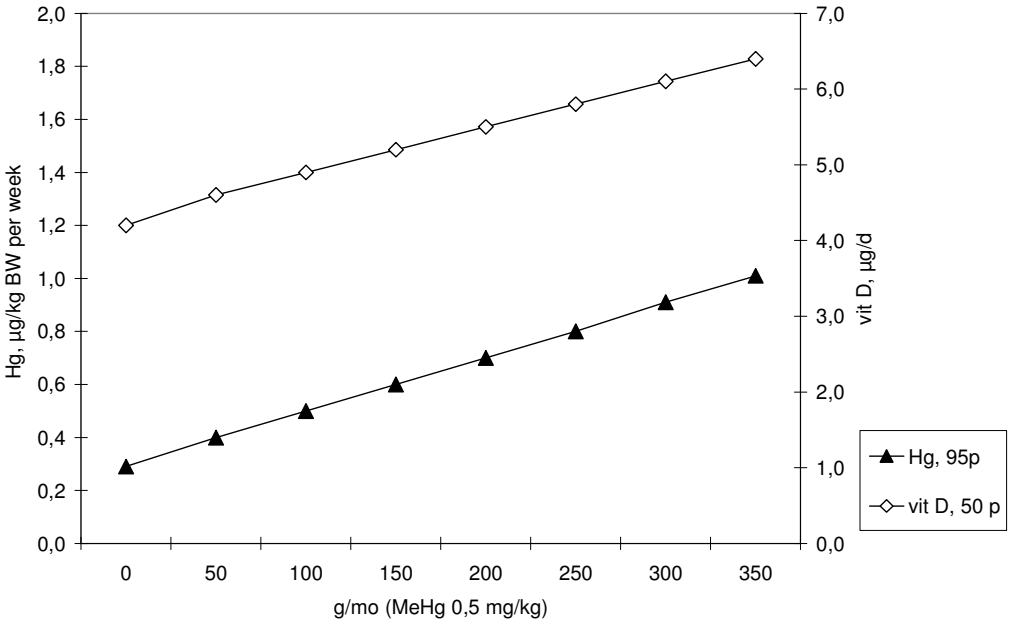

Fig. 6a. The 95th percentile for intake of mercury and median intake (50th percentile) of vitamin D in relation to consumption of freshwater fish with a Hg-concentration of 0.5 mg/kg.

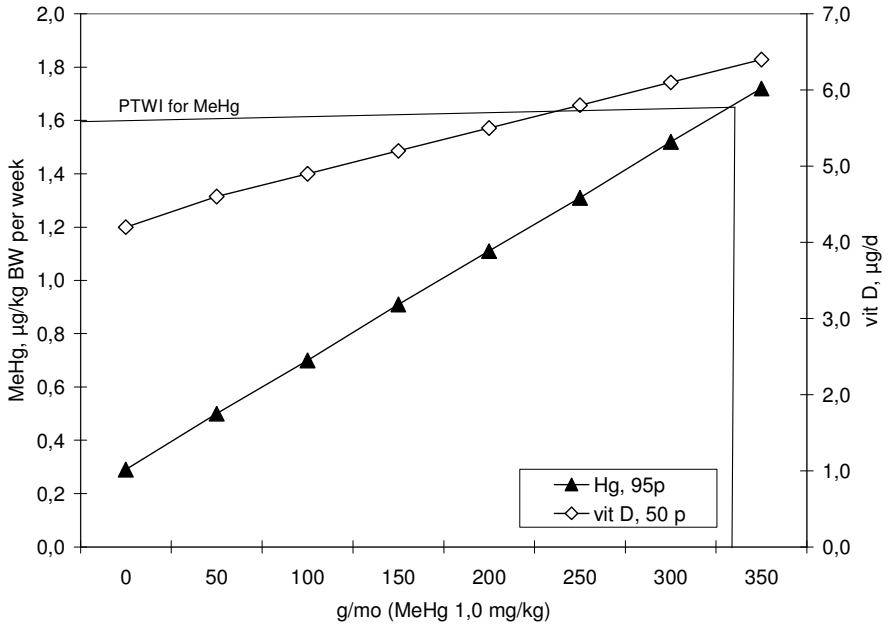

Fig. 6b. The 95th percentile for intake of mercury and median intake (50th percentile) of vitamin D in relation to consumption of freshwater fish with a Hg-concentration of 1.0 mg/kg.

Intake of environmental pollutants based on SNO

Intake of dioxin/PCBs and MeHg was also calculated based on food lists according to the SNO model (Swedish Nutrition Recommendations Objectified; Enghardt Barbieri & Lindvall, 2003). These calculations refer to a female reference individual and are presented in Tables9 and 10.

For dioxins/PCB, the concentration data used were those reported in the revised intake calculations according to Ankarberg & Petersson Grawé (2005). The reference individual's base intake of dioxin-TEQ amounts to 35 pg/d and includes the contribution from milk, cheese, eggs and butter/margarine. The contribution from different combinations of fish consumption have been added. The calculations show that consumption of fish according to the nutrient-based dietary advice gives little risk of TDI being exceeded. The calculations also show that consumption of oily Baltic fish 1 time per month in combination with varied consumption of lean and oily fish 2 times per week gives a dioxin intake that reaches TDI. Since around half the median consumer's dioxin intake comes from food groups other than fish, the choice of these other foods plays a not insignificant role for the total intake and this can lead to deviations from the calculations in Table 9.

Table 9. Intake of dioxins (total-TEQ) in a reference person (woman) who eats fish 2-3 times per week, with different combinations of fish types and with a constant base intake of dioxins from other animal products according to SNO.

Type of fish meal	No. fish meals per week	Dioxin intake, pg total-TEQ per week	% of TDI (60 kg body weight)
Lean sea fish 2 times/wk + oily fish 1 time/wk	3	625	74
Lean sea fish 1 time/wk + oily fish 2 times/wk	3	828	98
Lean sea fish 1 time/wk + lean freshwater fish 1 time/ wk + oily fish 1 time/wk	3	728	86
Lean freshwater fish 1 time/ wk + oily fish 2 times/wk	3	931	111
Lean sea fish 1 time/wk + oily fish 1 time/wk + oily Baltic fish 1 time/mon	< 3	891	106
Lean sea fish 2 times/wk + oily Baltic fish 1 time/mon	< 3	688	81

Lean sea fish: e.g. cod, saithe, fish fingers
Oily fish: e.g. farmed salmon, rainbow trout, char (not Lake Vättern alpine char), sea-trout, whitefish, mackerel
Lean freshwater fish: e.g. perch, pike-perch, pike
Oily Baltic fish: Baltic herring, Baltic salmon

Table 10 shows how MeHg intake can vary based on the National Food Administration's dietary advice to eat fish 2-3 times per week, with one meal consisting of oily fish. According to investigations of dietary habits, the most common choice of lean and oily fish species gives a MeHg intake corresponding to 20% of PTWI for an adult person, actually women of childbearing age, and 40% of PTWI for children with a body weight of 30 kg.

If one portion each week is replaced by a fish species with a higher Hg content (0.5 mg/kg), the MeHg intake increases to 78% of PTWI, while children exceed PTWI. If instead the Hg concentration in one of the portions is 1.0 mg/kg, i.e. at limit level, this leads to PTWI being exceeded even for adults.

Calculating MeHg intake over a month, 3-4 portions of oily fish, 6-7 portions of lean sea fish with low Hg concentrations and 1 fish meal with a Hg concentration of 1.0 mg/kg represents a MeHg intake of approx. half of PTWI for adults and approx. 100% of PTWI for children.

Table 10. MeHg intake for consumption of fish 2-3 times per week, with varying combinations of fish species and Hg concentration. Intake of MeHg via foods other than fish is assumed to be negligible

Type of fish meals per week	No. fish meals per week	MeHg intake, µg/week	% of PTWI (60 kg body weight)	% of PTWI (30 kg body weight)
Lean sea fish 2 times/wk + 1 portion oily fish*	3	19	20	40
Lean sea fish 1 time/wk + 1 portion oily fish*+ 1 portion lean fish**	3	75	78	156
Lean sea fish 1 time/wk + 1 portion oily fish*+ 1 portion lean fish***	3	138	143	286
Lean fish** 2 times/wk + 1 portion oily fish*	3	131	137	274
Lean sea fish 2 times/wk + 1 portion oily fish****	3	63	65	130
Lean fish** 1 time/wk + 1 portion oily fish *	2	69	72	144

Lean sea fish: e.g. cod, haddock, saithe (Hg content 0.05 mg/kg)
*e.g. farmed salmon, rainbow trout, char, sea-trout, whitefish, mackerel (Hg content 0.05 mg/kg)
** e.g. perch, pike-perch, pike, tuna fresh or frozen, halibut (Hg content 0.5 mg/kg)
*** e.g. perch, pike-perch, pike, tuna fresh or frozen, halibut (Hg-halt 1.0 mg/kg)
****Oily freshwater fish: salmon, sea-trout, char from Lake Vänern/Vättern (Hg content 0.4 mg/kg)

Conclusions

These model calculations exemplify the fact that increased consumption of fish provides health benefits in the form of improved nutrient intake. The risk of high intake of environmental pollutants is dependent on fish species and on concentration of environmental pollutants. For certain fish species the benefits of eating fish, e.g. as a source of n-3 fatty acids and vitamin D, predominate up to a certain level of consumption.

Overall conclusions

- An increase in fish consumption in accordance with current dietary advice (2-3 times per week) would probably result in a decreased incidence of cardiovascular disease in the population, particularly in those who eat little or no fish and in those with an increased risk of cardiovascular disease. A considerable proportion of the population aged 50 or over has at least one risk factor for an increased risk of cardiovascular disease.

- Increased fish consumption by women of childbearing age who eat little or no fish would probably be positive. n-3 fatty acids are required for normal development of children during the gestation period and early infancy. Fish consumption 2-3 times a week, with 1 portion consisting of fatty fish, provides a satisfactory intake of long-chain n-3 fatty acids for the majority of the population.

- Intake of vitamin D is low in relation to nutritional recommendations for a large proportion of the population. Increased consumption of fish by those who eat little or no fish would considerably improve the intake of vitamin D. Increased intake of vitamin D contributes to improved vitamin D status and thereby decreases the risk of osteoporosis and fractures.

- Regular consumption of certain types of fish (e.g. fatty Baltic fish and freshwater fish) with increased concentrations of environmental toxins can lead to the so-called tolerable intake levels regarding dioxins/dioxin-like PCBs and methyl mercury being exceeded. This primarily concerns children and women of childbearing age as regards dioxins/dioxin-like PCBs, and pregnant and lactating women and children as regards methyl mercury. However, consumption of these types of fish is low for most individuals.

- An estimated 5% of women in the ages 17-40 years have a dioxin intake that exceeds TDI of 2 pg/kg body weight/day, but many of these eat oily Baltic fish more often than the Administration's current advice of at most once a month. For a woman who eats fish in accordance with the general advice (lean sea fish/freshwater fish 2 times per week and oily fish, e.g. farmed salmon, 1 time per week) and who otherwise eats a diet in accordance with nutritional recommendations, TDI is not exceeded. However, the proportion that exceeds TDI can be around 35% in the following scenario: Total consumption of fish 3 times per week, of which oily Baltic fish 1 time per month (i.e. corresponding to the current dietary advice) and other oily fish (e.g. farmed salmon) 3 times per month. It is

therefore not advisable to generally recommend an increase in consumption of oily Baltic fish, since the scope for increased consumption is highly limited for certain groups. However there is no reason to completely advise against consumption of oily Baltic fish.

- It should be emphasised that PCB and dioxins are accumulated in the body over a long time and that it is the total body load of these compounds, and not the actual intake, that is critical from a risk perspective. Exceeding the tolerable intake thus does not mean that health effects immediately arise, but that the safety margin decreases.

- Consumption of freshwater fish is low in the population and intake of methyl mercury does not exceed the JECFA's provisional tolerable weekly intake (PTWI) of 1.6 µg/kg. Limited consumption of fish with up to 1 mg/kg methyl mercury (at most once per month) is estimated to give a small risk of the tolerable intake being exceeded. However, regular consumption of freshwater fish with higher concentrations can lead to the tolerable intake being exceeded. Pregnant women are the group in the population that is most sensitive to methyl mercury due to the greater sensitivity of effects on the foetus.

- In a large proportion of the population there is scope to increase fish consumption without any fear of the tolerable intake levels of environmental pollutants being exceeded. Consumption of the commonest fish species 2-3 times a week, with a mixture of lean and oily fish species, carries a small risk of exceeding tolerable intake levels. The model calculations carried out demonstrate that increased consumption of fish provides health advantages in the form of improved nutrient intake. However, the scope for oily Baltic fish and fish containing high concentrations of MeHg is limited for certain groups.

- In some examples, balanced quantitative risk parameters such as QALYs (Quality Adjusted Life Years) have been applied to fish consumption and the health effects of n-3 fatty acids and methyl mercury have been compared. The net result in the form of positive or negative health effects is dependent on whether the entire population is studied or whether different groups are studied separately.

- In some examples, DALYs (Disability Adjusted Life Years) have been applied to nutritional, microbiological and toxicological food-related aspects in order to estimate the consequences for public health at present and after desirable changes in dietary patterns, incl. increased consumption of fish. The results indicate that an increase in fish consumption would provide health benefits expressed as DALY.

- The scientific basis at present does not allow balanced quantitative risk/benefit assessments of all the health effects associated with fish consumption. However from a consumer perspective it is an advantage for experts from different disciplines to jointly draw up a complete picture that illustrates both risk and benefit aspects. This area is being developed and should be actively monitored by the National Food Administration.

Recommendations for future work

There is currently great interest within Europe in risk-benefit assessments of food components and a number of countries have studied the risks and benefits of eating fish, e.g. the UK, Denmark and Norway. In its statement on fish, the European Food Safety Authority (EFSA) also discusses the issue (EFSA, 2005) and comprehensive analyses have recently been carried out in the USA (Cohen et al., 2005a; Mozaffarian & Rimm, 2006). Even though some progress has been made, a range of problems remains as regards methods and data support. In most cases, qualitative risk-benefit assessments have been reported.

Of tradition, the risks and benefits associated with consumption of a particular food have been dealt with in separate processes by both the National Food Administration and corresponding authorities in other countries. The risk assessment model applied by the National Food Administration is primarily intended for risks associated with various undesirable substances in food. It can also be directly applied for risks associated with high intake of micronutrients. However it has not been applied in evaluating the positive health benefits of food consumption.

This pilot project demonstrates the advantages of nutritionists and toxicologists meeting in a joint process to provide as complete a picture as possible of the consequences regarding risks and benefits at population level, so that the choice of risk management measures is optimal from a public health perspective. The most probable scenario in any future risk-benefit assessments is that the potential to quantify both the risks and benefits is generally limited due to lack of quantitative data regarding exposure and effects. Even though there are difficulties in performing quantitative risk-benefit assessments, there are still great advantages in making as balanced an assessment as possible of both risk and benefit in order to provide the consumer with a complete picture. Such an assessment would then be semi-quantitative or qualitative, which is probably preferable to a one-sided risk or benefit assessment.

Experiences of applying DALY or QALY to food-related risks indicate that this method can provide additional support for deliberations regarding prioritisation of work areas. These calculations require access to comprehensive supporting data, while for environmental pollutants such as mercury and dioxin, data on health

effects, prevalence, incidence and dose-response relationships in humans are lacking. In April 20005, the National Food Administration organised a seminar on DALY calculations. At this seminar, various applications of DALY calculations of relevance for e.g. the food area were presented. It was also revealed at this seminar that DALY have proven to be applicable for quantifying the health risks and health advantages relating to food and dietary habits. Dutch DALY calculations for nutritional, microbiological and chemical health effects were presented, but they did not include any DALY calculations for PCBs/dioxins and MeHg. However, it was estimated that the contribution from these was low.

Probability-based intake calculations can provide complementary data for risk-benefit assessments and account can be taken of variability and uncertainty in the data that form the basis for the calculations. In descriptions of acute exposure and risks, it is generally very important to take account of the variability in concentration and consumption. In calculations of chronic exposure, the mean value of the input data has a great impact in estimation of the exposure. In such cases, it is very important to take into account the uncertainty, rather than the variability, in the input data (estimates of lifetime consumption from short dietary studies, concentrations, etc.), even though the ideal is naturally to take account of both. Another advantage with probability models is the potential to carry out an analysis to describe and estimate intake in different scenarios, e.g. variations in intake over time, or on the basis of consumption patterns.

Resource and expertise requirement

If the National Food Administration is to expand its risk assessment work to also include the beneficial aspects, current methods would need to be complemented with others that can evaluate and grade both the risks and benefits. This area is still under development internationally and there is currently no accepted methodology available for use. New methods for risk assessments are increasingly being based on the so-called benchmark method (methods that involve using all the supporting data to model dose-response, including the variation in sensitivity, in order to establish a lowest exposure level with a defined response level that is assumed to represent the background level). Expertise in understanding and the ability to use these methods is required by the National Food Administration. Methods for intake calculations need to be developed and complemented with e.g. probability-based calculation models, both for acute and long-term exposure, in order to provide better estimates of uncertainty and variation in the exposure. Experience of working with probability models exists in the Microbiology and Toxicology Units and could be utilised for exposure analyses within other areas in the National Food Administration. The fundamental expertise required is mainly "mathematical, statistical" thinking and as much of the work consists of analysis and description of data, as of the actual development and application of the probability models. It is important that such expertise be incorporated into the base organisation.

One conclusion from the DALY seminar is that there is a need for increased expertise within epidemiology and access to empirical model calculations or similar in order to work with DALY calculations within the National Food Administration's areas of activity. It is the opinion of the project group that it is not a primary objective for the National Food Administration to carry out its own DALY calculations. On the same basis, we consider that the National Food Administration with its current resources cannot itself develop methods for quantitative risk-benefit assessments. Such development work is being carried out within the EU, and the National Food Administration can actively monitor this development and also participate in projects on these issues. Resources should instead be devoted to improving the underlying supporting data regarding e.g. concentrations of environmental pollutants and nutrients, consumption data, exposure calculations, health effects and dose-response relationships in humans. Such data can be of benefit in e.g. DALY calculations or other types of risk-benefit assessments, in collaboration with external experts.

Appendix 1: Health Effects of Fish Consumption

Introduction

This section describes the health effects of fish consumption with the focus mainly on n-3 fatty acids, dioxins/PCBs and MeHg, plus a short description of the metabolism of these compounds. The underlying data were obtained from reports and articles in the scientific literature published up to January/February 2007.

The positive health effects proposed for fish are primarily linked to the content of long-chain n-3 fatty acids. Several of the long-chain fatty acids in both the n-6 and n-3 series can form eicosanoids, which affect blood coagulation, vascular function and various inflammatory processes (Mori & Beilin, 2004). In addition, the long-chain n-3 fatty acids, particularly DHA, are important for foetal development and for normal vision and brain function. Fish is also an important source of vitamins and minerals, e.g. vitamin D, iodine and selenium.

Negative effects of fish consumption can be associated with the incidence of deleterious environmental pollutants such as MeHg and persistent organic compounds such as dioxins and PCBs, which can all give rise to damaging effects on health at high concentrations. Dioxins and PCBs can in the first instance affect development of certain organs in the body, e.g. the genital organs, the central nervous system and immunological functions. IARC has classed 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD) as a human carcinogen substance (group 1) (IARC, 1997). However, other chlorinated dibenzo-p-dioxins and dibenzofurans are not classified with regard to carcinogenicity for humans due to lack of data (group 3). MeHg can damage both the peripheral and the central nervous system. When the central nervous system is developing during the prenatal stage, sensitivity is greatest. Effects in children exposed to high concentrations of MeHg during the prenatal stage have been observed in certain epidemiological investigations (WHO, 2003).

Conversion in the body

n-3 fatty acids

Linoleic acid (18:2, n-6) and α-linolenic acid (18:3, n-3) are essential for humans and therefore need to be supplied by the diet. In the body, further long-chain fatty acids can be formed through chain extension and desaturation in the cell enzyme system. Linoleic acid is used to form e.g. arachidonic acid (AA), while eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) are formed from α-linolenic acid. The long-chain n-3 and n-6 fatty acids have essential activity, but are normally not essential *per se* if the supply of linoleic acid and α-linolenic acid via the diet is adequate.

Linoleic acid and α-linolenic acid compete for the same enzyme system for conversion to higher fatty acids. Since n-3 fatty acids are more easily bound to these enzyme

systems, a high intake of e.g. EPA and DHA can result in inhibition of AA formation from linoleic acid in the body. In the same way, high intake of linoleic acid in relation to n-3 fatty acids can e.g. lead to decreased formation of long-chain n-3 fatty acids.

Certain long-chain polyunsaturated fatty acids, incl. EPA and AA, are mother compounds to the eicosanoids, a heterogeneous group of hormone-resembling, biologically very active compounds that participate in regulation of e.g. blood pressure, lipolysis, gastric juice secretion, thrombocyte aggregation and inflammatory processes. As a rule, the eicosanoids formed from AA are more active than those formed from EPA and have been associated with inflammatory processes, stimulation of thrombocyte aggregation and increased vascular activity. Increased formation of eicosanoids from AA at the expense of eicosanoids from n-3 fatty acids has been proposed as a potential mechanism in the development of blood clots and inflammatory mechanisms.

The ratio of n-6 to n-3 fatty acids in the diet has been proposed as a factor that can affect susceptibility to inflammation and risk factors for various diseases such as diabetes and cardiovascular disease. A high ratio, in the range of magnitude of 10:1 or above, would be associated with increased risk, while ratios of around 5:1 or lower would be associated with a lower risk. However, the importance of the relationship between n-6- and n-3 fatty acids for the risk of disease is controversial (FNB, 2005). For example, it is not always clear which fatty acids should be included in the ratio, while the degree to which the absolute intake of the various fatty acids affects conversion and storage in tissues is also unclear. Animal studies show that the ratio between linoleic and α-linolenic acid affects conversion to long-chain fatty acids, even if the absolute intake varies. Controlled trials on humans have not been able to show a similarly clear effect, and there are some indications that the absolute intake is of greater importance than the ratio. However, interpretation of such studies is complicated by fact that the intake of fatty acids by the trial subjects before the study is reflected in the fat reserves and cell membranes of the body, and thus affects the results.

A number of intervention studies have investigated the importance of the relationship between n-6 and n-3 fatty acids in the diet for blood lipid levels, insulin resistance, blood vessel reactivity, blood coagulation and other risk factors for cardiovascular diseases and diabetes (Minihane et al., 2005; Sanders et al., 2006; Griffin et al., 2006). In these studies, which lasted between 3 weeks and 6 months, the n-6:n-3 ratio varied between 3:1 and 16:1. The n-3 fatty acids comprised either α-linolenic acid, mixtures of α-linolenic acid and EPA+DHA, EPA or DHA alone or EPA+DHA, while the n-6 fatty acids comprised linoleic acid. Intake of linoleic acid and other n-6 fatty acids was between 3 E% and 10 E%, while intake of n-3 fatty acids was between 0.6 E% and 1.6 E%, of which 0.2-0.7 E% was EPA+DHA. In general, marginal or no effects were found on blood glucose, insulin resistance or blood coagulation tendencies (Minihane et al., 2005; Sanders et al., 2006; Griffin et al., 2006). Increasing intake of EPA and DHA from 0.2 E% to in the order of 0.6-0.7 E% led to lower fasting levels of triglycerides in the blood and also to a lower rise in triglyceride levels after a meal (Griffin et al., 2006). However, intake of α-linolenic acid alone did not give this effect. It is well known that

high intake of n-3 fatty acids (3-4 g EPA+DHA per day) in the form of fish oil can decrease triglyceride levels in the blood (Harris et al., 1997).

According to the Nordic nutrition recommendations (NNR, 2004), the ratio of n-6 to n-3 fatty acids should lie between 3 and 9, but it is noted that the scientific basis for establishing an exact ratio is relatively weak.

Results from dietary investigations on children and adults in Sweden show that this ratio is on average around 4:1 or 5:1 (Becker & Pearson, 2002; Enghardt Barbieri et al., 2006). Some researchers claim that there are data indicating that mankind during its evolution lived on a diet where the ratio was in the order of 1:1. American literature contains data showing that the ratio in the current Western diet is high, and ratios of 15:1-17:1 (Simopoulos, 2002) and even up to 25:1 have been reported (Mickleborough & Rundell, 2005). However, it is unclear what these data are based on. According to national dietary data from e.g. the USA, the ratio is on average around 9:1 (FNB, 2005). Data from dietary investigations in Europe show that the ratio is between 3:1 and 8:1 as a rule (NNR, 2004; Astorg et al., 2004; Sioen et al., 2006).

Adults

Adults can thus convert α-linolenic acid contained in the diet into EPA, DPA and DHA. This conversion is primarily to EPA, while formation of DPA and, in particular, DHA is limited (Burdge & Calder, 2005; Burdge, 2006). Most studies indicate that the conversion of α-linolenic acid to DHA is very limited, less than 1%. Burdge & Wootton (2002) estimated that 6% of a single dose of α-linolenic acid was converted to DHA 21 hours after ingestion in women, while no conversion to DHA could be shown in men (Burdge et al., 2002).

In vegetarians, α-linolenic acid as a rule represents the only dietary source of n-3 fatty acids, and tissue levels of DHA are lower than in individuals who eat a mixed diet. Studies of male vegetarians with a low intake of α-linolenic acid showed that increased intake of α-linolenic acid led to an increase in the total content of n-3 fatty acids in various tissue lipids, but that the content of DHA was unaffected (Li et al., 1999). The content of EPA in phospholipids in plasma of female vegetarians was around one-third, and the content of DHA around half, of that in age-matched women who ate a mixed diet (Reddy et al., 1994). For other n-3 fatty acids and n-6 fatty acids, no differences were observed between the groups. Intake of α-linolenic acid was 0.5-0.6% of energy intake (E%) in both groups, while EPA and DHA contributed 0.04 and 0.05 E% among women who ate a mixed diet.

In a study of adult men and women, where the majority of the fats used as spreads or in cooking were replaced with rapeseed oil-based fats (around 50 g rapeseed oil/day, corresponding to 2 E% α-linolenic acid), it was estimated that the content of EPA in the blood fats corresponded to around one fish meal (50-100 g oily fish) per week (Valsta et

al., 1996). However, the results did not indicate any conversion of α-linolenic acid to DHA.

Based on calculations of the amount of DHA accumulated by the foetus or secreted in breast milk, a British expert group estimates that intake of DHA should be around 0.2 g DHA per day in the latter part of pregnancy and 0.16-0.17 g per day during the lactation period (SACN/COT 2004). This amount could theoretically be largely covered by formation in the body from α-linolenic acid. On the basis of the Burdge studies (Burdge & Wootton, 2002) with a 6% conversion of α-linolenic acid to DHA, an intake of 2.5 g/day of α-linolenic acid would represent a supply of 0.15 g/d of DHA for women. This is on a par with the British expert group's recommendations for pregnant and breastfeeding women, but it is unclear whether the results can be extrapolated in this way.

In a Dutch study, pregnant women received a supplement of either 2.8 g α-linolenic acid and 9 g linoleic acid or 10.9 g linoleic acid per day from week 14 until parturition (de Groot et al., 2004). The concentration of EPA and DPA in the blood (phospholipids) of mothers and neonates increased, while the concentration of DHA decreased in both groups.

Analyses of umbilical cord blood from pregnant vegetarians of south Asian ethnicity showed that the concentration of DHA in the phospholipids was around two-thirds of the concentration in age-matched pregnant women who ate a mixed diet (Reddy et al., 1994). However, the concentration of DPA (22:5 n-6) was higher. The concentration of other n-6 and n-3 fatty acids did not differ significantly between the groups. Studies of vegetarians clearly showed that there was conversion of α-linolenic acid in the diet into long-chain n-3 fatty acids. The fact that it has not been possible to influence the concentration of DHA in tissue lipids in other studies may be due to the content in the structural phospholipids being stable and slowly affected.

Children

The enzyme system required for formation of DHA from α-linolenic acid has been demonstrated in the foetus, while full-term and premature babies have been shown to be capable of forming DHA from α-linolenic acid (Uauy et al., 2000; Mayes et al., 2006). Both AA and DHA occur in breast milk and should be regarded as conditionally essential for premature babies (NNR, 2004). However it is unclear whether this is the case for full-term babies. The EU Scientific Committee on Food (SCF 2003) gives no specific recommendations that milk replacement and bottle formula for full-term babies should contain both AA and DHA in concentrations normally occurring in breast milk.

Dioxins/PCB

Dioxins and PCB are absorbed fairly readily from the gastrointestinal tract. In the case of dioxins, both WHO and EU-SCF in their assessments have assumed a general degree of absorption of 50%, but certain studies indicate even more efficient uptake. In human

studies, dioxin uptake in adults has been calculated to be up to 63% (Schlummer et al., 1998) or more than 86% (Poiger et al., 1986) of the dose consumed, while in teenagers a value of 88% uptake has been reported (Price et al., 1972). Regarding uptake of dioxins by infants through breast milk, there are a number of calculations showing uptake of over 90% (see McLachlan, 1993; Abraham et al., 1994). Once dioxins and PCBs have been taken up in the body, it takes a very long time to eliminate them. Their future fate in the organism is determined mainly by three factors, namely rate of metabolism, binding ability to a liver enzyme, CYP1A2, and fat solubility (van Birgelen & van den Berg, 2000). For the most toxic dioxin (2,3,7,8-TCDD), the half-life in humans is calculated to be 7-8 years. However, there are differences in biological half-life between congeners, and the lower chlorinated compounds often have a lower persistence and therefore a shorter half-life. A half-life of 3.7 to 15.7 years has been calculated for the dibenzodioxins (Flesch-Janys et al., 1996), while the half-life for pentachlorinated dibenzofurans has been reported to be between 2 and 7 years (van den Berg et al., 1994). Half-life tends to increase with age, presumably due to the increasing amount of body fat and declining metabolic activity (Flesch-Janys et al., 1996).

In the body, these compounds distribute themselves in the body fat and can generally be said to be evenly distributed in the various fat depots of the body. This means that analyses of matrices such as blood lipids or breast milk fats provide an estimate of the total body load of these compounds. A factor that can partly alter this distribution is binding to CYP1A2, a microsomal drug-metabolising enzyme in the liver. In experimental animals, a clear redistribution of dioxins is observed in the body when the specified dose is increased, something that has been interpreted as induction of the actual enzyme in the liver and binding of dioxins to it (de Vito et al., 1998). In humans, there are also indications of binding to the liver upon exposure to high dioxin concentrations (Carrier et al., 1995). However in both animals and humans, this binding to the liver seems to be insignificant at exposure to background or low concentrations of dioxins (Thoma et al., 1990; Diliberto et al., 1998).

Transport of dioxins and PCBs from mother to foetus during pregnancy is modest in relation to the amount that can be transferred during breastfeeding if this occurs in the normal range, i.e. full breastfeeding for 4-6 months. This relatively significant transfer via the breast milk also means that the mother gets rid of part of her own body load (Abraham et al., 1997) and in many cases she will have lower dioxin concentrations in the breast milk if she gives birth to a number of babies that breastfeed. This can also be noted in the concentrations of dioxin-like compounds in the blood of the first and second child born to the same mother, sampled at 12 months of age (Abraham et al., 1997). Breastfed babies generally have higher dioxin concentrations in the body than bottlefed babies. However, the body loads of dioxins in nursing infants never exceed those measured in adults (Thoma et al., 1990; Kreuzer et al., 1997), and viewed over the whole life span, breastfeeding should not involve any increase in dioxin concentrations in the body fat (Kreuzer et al., 1997; Liem & Theelen, 1997). However, there are data indicating that the breastfeeding history of Swedish primagravida in their own infancy is reflected in the concentrations of dioxins and PCB they themselves have in breast milk. In this case, a transfer of environmental toxins from grandmother to grandchild can thus be detected (A. Glynn, pers. comm.).

As previously mentioned, dioxins and dioxin-like PCBs generally have long half-lives in the body and metabolic formation is slow. However, hydroxylated and methylsulphonyl metabolites of PCB are gradually formed and these metabolites, particularly the methylsulphonyls, can remain in the body for a long time. A number of studies have been able to show that hydroxylated and methylsulphonyl metabolites have effects on hormonal systems (sex hormones, thyroid hormones). However, it is unclear whether the concentrations found in these investigations are sufficiently high to cause any damaging effects *in vivo* (Johansson et al., 1998; Vakharia & Gierthy, 2000; Soechitram et al., 2004; Pliskova et al., 2005).

MeHg

MeHg in food is mainly absorbed completely (> 95%) in the gastrointestinal tract of humans. MeHg passes easily over the cell membrane and is distributed to all the tissues in the body. MeHg also passes over the blood-brain barrier and over the placenta to the foetus (review: WHO, 2000). As a rule, the concentration of MeHg is higher, in the order of twice as high, in the blood of the foetus or neonate compared with the concentration in the mother's blood (Sakamoto et al., 2004; Björnberg et al., 2005b). Exposure to MeHg can be measured in blood and in hair (Elinder et al., 1988; Berglund et al., 2005). The blood concentration reflects the current exposure, while the concentration in hair provides a retrospective measure. In blood analyses, account must be taken of the concentration of inorganic Hg, which in non-occupationally exposed individuals derives from dental amalgam fillings, while the hair concentration reflects exposure to MeHg. The ratio of hair concentration to blood concentration is usually reported as 250:1, but the inter-individual variation is great (140-370:1) (Berglund et al., 2005). It is estimated that hair grows at approx. 1 cm/month and by analysing fragments of hair a measure can be obtained of exposure backwards in time, e.g. during a pregnancy (review: NRC, 2000). Similarly, the MeHg concentration in umbilical cord blood can be used as a measure of prenatal exposure (Grandjean et al., 1999).

The half-life for MeHg in humans is approx. 2-3 months, based on relatively few observations (reviews: NRC 2000; WHO 2003). MeHg is slowly demethylated in the body, e.g. in the brain, to inorganic Hg. Excretion occurs mainly (approx. 90%) via the gall bladder and faeces, primarily in the form of inorganic Hg, while the rest is excreted via the urine in inorganic form. In the lactating mother there is also some excretion of MeHg and inorganic Hg in breast milk, which results in some exposure in the infant. In comparison with foetal exposure during the last months of pregnancy, however, the exposure via breast milk is low (Björnberg et al., 2005b).

Effects on reproduction and pregnancy

n-3 fatty acids

In some epidemiological studies, high intake of fish and long-chain n-3 fatty acids has been associated with prolonging length of pregnancy by a few days (Olsen et al., 1991; Grandjean et al., 2001a; Lucas et al., 2004) and decreased risk of premature births (Olsen & Secher, 2002), while other studies have not been able to confirm these findings (Olsen et al., 1995; Rogers et al., 2004; Oken et al., 2004).

Grandjean et al. (2001a) analysed n-3 fatty acids (phospholipids) in the umbilical cord blood of 182 mothers on the Faroe Islands and found a 1% increase in DHA concentration to be associated with an increase in pregnancy length of 1.5 days. Furthermore, a 1% increase in EPA concentration was related to a 246 g decrease in birth weight (adjusted for pregnancy length). However, the concentration of environmental pollutants such as MeHg and PCBs did not appear to be related to these effects.

In a cross-sectional study of around 8,700 pregnant Danish women, the risk of premature births and low birth weight was lower among those who ate fish at least one time per week compared with those who never ate fish (Olsen & Secher, 2002). Based on survey data on fish consumption collected during weeks 16 and 30 of pregnancy, it was estimated that this effect was achieved at intake of around 15 g fish or 0.15 g n-3 fatty acids per day. However, a similar study of 965 pregnant Danish women observed no relationship between n-3 intake, calculated from dietary data collected during week 30 of pregnancy, and birth weight and length (Olsen et al., 1995).

Rogers et al. (2004) studied fish intake during the latter part of pregnancy (week 32) and compared these data with pregnancy outcome in over 11 000 British mothers. They found that the risk of impaired foetal development was greater in mothers who did not eat fish than among those who ate fish just over four times per week. However, no correlation was found between intake of fish or long-chain n-3 fatty acids and birth weight or pregnancy length.

In a study of the Inuit people, pregnancy length and birth weight were higher in mothers with a high concentration of long-chain n-3 fatty acids (top one-third) in umbilical cord blood compared with those with low concentrations (bottom one-third) (Lucas et al., 2004).

In a study by Reddy et al. (1994) shorter pregnancy length and lower birth weight and length were observed among neonates born to vegetarians compared with babies born to mothers who ate a mixed diet, but this finding could not be related to the DHA concentration in umbilical cord blood or plasma.

Thorsdottir et al. (2004) investigated the relationship between intake of fish and fish liver oil and pregnancy outcome in Icelandic women and found that birth length and

head circumference were linked to consumption frequency and that these parameters were lowest in babies born to women who ate fish more seldom than 4 times per month. Babies born to mothers with a fish intake of 0-20 g per day weighed less, were shorter and had smaller head circumference than babies born to mothers who ate more fish. No relationship was found between intake of fish or fish liver oil and pregnancy length. After correction for e.g. fish intake, intake of fish liver oil was inversely related to birth length and head circumference. The same results were observed for total intake of n-3 fatty acids from fish, fish liver oil and other fish supplements. Intake of fish liver oil was highest in this group, which also contributed to high intake of retinol and vitamin D.

In another cross-sectional study of Icelandic women, Olafsdottir et al. (2005) found that babies born to women who ate fish liver oil during early pregnancy (before week 15) had higher birth weight than babies born to women who did not eat fish liver oil.

In a study of pregnant American women, intake of fish and n-3 fatty acids was measured during the first trimester and related to foetal growth (measured as birth weight for pregnancy length) and pregnancy outcome (Oken et al., 2004). It was found that birth weight and foetal growth were lower in mothers with a high intake (top quarter) of fish or long-chain n-3 fatty acids compared with mothers with low intake (bottom quarter). However, no differences were observed in pregnancy length or risk of premature birth.

Controlled intervention studies in which pregnant women were given supplementary long-chain n-3 fatty acids in the form of fish oil or DHA preparations have produced conflicting results (Olsen et al., 1992; Helland et al., 2001; Smuts et al., 2003; Malcolm et al., 2003a). Thus Olsen et al. (1992) found that giving a supplement of 2.7 g n-3 fatty acids per day as fish oil to pregnant Danish women from week 30 until birth increased both pregnancy length (+4 days) and birth weight (100 g) compared with women who were given olive oil. However, no difference in pregnancy length was observed when the fish oil group was compared with a control group that was not given any supplement.

Helland et al. (2001) gave pregnant Norwegian women daily supplements of either cod liver oil (10 mL/d, ~2.6 g n-3 fatty acids) or maize oil (10 mL/d) from week 17-19 until 3 months after birth. They found no difference in pregnancy length or birth weight between the groups. However, pregnancy length was related to DHA concentration in umbilical cord blood, with an average difference of 7 days between the top and bottom quartiles.

Giving supplements of only 0.13 g DHA per day in the form of eggs to pregnant American women during the third trimester led to increased pregnancy length by on average 6 days, compared with a control group that was given 0.033 g DHA (Smuts et al., 2003).

In a randomised study of pregnant women who from week 15 of pregnancy received a supplement of fish oil (with 0.2 g DHA/d) or sunflower oil, no difference was found

with respect to pregnancy length, birth weight or DHA concentration in umbilical cord blood (Malcolm et al., 2003a,b).

A meta-analysis of six selected, controlled intervention studies of supplementary long-chain n-3 fatty acids on pregnancy outcome showed significantly increased pregnancy length (1.57 days CI: 0.35-2.78) (Szajewska et al., 2006). However, there was great variation in dose (from 0.13 g from eggs to 2.7 g/d from fish oil) and treatment time (from week 15 of pregnancy to birth, or from week 27-28 to birth), which renders the results difficult to interpret.

Knudsen et al. (2006) could not show any significant effect on pregnancy length of supplements containing different amounts of n-3 fatty acids, either as fish oil or linseed oil. The supplements were given from during week 17-27 up to birth. However, compliance among the women was relatively low. In an Australian intervention study, pregnant women ate either a supplement of fish oil (2.2 g DHA and 1.1 g EPA per day) from week 20 to birth, or a supplement of olive oil (Dunstan et al., 2006). Exclusion criteria were e.g. fish consumption more than 2 times per week. No difference was observed between the groups as regards either pregnancy length or birth weight or length among the babies born, who were monitored up to 2½ years of age.

Conclusions

The differences between the results as regards pregnancy length, birth weight and the risk of premature births in these studies can be due to e.g. differences in initial n-3 status and fish intake in the women, intake during pregnancy and factors generally affecting nutritional status, exposure to other compounds, etc. Intake of long-chain n-3 fatty acids in a study by Helland et al. (2001) was on average 0.55 g/d (of which 0.3 g DHA), which is considerably higher than intake reported from the USA (0.12 g/d) and Denmark (0.2-0.25 g/d).

In some of the cross-sectional studies, the birth weight was inversely related to intake of n-3 fatty acids (Oken et al., 2004) or the EPA concentration in the umbilical cord (Grandjean et al., 2001). High intake of fish liver oil was correlated to shorter length at birth and smaller head circumference in babies born to Icelandic women with high intake of fish liver oil and of n-3 fatty acids in total (Thorsdottir et al., 2004). No negative effects were reported in the intervention studies.

The meta-analysis by Szajewska et al. (2006) showed that supplements of long-chain n-3 fatty acids during pregnancy gave significantly increased pregnancy length (1.6 days), but the doses varied considerably. Increased supply of long-chain n-3 fatty acids can probably be favourable if n-3-status before pregnancy is low. The studies by Thorsdottir et al. (2004) and Olsen & Secher (2002) indicate that intake of around 15-20 g fish per day, corresponding to 0.15-0.2 g n-3 fatty acids, can be sufficient.

Dioxins/PCB

Epidemiological studies have been unable to show clear correlations between dioxin exposure and reproduction effects. Studies from Seveso in northern Italy, where a factory exploded in 1976 and a dioxin cloud spread out over the surroundings, showed a change in the sex distribution of boys and girls born 9 months to 7 years after the accident (more girls than boys) (Mocarelli et al., 1996). The mechanism for this change is unclear. Certain studies have been able to show a correlation between dioxin exposure on the one hand and length and regularity of the female menstruation cycle and female serum concentrations of sex hormones on the other (Axmon et al., 2004; Yang et al., 2005). In studies of Swedish commercial fishermen, it has been shown that certain effects on sperm status can be correlated to exposure to POPs: Sperm motility was somewhat lower in individuals who had the highest PCB-153 concentrations in their blood (Rignell-Hydbom et al., 2004), and a relationship was also observed between PCB-153 and effects on the structure and integrity of sperm chromatin (Rignell-Hydbom et al., 2005). However, these effects are small and usually not significant, and thus have little importance in assessment of reproduction effects. In a Swedish 'time-to-pregnancy' investigation, no correlation was observed between this period (from when a couple stop using anticontraceptive measures until pregnancy is confirmed) and exposure to Baltic sea fish with high concentrations of organic environmental toxins, or exposure to PCB-153 (concentrations of PCB-153 correlate fairly well with dioxin concentrations) (Axmon et al., 2000; 2002; 2004).

In experimental studies, dioxins gave rise to reproduction effects in Rhesus monkeys, e.g. in form of spontaneous abortions and incomplete pregnancies (Allen et al., 1979; Bowman et al., 1989). The monkeys in the study by Bowman et al. later developed uterine cysts (Rier et al., 1993). However, this effect as a result of TCDD exposure could be questioned, since the monkeys also had high concentrations of planar PCB congeners in their blood and since the source of these PCBs was unknown (Rier et al., 2001). In rats too, dioxin-like compounds (3,3',4,4'-tetra CB) gave rise to foetal death at higher doses (Wardell et al., 1982), and in mice foetal death and characteristic malformations of the hard palate, kidneys and changes to the thyroid gland (d'Argy et al., 1987).

MeHg

There is a lack of data on the effects of MeHg in humans as regards reproduction and pregnancy, although there are indications from Iraq of a lower number of pregnancies at very high exposure (Bakir et al., 1973). However, miscarriages, decreased litter size and survival and malformations have been observed in a number of animal studies on mice, rats, guinea pigs and monkeys at relatively high doses of MeHg (review: NRC, 2000). However, other effects arise at lower exposure.

Effects on cognitive development and mental health

n-3 fatty acids

Cognitive and visual function

A number of observation studies have related n-3 fatty acid status at birth to neurological indicators, visual ability and intelligence during infancy and early childhood. However, long-term studies have not been able to show any correlation between DHA or AA concentration in umbilical cord blood and cognitive ability in children at 7 years of age (Bakker et al., 2003) or between concentration of long-chain PUFA and cognitive ability at 3.5 years of age (Ghys et al., 2002). Results from the same study showed that the DHA concentration in umbilical cord blood was significantly related to motor ability and visual acuity at 7-8 years of age and with behaviour at 7 years of age (Hornstra, 2005).

Gustafsson et al. (2004) related fatty acid composition in colostrum and breast milk at 1 and 3 months respectively to IQ at 6.5 years of age in 73 breastfed full-term babies. They found no significant relationship between concentration of polyunsaturated fatty acids and cognitive development, but pregnancy length, breastfeeding duration and the ratio of DHA/AA explained 76% of the variation in IQ, which indicates that both DHA and AA are important for cognitive development.

In a cohort study comprising just under 12,000 pregnant women in the UK, fish consumption was measured during week 32 of pregnancy. When the child was 8 years old, verbal IQ was measured using a standardised test (Hibbeln et al., 2007). In addition, the mother recorded the child's behaviour (motor abilities, communication, social skills) with the help of a questionnaire at 6, 18, 30 and 42 months of age and based on the responses, various indices were constructed. Fish consumption was divided into >340 grams, 1-340 grams and <1 grams per week. The background to choosing these intake levels is that pregnant women in the USA are recommended to eat up to 3 portions of fish per week, which was recalculated to 340 grams with the use of standard portions. Fish consumption over 340 grams per week was linked to better results for verbal IQ compared with no consumption (<1 gram/week), although not compared with consumption of 1-340 grams per week. Frequent fish consumption was also related to a somewhat better index for behaviour, fine motor ability and communication. Calculations of fish intake were based on frequency questions with varying consumption intervals, which gives an uncertainty in the estimation.

Helland et al. (2003) gave supplements of either cod liver oil or maize oil to 340 pregnant women from week 18 of pregnancy until 3 months after the birth and measured IQ in a sub-sample (84) of the children at 4 years of age. They found that IQ was on average 4.1 units higher in the group that had received the supplement of fish oil and that IQ was correlated with maternal intake of EPA and DHA. IQ was also related to the

DHA concentration in serum phospholipids at 4 months of age, although not at birth. Intake of DHA in a small sub-sample of the women who received fish oil was estimated to be on average 1.4 g/d, compared with 0.2 g/d in the group that received maize oil.

In an Australian intervention study, 98 pregnant women were selected to take either a fish oil supplement (2.2 g DHA and 1.1 g EPA per day) from week 20 until birth, or a supplement of olive oil (Dunstan et al., 2006). Exclusion criteria were e.g. fish consumption more often that 2 times per week, smoking, fish allergy, etc. Compliance was measured by analyses of the fatty acid composition of phospholipids in blood cells from umbilical cord blood. Otherwise, no details are reported on the women's intake of different fatty acids and other dietary components. When the children were 2½ years of age, growth, mental development, speech ability and behaviour criteria were measured. The mothers in the fish oil group were somewhat younger than the mothers in the control group, but otherwise there were no statistically significant differences between factors such as education, number of children, breastfeeding, pregnancy length, birth weight, etc. After control for these and other individual factors, it was found that children born to mothers who received fish oil (33 individuals) had significantly better eye-hand coordination than children born to mothers who received no supplement (39 individuals). Otherwise, no differences were found between the groups. No negative effects of fish oil in the pregnant women were reported. This is the first study showing potential beneficial effects of supplements of n-3 fatty acids given only during pregnancy.

In a randomised study of pregnant women who from week 15 of pregnancy week received a supplement of fish oil (med 0.2 g DHA/d) or sunflower oil, no increase was observed in the DHA level in umbilical cord blood. Furthermore, there was no difference between the groups as regards retinal function (electroretinography, ERG) and nerve potential (visual evoked potential, VEP). However, a significant relationship was observed between DHA status at birth (umbilical cord blood) and these indicators on retinal function, both soon after birth and during weeks 50 and 66 after birth (Malcolm et al., 2003a,b).

A meta-analysis of intervention studies indicated that premature babies who had received milk replacement with added DHA had better visual function during their first months compared with babies who had received replacement without DHA (SanGiovanni et al., 2000).

A few intervention studies have investigated the effect of supplementary n-3 fatty acids during the breastfeeding period on visual function and neurological development in full-term babies. In a study by Gibson et al. (1997), five groups of lactating women received a supplement of 0 g, 0.2 g, 0.4 g, 0.9 g or 1.3 g/d DHA in the form of a DHA-rich algal oil during the first 12 weeks after parturition. Visual acuity was measured in the babies at 12 and 16 weeks of age and neurological development at 1 and 2 years of age. No relationship was observed between DHA concentration in the phospholipids in red blood cells in the babies and visual acuity. There was a correlation between DHA concentration at 12 weeks and neurological development at 1 year of age, but not at 2 years of age.

In another study, lactating women received a supplement of either fish oil (4.5 g fish oil with 1.3 g/d long-chain n-3 fatty acids) or a corresponding amount of olive oil during a period of 4 months after partuition (Lauritzen et al., 2004). The women had a fish intake that was lower than the median and women with a higher fish intake were the control group. No difference was found in visual acuity (measured as swept visual evoked potential) in the babies in the fish oil group compared with the babies in the olive oil group. However, a positive relationship was observed between visual acuity and DHA concentration in red blood cells at 4 months of age. In a follow-up study, no clear differences were found in various cognitive tests at 9 months, 1 year or 2 years of age (Lauritzen et al., 2005).

Jensen et al. (2005) studied visual function and neurological development in babies of breastfeeding mothers who had received a supplement of 200 mg/d DHA in the form of an algal oil (approx. 0.5 g) or vegetable oil (1 g soya and maize oil) for 4 months after partuition. They found no differences between the groups as regards neurological development of the babies at 12 months of age or visual function (VEP) at 4 or 8 months of age. At 30 months of age the results of tests of motor ability (Bayley Psychomotor Development Index) were better in the DHA-supplemented group, while no difference was observed between the groups in tests of mental development (Mental Development Index, measures speech development, eye and motor coordination).

Conclusions
These studies indicate that supplementation with n-3 fatty acids during pregnancy and early development is related to e.g. cognitive and motor ability in babies. Some intervention studies have shown beneficial effects on e.g. visual function, intelligence and motor ability after supplementation of long-chain n-3 fatty acids in the form of fish oil during pregnancy and breastfeeding. The doses have been considerably greater than intake normally achieved through the diet (2.5-3.3 g/day, of which 0.8-1.1 g EPA and 1.4-2.2 g DHA). In a study of breastfeeding women, certain positive effects on psychomotor development were seen in the babies at 30 months after a supplement of 0.2 g/d DHA. More studies are needed to establish the intake levels at which effects can be achieved and whether any such effects are persistent. Some expert groups recommend e.g. an intake of 0.1-0.3 g DHA per day via the diet during pregnancy and lactation (SACN, 2004: Akabas & Deckelbaum, 2006). This corresponds to a fish consumption of 2-3 times per week, of which one portion is oily fish.

ADHD, dyslexia etc.
The term ADHD comprises a number of conditions characterised by attention deficiency, concentration difficulties, hyperactivity and lack of impulse control (National-encyklopedin). The condition primarily presents in children but has also been observed in adults (Young & Conquer, 2005). Inadequate supply of n-3 and n-6 fatty acids or disrupted formation of these have been proposed as potential contributory causes of ADHD, dyslexia and similar neurological impairments. Some intervention studies have tested the hypothesis that supplementation of e.g. long-chain n-3 fatty

acids, but also n-6-fatty acids, can improve the symptoms, but the results are contradictory (Young & Conquer, 2005; Richardson & Montgomery, 2005). Treatment with fish oil has also been tested for other conditions such as autism (Amminger et al., 2007). This pilot study showed no statistically significant difference in symptom changes after 6 weeks of treatment. Interpretation of these studies is complicated by e.g. the fact that research groups included individuals with different types of diagnoses and that different types of preparation were used (fish oil, combination of fish oil, vegetable oils and vitamins or individual fatty acids, e.g. DHA).

Dementia, Alzheimer's disease

Intake of fat and fatty acids have been discussed as factors that can affect the risk of age-related impairment of cognitive function and dementia (Solfrizzi et al., 2005; Yehuda et al., 2005; Young & Conquer, 2005). Several epidemiological studies have e.g. indicated a relationship between intake of fish or n-3 fatty acids and the risk of developing symptoms of dementia (Young & Conquer, 2005; Issa et al., 2006).

In a prospective study of adults aged 50-65 years, the fatty acid composition in plasma (phospholipids and cholesterol esters) was related to the results of three cognitive tests after an average of 6 years monitoring (3-9 years) (Beydoun et al., 2007). A decreased risk of impaired word fluency was found with increased concentration of EPA+DHA, especially among individuals with high blood pressure and blood lipid imbalances. However, no statistically significant relationship was observed between EPA+DHA and the results of the other two tests (psychomotor speed or word recall) or general deterioration of cognitive ability, measured as a combination of these three tests. However, low concentration of linoleic acid and high concentration of palmitic acid and arachidonic were linked to increased risk of deterioration of general cognitive ability.

De Groot et al. (2007) studied the relationship between fatty acid composition in plasma phospholipids and the results of four different cognitive test batteries among 54 women aged 20-40 years who ate fish at most 1 time per week. The tests were carried out at the start of the study and after 3, 15 and 22 weeks. Education level and number of children borne explained a considerable proportion of the variation in the results of several tests. The concentration of various fatty acids (arachidonic acid or individual long-chain n-3 fatty acids) at the start of the study or after 22 weeks provided no further degree of explanation. However, it was found that increased concentration of arachidonic acid was associated with better results in tests measuring learning ability, while the converse relationship was observed for DHA. After correction for multiple tests, however, the relationship was no longer statistically significant. An earlier study on pregnant women carried out by the same research group (de Groot et al., 2006) indicated that higher plasma levels of DHA were correlated with poorer results of cognitive tests. The results indicate that the relationship between intake and tissue levels of n-3 fatty acids and cognition is relatively weak and complex.

A few intervention studies have tested the hypothesis that supplements of long-chain n-3 fatty acids from fish would be beneficial for individuals with dementia or Alzheimer's.

In three Japanese studies of elderly individuals with various forms of dementia, supplements of DHA (Terano et al., 1999), DHA + EPA (Suzuki et al., 2001) or EPA (Otsuka, 2000) were given for 6-12 months. Certain improvements in tests for dementia and psychoma were demonstrated. However, these results should be interpreted with care since they refer to relatively small and in some cases non-controlled studies.

In a Swedish intervention study, 204 patients with Alzheimer's were randomly allocated to eat a supplement of either fish oil capsules (0.6 g EPA + 1.7 g DHA per day) or maize oil capsules (4 g per day) for 6 months (Freund-Levi et al., 2006). Among the 174 patients who completed the study, no differences were shown in symptom pattern between the groups. However, a slower deterioration was observed in a small group of patients with mild symptoms. This may indicate that intake of e.g. n-3 fatty acids can be of importance in the early development of the disease.

A systematic assessment of treatment studies giving supplements of n-3 fatty acids to individuals without symptoms of dementia (Lim et al., 2006) concludes that there is a lack of well-controlled studies, but that observational studies and epidemiological studies indicate that supplements of n-3 fatty acids could be beneficial. More controlled studies are required before any definitive conclusions can be drawn.

Schizophrenia, depression

Several studies indicate that conversion of essential fatty acids can be disrupted in patients with schizophrenia, but little is known on whether intake via the diet can play a part in emergence of this disease. Treatment with large doses of marine n-3 fatty acids has been tested. In an analysis of six controlled studies where individuals suffering from schizophrenia received supplements of n-3 fatty acids (EPA, DHA), an improvement was observed in one study (Joy et al., 2006).

Based on statistical comparisons between countries, intake of fish and n-3 fatty acids has been linked to the incidence of depression and manic-depressive conditions. A cross-sectional study showed a statistically significant relationship between incidence of depression and concentration of e.g. DHA in fatty tissues (Mamalakis et al., 2006a,b). Cross-sectional data from a Dutch cohort study of elderly men (70-90 years) showed a decreased risk of depression among men with intake of long-chain n-3 fatty acids (EPA + DHA) in the top quartile (0.4 g/d) than among men with intake in the bottom quartile (0.02 g/d) (Kamphuis et al., 2006).

Some intervention studies in which individuals with depression received supplements containing large doses of EPA, DHA or fish oil have shown some improvements, while others have not shown any effect (see Young & Conquer, 2005; Appleton et al., 2006; Frangou et al., 2006).

Appleton et al. (2006) identified 18 randomised intervention studies that tested the effects of supplementary long-chain n-3 fatty acids (EPA and DHA) on depression and similar conditions (schizophrenia, manic depression, bipolar disorder, chronic fatigue,

etc.). For 12 of these, the supporting data were sufficient for them to be included in a meta-analysis. All except one study involved adults. The number of individuals in the research groups varied from 10 to 229 and the treatment time from 4 weeks to 6 months. The fatty acids were most often given as fish oil (EPA and DHA reported), in some studies as ethyl esters of EPA, or as fish. The dose of n-3 fatty acids varied from 0.2 g/d to 9.6 g/d. The analysis showed a weak, but significant, positive effect in the treatment group, but the variation between studies was large. One study, the main aim of which was to test the effects of increased fish consumption on the risk of cardiovascular disease, comprised men with angina (Ness et al., 2003). In this study no effect of fish consumption on the incidence of depression or anxiety was observed. When this study was excluded from the meta-analysis, a more clear positive effect was observed on the symptom pattern. In addition, a stronger effect was observed in studies of groups with major depression (unipolar or bipolar depressive illness). For other conditions, no effect of supplementation was observed. The authors drew the conclusion that the analyses show that the documentation on beneficial effects of n-3 fatty acids on different depressive conditions is weak. At the same time, a certain effect could be discerned in the eight studies that comprised groups with major depression. All these were relatively small studies and the doses of n-3 fatty acids for adults ranged from 2 g EPA till 6.2 g EPA + 3.4 g DHA per day, while the dose in a study of children was ~0.4 g EPA + ~0.2 g DHA per day. No dose-response relationships could be demonstrated.

Conclusions

n-3 fatty acids are essential for normal neurological development and function. Lower blood levels of long-chain n-3 fatty acids have been demonstrated in various neurological disorders. The importance of intake from the diet for emergence of these disorders is unclear, but there are epidemiological data that indicate that low intake or low tissue levels of long-chain n-3 fatty acids can be of importance for the development of certain disorders. At the same time, there are some studies that indicate a relationship between increased concentration of plasma DHA and poorer results in certain cognitive tests among women. The results of controlled intervention studies in which supplements of e.g. long-chain n-3 fatty acids were given have not shown any definitive positive effects in patients with various neurological disorders.

Dioxins/PCBs

A number of human studies have shown negative effects on child development after exposure to dioxins and PCBs during the prenatal and breastfeeding period. Such exposure occurred after the Yusho accident in Japan and the Yusheng accident in Taiwan, when people ate rice oil contaminated with dioxins and PCBs. The effects on babies included low birth weight, delayed development during childhood with behavioural changes and hearing impairment, and changes/malformations of e.g. the genital organs (Kuratsune et al., 1966; Rogan et al., 1988). After the Seveso accident, dioxin exposure led to certain developmental effects, in this case observed as changes in

dentition in children under 5 years of age at the time of the accident (Alaluusua et al., 2004).

As regards background exposure to PCBs and dioxins during the prenatal and breastfeeding period and emergence of potential effects on the central nervous system, it is often very difficult to draw conclusions from epidemiological studies, since many factors affect neuromotor and cognitive development in children (e.g. heredity, toxic substances, stimulation, etc.). Batteries of psychometric tests are often used in these studies and these tests often have limitations that must be taken into consideration in the evaluations. However, studies in Michigan (USA), New York (USA), Holland, Germany and the Faroe Islands all reported that increased prenatal exposure to PCBs and dioxins has been associated with depressed cognitive function in children (review: Schantz et al., 2003). In the Dutch study, a negative association was found between PCB/dioxin-exposure and psychomotor development during early development (3-18 month old babies) (Huisman et al., 1995 a, b; Koopman-Essebom et al., 1996), while cognitive development appeared to be unaffected (Koopman-Essebom et al., 1996). At 42 and 84 months of age, psychomotor development appeared to be normal, while cognitive ability was affected (Lanting et al., 1998; Patandin et al., 1998; Vreugdenhil et al., 2002). Similar results have been shown in other studies (Jacobson et al., 1985; Gladen et al., 1988; Jacobson et al., 1990; Rogan & Gladen, 1991; Jacobson & Jacobson, 1996).

Other developmental effects of dioxins indicated at background exposure, apart from the neurological effects mentioned above, include dental defects. Finnish studies have shown that tooth development can be disrupted as a result of dioxin exposure during early development, perhaps in the first instance during the breastfeeding period (Alaluusua et al., 1996; 1999). Effects on development of the immune system can also be mentioned. This area is dealt with in a separate section (below).

Effects that in some cases support epidemiological data from children of PCB-dioxin exposed parents have been clearly shown in a number of studies involving animal trials. Effects on motor and cognitive development have been shown in a number of studies on rodents and monkeys, which show that postnatal exposure to PCBs (both dioxin-like and non-dioxin-like) can affect behaviour later in life (Eriksson & Fredriksson, 1996; Holene et al., 1998; Rice, 1999). Of particular interest is the study on monkeys showing that PCB levels in plasma are similar to those measured in humans (Rice, 1999). In a number of cognitive tests, a change in behaviour was observed in monkeys exposed to the dioxin-like congener PCB 126. Dental damage has been shown in mice and rats exposed to dioxins (Alaluusua et al., 1993). Other effects on progeny include hearing impairment (Goldey et al., 1995) and (in mice) a syndrome involving cleft palate and kidney damage (Birnbaum, 1991).

Experimental studies show that dioxins affect reproductive ability in the progeny of exposed animals. Multigenerational studies on rats showed decreased fertility, litter size and neonatal survival in the F1 and subsequent generations after exposure of F0 to TCDD and PCB-169 (Murray et al., 1979; Smits-van Prooije et al., 1993; Faqi et al., 1998). Effects of dioxin exposure could also be observed on daily sperm production,

number of sperm in the cauda epididymis and number of abnormal sperm. At higher doses, effects were also observed on testosterone levels and in testicular tissue (Kociba et al., 1976; Faqi et al., 1998). In the female progeny, morphological deviations occurred in the genitalia (Gray et al., 1995, 1997a,b*).* These studies form part of the data support used to develop the tolerable daily intake for dioxins that currently applies (2 pg TEQ/kg body weight/day) (SCF-EU).

Conclusions

Animal studies have shown effects of dioxin/PCB-exposure on e.g. cognitive and psychomotor development and effects on development of genital organs, teeth and the immune system. In epidemiological studies, the relationship between dioxin/PCB-exposure and incidence of many of these effects has been demonstrated at very high exposure or indicated at background exposure, although with consideration of the deficiencies that are always associated with epidemiological studies (matching, confounding, drop-out, etc.).

MeHg

In Japan and Iraq, events occurred during the 1950s, 1960s and 1970s that led to a large number of people suffering from MeHg poisoning. The effects reported were in many cases very serious (see section on acute toxicity effects). In adults, the symptoms appeared as damage to the peripheral and central nervous system. At lower exposure, effects were also observed on the central nervous system of foetuses.

A lowest exposure level not causing effects on the CNS of the foetus could not be established and it became a priority to identify such a level. Therefore, during the 1980s and 1990s a number of epidemiological studies were carried out on population groups throughout the world who consumed large amounts of fish and were thereby subjected to higher chronic exposure to MeHg than other population groups. Indications of increased MeHg exposure before birth leading to effects on neurological status (e.g. muscle reflexes, muscle tension, fine motor ability) have been observed in some studies (Grandjean et al., 1997; Steuerwald et al., 2000; Cordier et al., 2002), while others found no such correlation (Marsh et al., 1995; Myers et al., 1995a,b). In neurophysiological studies of children on the Faroe Islands and Madeira, a relationship has been reported between increased MeHg exposure and decreased activity in the brain in response to aural or visual stimuli (Murata et al., 1999a, b; Murata et al., 2004). However, it should be pointed out that measurements of depressed activity in the brain (as brain auditory evoked potential or visual evoked potential) is an area that is relatively unresearched. An advantage with such parameters is that they are not affected by e.g. socioeconomic factors, as are the neuropsychological empirical methods. Sight and hearing were not correlated to exposure to MeHg in children on the Faroe Islands (Grandjean et al., 1997), whereas indications of a slight hearing impairment effect were observed in a small study on children in Ecuador (Counter et al., 1998). A correlation between exposure to MeHg via breast milk and early motor development (sitting,

crawling, walking) was observed on the Faroe Islands (Grandjean et al., 1995), while no such correlation has been reported in children on the Seychelles (Myers et al., 1997; Axtell et al., 1998) or in Peru (Marsh et al., 1995).

The epidemiological studies that have had the greatest importance in risk assessment of MeHg have been carried out in New Zealand, the Faroe Islands and the Seychelles, and are therefore described in more detail here. In New Zealand, development in 74 babies whose mothers had high MeHg exposure during pregnancy (>6 mg/kg in hair, variation 6-86 mg/kg, median 6-10 mg/kg) was compared with that in children who had lower prenatal exposure to MeHg (Kjellström et al., 1986). At 4 years of age, the group with high prenatal MeHg exposure had poorer test results as regards psychomotor, neurological and cognitive functions than the group with low prenatal MeHg exposure. At 6 years of age, extensive testing was carried out on the children's development, but with more children in the control group than in the earlier study (Kjellström et al., 1989). Depending on the choice of statistical method used for analysis, the outcome varied somewhat but in general a correlation was found between increased prenatal exposure to MeHg and impaired general cognitive and speech ability (Kjellström et al., 1989; Crump et al., 1998). However, the study in New Zealand has been criticised because e.g. it had not undergone scientific examination by external experts and the number of pairs of mothers and babies was small.

On the Faroe Islands, a prospective study was carried out on 917 pairs of mothers and babies, who were monitored from the birth of the babies in 1986-87 onwards (Grandjean et al., 1997). The women had high consumption of fish, mostly fish species with low concentrations of Hg, but above all they often ate whale meat, which can have high concentrations of Hg, which appeared to be of greater significance for MeHg exposure than consumption of fish (Grandjean et al., 1992). They also ate whale blubber that contained elevated concentrations of PCBs (Wiehe et al., 1996). The Hg concentration in the hair of the mothers at birth of the babies was on average 4.3 mg/kg, while for the 25th and 75th percentile it was 2.6 and 7.7 mg/kg respectively (Grandjean et al., 1997). In 15% of the mothers, the Hg concentration in hair was $\geq$10 mg/kg. The concentration of MeHg in umbilical cord blood was used as a measure of foetal exposure and the mean concentration in umbilical cord blood was 22.8 µg/L. At 7 years of age neurophysiological function was measured as mentioned earlier, but also neurological status and cognitive ability of the children. A relationship was found between MeHg exposure and poorer test results as regards concentration, speech and memory, and to a certain extent motor and visuospatial function. These differences remained when children whose mothers had a hair concentration above 10 mg Hg/kg were excluded from the calculations. A potential error source in the study is that individuals were simultaneously exposed to the PCBs in whale blubber, which could in itself have affected the test results. However when correction was made for this PCB exposure in approx. half the children studied, it was found that the statistical differences in the test results between groups with low and high MeHg exposure remained (Budtz-Jørgensen et al., 1999). However the PCB load was analysed in umbilical cord tissue and the analyses were carried out at two different laboratories. In a later analysis of the material, it was concluded that MeHg is probably a more important factor in explaining the effects observed on the CNS than PCB, but that simultaneous PCB exposure could

possibly enhance the MeHg-induced effects at high MeHg exposure. However, it is emphasised that interpretation is difficult (Grandjean et al. 2001b).

The effects of simultaneous exposure to MeHg and PCBs have also been studied in a group of 212 children in the USA (Stewart et al., 2003). The MeHg concentration in the hair of the mothers during pregnancy was 0.50 mg/kg (median), and a weak interaction was found between prenatal exposure to MeHg and PCBs and cognitive ability, but the relationship was difficult to interpret. The interaction effects observed at 38 months of age were not observed at 54 months of age. Further studies are probably required to clarify any possible interactions between PCBs and MeHg with prenatal exposure.

In a similar longitudinal study on the Seychelles group of islands, 779 pairs of mothers and children were monitored (Myers et al., 1995b). Approximately 85% of the population of the Seychelles eat sea fish every day, and the women included in the study reported that they ate fish around 12 times per week. The median concentration of Hg in fish varied between 0.5 and 0.25 mg/kg depending on fish species. The measure of exposure to MeHg selected was the concentration of Hg in the hair of the mother during pregnancy, the mean concentration being 6.8 mg/kg (range 0.9-25.8 mg/kg). The study was preceded by a pilot study that included 804 children whose mothers had median Hg concentrations in hair of 6.6 mg/kg during pregnancy (Myers et al., 1995a). The pilot study found that the results in a development test carried out between 1 and 25 months of age were more often abnormal or doubtful in children whose mothers had Hg concentrations in hair of over 12 mg/kg than in children whose mothers had lower Hg-concentrations in hair (Myers et al., 1995a). No correlation was found between prenatal MeHg exposure and mental and psychomotor development in 740-780 children at 6, 5, 19 or 29 months of age (Myers et al., 1995b; Davidson et al., 1995). At around 5 years of age, 711 of the children were tested as regards cognitive ability, speech, reading, spatial orientation ability, problem solving and social behaviour (Davidson et al., 1998). No negative relationship was found between early exposure to MeHg and development in the children, but a positive correlation was found between prenatal MeHg exposure and the results of speech abilities and problem solving tests, and in boys also spatial ability. At 9 years of age, 21 different parameters for development of the CNS were examined in 643 of the children (Myers et al., 2003). Improved test results for hyperactivity index with increasing prenatal MeHg exposure and a negative relationship with the outcome of one of the tests in boys was reported, but overall the results were not considered to be of biological relevance. Otherwise, no MeHg-related relationship was observed. At 9 years of age, 87 of the children from a pilot cohort on the Seychelles were tested with respect to cognitive ability, sight and motor ability (Myers et al., 1995a; Davidson et al., 2000). No negative relationship could be observed between the children's ability/neurological function and prenatal MeHg-exposure, although a positive relationship was observed in boys.

The results from a large number of animal studies on both rodents and monkeys also show that effects similar to those observed in humans on the CNS during development after prenatal or early postnatal exposure is a sensitive parameter (review: NRC, 2000).

Conclusions
Effects on the nervous system from exposure to MeHg during the prenatal period have been studied in several populations with elevated chronic exposure. From the two most important studies, contradictory results have been reported. On the Seychelles, no relationship was observed between prenatal MeHg exposure and negative effects up to 9 years of age, while for the Faroe Islands a significant relationship was reported between prenatal MeHg exposure and child development, in particular as regards concentration, speech and memory at 7 years of age.

Effects on the immune response and inflammatory processes

n-3 fatty acids
Increased formation of eicosanoids from n-6 fatty acids (AA) in relation to eicosanoids from n-3 fatty acids has been proposed as a potential mechanism for blood clot formation and for diseases with an inflammatory or immunological background, e.g. allergies, rheumatism and intestinal disorders (Mori & Beilin, 2004). Certain leukotrienes formed from AA have proinflammatory properties. Several of the leukotrienes formed from EPA and also DHA have a low inflammatory effect and greater intake has been shown in certain studies to inhibit formation of markers for inflammation in the blood, such as cytokines (TNF-a, IL-6 and IL 1-b), CRP, and decrease proliferation of lymphocytes and reactive oxygen radicals.

Intervention studies on humans have not produced unambiguous results as regards the effects of different n-6 and n-3 fatty acids on inflammatory markers in the body (Devaraj et al., 2006). In general, small or no effects have been shown in healthy adults of intake via the diet or a fish oil supplements (Blok et al., 1997; Thies et al., 2001; Devaraj et al., 2006; Murphy et al., 2006; 2007).

In the study by Blok et al. (1997), adult subjects received a supplement of n-3 fatty acids in the form of fish oil during a period of one year. The dose varied from 1.06 g/d till 3.2 g/d n-3 fatty acids. Compared with a control group, no effects were observed on *ex vivo* stimulated formation of cytokines in whole blood (IL-1β, TNF-α or interleukin 1 receptor antagonist, IL-RAa).

Intake of either 2 g α-linolenic acid, 0.7 g AA, 0.7 g DHA or 1 g EPA+DHA (as fish oil) per day for 12 weeks also did not affect a range of markers for inflammation in older adults (Thies et al., 2001). However, a decrease was noted in concentrations of certain markers for arterial activity after intake of α-linolenic acid and fish oil, which can be beneficial from a cardiovascular perspective .

Supplements of 0.12-0.15 g/d long-chain n-3 fatty acids (EPA, DPA, DHA) for 6 weeks in the form of e.g. fish oil did not affect markers for inflammation in healthy adults with

low dietary intake of these fatty acids (Murphy et al., 2006). In another study, no effect was seen on inflammation markers (CRP in blood or TXB_2 in urine) in overweight adults with hypertriglyceridaemia after supplementation with 1 g/d EPA+DHA for 6 months (Murphy et al., 2007). However, it was found that concentrations of long-chain n-3 fatty acids in red blood cells were linked to lower levels of these markers.

Supplements of 0.57 g EPA and 0.38 g DHA per day in the form of fish oil given to full-term infants from 7 to 12 months of age did not affect markers for inflammation, e.g. C-reactive protein, IL-2 receptor, TNF-α, IL-10, or plasma IgE (Damsgaard et al., 2007). However, an increase was observed in INF-γ stimulation *in vitro*, which has been proposed as marker for maturity of the immune system.

For comparison, it can be noted that mean intake of n-3 fatty acids in the adult Swedish population is: α-linolenic acid 1-2 g/d, AA 0.1 g/d, EPA 0.1 g/d and DHA 0.2-0.25 g/d (Becker & Pearson, 2002).

Allergies and atopia

Some epidemiological studies have indicated that n-3 fatty acids, particularly long-chain n-3 fatty acids from fish, or the balance between n-6 and n-3 fatty acids plays a role in the development of various allergic disorders such as asthma and atopic conditions (Dunder el al., 2001; Nafstad et al., 2003; Prescott & Calder, 2004; Oddy et al., 2004; Trak-Fellermeier et al., 2004; Hoff et al., 2005; Wong, 2005). However, the results from clinical intervention studies on allergic individuals are contradictory.

The study by Dunder et al. (2001) measured e.g. fatty acid composition in serum (cholesterol esters) in Finnish children of different ages with atopic dermatitis, rhinitis or asthma and in healthy matched controls. In children who at the time of the base measurements had atopic dermatitis, the concentration of EPA and DHA in serum was lower, but no other statistically significant differences in fatty acid pattern were observed for any form of allergy. Intake of fish at the base measurements did not differ between the groups, but it was significantly lower during follow-up in the children who had developed atopia in the interim.

In a German cross-sectional study of adults, a lower risk of allergic sensitisation and rhinitis was observed in individuals with the highest intake (divided into quartiles) of α-linolenic acid and the highest concentration of EPA in red blood cells (Hoff et al., 2005). However, no relationship was found with n-6/n-3 ratio or other fatty acids.

Broadfield et al. (2004) found no relationship between intake of n-3 fatty acids or concentration of n-3 fatty acids in red blood cells in individuals with asthma and healthy controls. However, increased concentration of linoleic acid (n-6) was associated with a significantly decreased risk of asthma.

Nafstad et al. (2003) found that the risk of allergic rhinitis (hay fever) was significantly lower in Norwegian children who during their first year of life regularly ate fish

compared with those who did not eat fish. A Swedish study found that regular fish consumption before one year of age was associated with a decreased risk of developing allergic disorders at 4 years of age (Kull et al., 2006).

A meta-analysis of nine randomised, controlled trials in which children (> 2 years) with asthma received a supplement of long-chain n-3 fatty acids for more than four weeks displayed no significant effects on symptoms (Thien et al., 2003). Supplements of n-3 fatty acids in the form of fish oil given to children with asthma in the family showed a moderate decrease in the incidence of coughing in atopic children but not among children without atopia. No effect was observed on the development of symptoms such as wheezing (Peat et al., 2004). Studies of supplementation with n-3 fatty acids during pregnancy indicate that immune function in the baby can be affected (Dunstan & Prescott, 2005). Further studies are required to determine the importance of n-3 fatty acids.

Rheumatoid arthritis

Some epidemiological data indicate a relationship between consumption of fish and the risk of developing rheumatism (James et al., 2003). Several intervention studies have shown that supplements of n-3 fatty acids in the form of fish oil can relieve symptoms or decrease the need for medicine (James et al., 2003; Rennie et al., 2003). A couple of later studies have not been able to show any clear effect (Remans et al., 2004; Sundrarjun et al., 2004). In one study, an improvement in symptoms was found in patients who received either fish oil or a combination of fish oil and olive oil, with the improvement being most distinct in the latter group (Berbert et al., 2005). The doses of n-3 fatty acids were between 1-7 g/d and study length was 3-12 months. A range of factors can have affected the results in these studies, including study length, dosage, compliance, drop-out, dietary composition, degree of disease and duration of disease.

Other conditions

Other conditions with an inflammatory background that have been related to intake of n-3 fatty acids include e.g. cystic fibrosis, inflammatory bowel diseases (ulcerative colitis, Crohn's disease) and psoriasis. Intervention studies with high doses of n-3 fatty acids in the form of fish oil have not shown any clear effect in cystic fibrosis (Beckles-Wilson et al., 2005) and results for various inflammatory bowel diseases are also contradictory (Belluzi, 2002; MacLean et al., 2005). Merchant et al. (2005) found that increased intake of α-linolenic acid and to a certain extent linoleic acid, but not long-chain n-3 fatty acids or fish consumption, was associated with a decreased risk of pnemonia among middle-aged and elderly men in the USA.

Conclusions

It can be concluded that the importance of intake of fish and n-3 fatty acids for the risk of developing allergies and various inflammatory conditions is still unclear. However,

there are studies that show beneficial effects of supplementation with large doses of long-chain n-3 fatty acids in the form of fish oil for certain conditions, e.g. rheumatoid arthritis, while supplementation has not had any clear effects on asthma, cystic fibrosis or inflammatory bowel diseases.

Dioxins/PCBs

Epidemiological studies have investigated the relationship between dioxin exposure and function of the immune response system, both in adults and in children. In studies of occupationally exposed individuals, high exposure to the most toxic dioxin (TCDD) has been related to changes in markers of immune system function, for example a change in the amount of white blood cells and antibodies in the blood (Jennings et al., 1988; Neubert et al., 1993; Ott et al., 1994; Halperin et al., 1998). However, this relationship is unclear and it is also not possible to establish whether the changes observed have any significance for health.

Results from studies of immune system markers in children in the USA (Karmaus et al., 2001) and Holland indicate a relationship between prenatal dioxin and PCB exposure and small changes in the amount of white blood cells and antibodies soon after birth. In certain studies, a relationship was also observed between prenatal PCB and/or dioxin exposure and growth, and increased risk of ear infection (Weisglas-Kuperus et al., 1995; Weisglas-Kuperus et al., 2000; Karmaus et al., 2001; ten Tusscher et al., 2003; Weisglas-Kuperus et al., 2004). In most of these studies, effects were observed on the frequency and severity of asthma and allergies, but these results are difficult to interpret and both positive and negative correlations with dioxin/PCB-exposure have been observed.

The relationships have been observed in populations with dioxin and PCB levels in the vicinity of those currently occurring in pregnant women in Sweden (Glynn et al., 2001). However, on the basis of these studies it is not possible to draw conclusions about any possible health-related relationship between PCB or dioxin exposure and immune system function, since the individual studies have often not been able to take account of medical factors or lifestyle factors that could be expected to have affected the results found. However, animal studies support the findings made in epidemiological studies. For example, dioxin affects thymus function, which causes down-regulation of the immune response in research animals, mainly through affecting the composition of T-lymphocytes in the body (Van Loveren et al., 2003).

Conclusions

High TCDD exposure in occupationally exposed workers has been related to changes in markers of immune system function, but it is not possible to establish that these changes are significant for health. A relationship has also been observed in children between dioxin/PCB exposure and changes in the amount of white cells, antibodies and in certain cases an increased risk of ear infection. However, the relationship between

asthma/allergies and dioxin exposure is difficult to interpret. An effect on the immune status has also been observed in research animals, e.g. in the form of down-regulation of the immune system in rats.

MeHg

The effects on the immune system of exposure to mercury have been studied relatively little and no studies have been reported on the effects of MeHg on the immune system *in vivo* in humans, apart from a study of neonates in Quebec that were exposed prenatally to both PCBs and MeHg (Belles-Isles et al., 2002; Bilrha et al., 2003). In umbilical cord blood, a change was found in the composition of T-, B- and NK-cells, as well as an altered cytokine response. Changes in T- and B-cell composition have been correlated with occupational exposure to inorganic mercury (Hg^0) and autoimmune response (Moszczynski, 1998), but the results are not unambiguous. The effects of MeHg on the immune system have been studied in a number of *in vivo* studies on rats and mice, and in *in vitro* experiments. These studies vary in design and the immunological parameters studied. None of the *in vivo* studies has been able to identify a NOEL, i.e. a dose at which no effects have been observed, or alternatively only one dose has been used. The effects reported on exposure of adult animals to MeHg include decreased thymus weight, reduced NK-cell activity, decreased resistance to viral infections, changes in the composition of T- and B-cells, altered cell division response and autoimmunity (Ilbäck et al., 1991; Ilbäck et al., 1996; Ortega et al., 1997; Thompson et al., 1998; King et al., 2003 a,b; Häggkvist et al., 2005). Studies of the effects on immune system development of exposure to MeHg during the foetal stage or just after birth have also been reported in some studies. Effects on thymus and spleen weight, changes in the number of lymphocytes in the blood, NK-cell activity, cell division response and composition of T- and B-cells have been reported (Ilbäck, 1991; Thuvander et al., 1996; Wild et al., 1997). Altered levels of essential trace elements such as iron, calcium, manganese and zinc have also been observed in MeHg-exposed mice in a viral infection model (Ilbäck et al., 2000).

The sensitivity of immunological response varies between different strains of mice, which may be explained by differences in demethylation of methyl mercury to inorganic mercury, which then affects the immunological system (Hultman & Hansson-Georgiadis, 1999).

Conclusions

The few studies reported on rodents show that MeHg has the potential to affect the immune system in adults and foetuses. However, these studies do not provide any clear answers as regards identifying the most sensitive immunological parameters or the direction in which MeHg alters the respective parameters. The extent to which MeHg exerts effects in the immune system at low exposure levels is also still unclear, as is the highest exposure level that does not give rise to effects.

Cardiovascular disease, atherosclerosis

n-3 fatty acids

A range of meta-analyses and systematic analyses of intervention studies and epidemiological studies indicate that consumption of n-3 fatty acids in the form of fish or fish oil can protect against death from cardiovascular disease (Fødevaredirektoratet, 2003; SACN/COT, 2004; He et al., 2004a,b; EFSA, 2005, Studer et al., 2005; Wang et al., 2006). The documentation is best for individuals with a high risk of cardiovascular disease. However, one meta-analysis has shown no clear effects (Hooper et al., 2004).

The analysis by Hooper et al. (2004) included 48 randomised controlled intervention trials with at least 6 months of treatment time and 41 cohort studies comprising individuals with or with high risk of cardiovascular disease, and the general population. n-3 fatty acids of both vegetable origin (α-linolenic acid) and from fish, either as fish or as fish oil, were included. The general conclusion of the authors was that supplementation of n-3 fatty acids was not associated with clear benefits as regards overall mortality, morbidity or death from cardiovascular disease.

However, the conclusions of this meta-analysis are strongly influenced by a large intervention study of male patients with angina (Burr et al., 2003). This study included 3000 men with angina, of which around half had suffered a cardiac infarction. The men were divided into four groups and advised to: eat two portions of oily fish per week (without specifying type of fish), or alternatively to take a daily supplement of fish oil capsules (3 g); to eat more fruit, vegetables and oats; both these pieces of advice; or more general dietary advice that did not include either of the first two pieces of advice. Fish oil was given to those in the fish group who had difficulty eating fish. In a later phase, the fish group was divided into a group that was allowed to continue eating fish and a group that received fish oil. In total, 1109 men were advised to eat fish and 462 to eat fish oil. After 3-9 years of monitoring, no difference was found in overall mortality between the control group and the group that was advised to eat fish, but the risk of death from heart attack was greater in the fish group, mainly evident in the group that received fish oil. Compliance with the advice was checked in around 40% of the men at 6 months by a questionnaire and by measuring plasma concentration of EPA in a smaller group (29 to 39 men). Both the questionnaire and EPA in plasma indicated that compliance was on average reasonably good. EPA intake in the fish group increased from 0.1 g/d to 0.5 g/d, but the variation was large.

The meta-analysis by Hooper et al. (2004) included 15 randomised controlled trials (RCT) with data on overall mortality, and the relative risk in the intervention group was 0.87 (CI: 0.73-1.03), but the heterogeneity between the studies was large. When the study by Burr et al. (2003) was excluded from the analyses, the relative risk was 0.83 (0.75-0.91), without significant heterogeneity. The analysis of cohort studies comprised three studies and the relative risk of overall mortality was 0.65 (CI: 0.48-0.88). In the analysis of all cardiovascular disease cases there were 18 RCT and the relative risk in

the intervention group was 0.95 (CI: 0.82-1.12). When the study by Burr et al. (2003) was excluded, the relative risk was 0.9 (CI: 0.82-0.98). For the seven cohort studies that were included, the relative risk for all cardiovascular disease cases in the intervention group was 0.91 (CI: 0.73-1.13), but the heterogeneity between the studies was considerable.

Studer et al. (2005) analysed the results from 14 controlled intervention studies in which n-3 fatty acids were given as a treatment for elevated blood lipids and for prevention of cardiovascular disease. Both primary and secondary preventive studies were included. In most studies the n-3 fatty acids were given in the form of fish oil, in some studies also in the form of fish or α-linolenic acid. The monitoring period was on average 1.9 year (0.5-5 years). No details of dosage are reported. The cholesterol levels in serum were not notably affected. A significantly decreased risk for CHD mortality was found (relative risk (RR) 0.68, CI: 0.52-0.90) and, in secondary preventive studies but not primary preventive studies, also significantly decreased overall mortality (RR 0.77, CI: 0.63-0.94).

A meta-analysis of 11 prospective population studies showed a decreased risk of dying from cardiovascular disease among individuals who ate fish at least once per week compared with individuals who ate fish more seldom than once per month (He et al., 2004a). The monitoring period was on average 12 years. The risk decreased with increased intake of fish, 7% for each 20g/d increase in fish consumption. In a similar analysis, He et al. (2004b) found that the risk of suffering a stroke was also related to fish consumption. Here, a statistically decreased risk was even demonstrated for consumption 1-3 times per month. The relative risk decreased with consumption, but the trend was not significant.

A systematic review by Wang et al. (2006) included studies that had lasted for at least one year. The analysis included one primary preventive RCT, 14 secondary preventive RCT, 7 case-control studies, 25 prospective cohort studies of healthy subjects and one prospective cohort study of individuals with previous cardiovascular disease. Intake of n-3 fatty acids in the form of fish, fish oil and α-linolenic acid was examined. The authors concluded that there is strong evidence of a beneficial effect of long-chain n-3 fatty acids on cardiovascular disease and mortality for secondary prevention, but that the evidence for primary prevention was weaker because the number of controlled intervention studies was small.

In a Japanese study, a decreased risk (-19%) of cardiovascular events was observed in men with elevated cholesterol values who in addition to treatment with statins received a supplement of 1.8 g/d EPA (as ethyl esters) for an average of 4.6 years compared with a control group that received only statins (Yokoyama et al., 2007). However, this risk decrease was only statistically confirmed in men with prior coronary heart disease. No differences were observed in mortality from cardiovascular disease between the intervention and control groups.

The results of these analyses and studies indicate that regular consumption of fish and n-3 fatty acids can decrease the risk of heart mortality and overall mortality, mainly among individuals with an elevated risk. In the meta-analysis of intervention studies by Hooper et al (2004), the study by Burr et al. (2003) resulted in it being impossible to confirm a risk decrease. The results of this study differ from those of previous secondary preventive studies, e.g. the DART study (Burr et al., 1989), which had a similar design, and the GISSI study (GISSI, 1999) where n-3 fatty acids were given as fish oil. Studer et al. (2003) include the study by Burr et al. (2003) but exclude it from their meta-analysis because they regard it as having a number of methodological failings.

The effect on cardiovascular mortality and stroke is ascribed as a rule to the long-chain n-3 fatty acids, which are believed to e.g. decrease the risk of arrhythmia, clot formation and inflammation (Din et al., 2004). There are also studies indicating that intake of fish can influence the atherosclerosis process (Erkkilä et al., 2005; McLaughlin et al., 2005). Consumption of fish and fish oils also influences other risk factors and can decrease triglyceride levels in the blood (Harris, 1997; Din et al., 2004).

Other conditions related to atherosclerotic changes in blood vessels include age-related macular degeneration. Some epidemiological studies have found frequent consumption of fish to be associated with a decreased risk (Cho et al., 2001; Seddon et al., 2005). In an analysis of the effects of n-3 fatty acids on glycaemic control and other risk factors for cardiovascular disease in patients with type 2 diabetes, it was concluded that the scientific evidence was insufficient to draw any firm conclusions other than that n-3 fatty acids can lower the triglyceride levels in the blood (MacLean et al., 2004).

Infants that received a supplement of long-chain n-3 fatty acids have been reported to have lower blood pressure later in childhood (Forsyth et al., 2003). Studies on adults show that supplements of large doses (several grams per day) of long-chain n-3 fatty acids can give a blood pressure decrease in the order of 1-2 mm Hg, especially among hypertonics (Geleijnse et al., 2002).

Conclusions

Regular consumption of fish can contribute to decreasing the risk of heart mortality. The evidence is strongest for individuals with an elevated risk. Cohort studies also indicate that relatively moderate consumption can decrease the risk in the general population. The estimates of dose-response that have been made are based on cohort studies and are variable, which can be due to e.g. uncertainly in dietary data, which are often based on frequency methods. In the analysis by He et al. (2004a), a decreased risk was observed for consumption 1 time per week or more often.

Dioxins/PCBs

Dioxin exposure has been linked to an increased risk of cardiovascular disease. In certain studies of occupationally exposed personnel, individuals who had come into

contact with Agent Orange in Vietnam and in studies on the Seveso population, an increased risk of ischaemic heart disease could be detected (summarised in JECFA, 57th meeting, WHO 2002). In addition, altered blood values, such as increased cholesterol concentration (Roegner et al., 1991) and increased triglyceride concentration (Roegner et al., 1991; Grubbs et al., 1995) can be correlated to dioxin exposure in the US Air Force cohort in Vietnam. However, other cohorts do not display the same changes in blood values. In the cohort of commercial fisherman on the east and west coasts of Sweden studied by Hagmar et al. (1992), it was found that mortality from cardiovascular disease was 12% lower in east coast fishermen compared with the normal population, and that this cohort of fishermen ate more oily east coast fish than the normal consumer and also had higher POP concentrations in their blood (Svensson et al., 1995a).

MeHg

The first study that reported a correlation between MeHg exposure and the risk of heart attack/mortality came from Finland and was based on a cohort of 1 833 men in eastern Finland (Salonen et al., 1995). Fish consumption was high; on average 46.5 g/day (min-max 0-619.2), and some of the most common fish species were whitefish, rainbow trout, pike and perch, i.e. lean, locally caught fish. The Hg concentration in hair was on average 1.92 (min-max 0-15.67 mg/kg) and was correlated to fish consumption. Individuals who ate more than 30 g fish per day had a relative risk (RR) of heart attack of 1.87 (CI: 1.13-3.09) compared with individuals with lower fish consumption. Similarly, the risk of heart attack was significantly elevated in those who had a Hg concentration in hair over 2 mg/kg compared with those with a concentration under 2 mg/kg (RR 1.69; CI: 1.03-2.76). Mortality from heart attack and overall mortality was also correlated to the Hg concentration in hair.

Two follow-up studies of the cohort have since been carried out (Rissanen et al., 2000). These investigated the relationship between serum concentrations of n-3 fatty acids and cases of cardiovascular disease (197 cases of coronary events according to the authors). In the group that had the 20% highest serum concentrations of n-3 fatty acids (DHA and DPA), the risk of contracting heart disease was significantly lower (47%) than in those who had the 20% lowest serum concentrations. In the one-third who had a Hg concentration in hair exceeding 2 mg/kg, there was no clear protective effect of the n-3 fatty acids. In the others, the relationship between serum concentrations of n-3 fatty acids and risk for cardiovascular disease was clearly dose-related, with a protective effect with increasing serum concentrations. In a later follow-up (Virtanen et al., 2005), similar results were reported. A total of 282 cases of acute coronary events were included in the study. The risk of contracting heart disease was 1.07 (CI: 0.77-1.49) in the one-third with Hg concentrations in hair in the range 0.84-2.03 mg/kg compared with the risk in those who had the lowest Hg concentrations in hair (<0.84 mg/kg). The one-third who had Hg concentrations in hair above 2.03 mg/kg had a risk of 1.66 (CI: 1.20-2.29) of contracting heart disease. At Hg concentrations in hair below 2.03 mg/kg there was a decreased risk of heart disease with increasing serum concentrations of DHA+DPA (RR 0.69, CI: 0.52-0.91), while no such relationship was observed at Hg concentrations in hair above 2.03 mg/kg.

A Swedish prospective case-control study examined the relationships between fish consumption, MeHg exposure and plasma levels of EPA and DHA (P-PUFA) and the risk of suffering an acute cardiac infarction (Hallgren et al., 2001). The study comprised 78 cases and 156 matched controls. Those who ate fish less than once a week had a median Hg concentration in red blood cells (Ery-Hg) of 3.3 ng/g, while those who ate fish once a week or more often had a median value of 5.2 ng/g. Compared with those who had Ery-Hg <3 ng/g, the relative risk of attack was 0.91 (CI: 0.49-1.69) in those who had Ery-Hg 3-6 ng/g, and 0.43 (CI: 0.19-0.95) for Ery-Hg >6 ng/g. Ery-Hg and P-PUFA co-varied. There were strong positive correlations between both P-PUFA and MeHg exposure and decreased risk of suffering an acute cardiac infarction.

A cross-sectional study of men with myocardial infarction and matched controls from several countries in Europe (Sweden not included) showed a relationship between the risk and the concentration of Hg in nails (N-Hg) and the concentration of DHA in fatty tissue biopsies, respectively (Guallar et al., 2002). The risk of acute myocardial infarction increased with rising N-Hg, and decreased with rising concentration of DHA in fatty tissues.

A prospective study of 1 014 men from eastern Finland found a significant relationship between hardening of the walls of the carotid artery over a 4-year period (a measure of progressive arteriosclerosis) and Hg concentration in hair (Salonen et al., 2000). The effect was observed in the group who had Hg-concentrations in hair of over 2.81 mg/kg compared with the others. The Hg concentration in hair was on average 1.8 mg/kg and the highest concentration was 23.3 mg/kg.

Effects on blood pressure have been reported in a study on 917 seven-year-old children from the Faroe Islands who were exposed to MeHg to varying degrees during the prenatal period (Sørensen et al., 1999). The Hg concentration in umbilical cord blood was on average 31.77 µ/L (min-max 1-300 µg/L). Systolic and diastolic blood pressure were 14.6 and 13.9 mm Hg higher respectively in children with a Hg concentration in umbilical cord blood of 10 µg/L compared with those who had the lowest exposure levels (1 µg/L). The effect was strongest in children with a birth weight < 3 700 gram. However, no further increase was observed at higher exposure levels. The Hg concentration in the hair of mothers at birth was also correlated to increased blood pressure, but not as strongly as the Hg concentration in umbilical cord blood. In Swedish studies, no relationship has been observed between MeHg exposure and blood pressure (Hallgren et al., 2001).

Variability in heart rhythm at seven years of age was also correlated to prenatal MeHg exposure and the Hg concentration in hair at seven years of age in children in the Faroe Islands (Sørensen et al., 1999; Grandjean et al., 2004, Murata et al., 2004). At 14 years age such a relationship was also observed, but only with the prenatal MeHg exposure. It was concluded that the changes were an effect of damage to the brain stem.

Conclusions
Epidemiological data indicate that there is a correlation between high MeHg exposure and increased risk of acute cardiac infarction, but the conclusions on the appearance of the dose-response curve are somewhat uncertain. In those Swedish studies that have been carried out, no such relationship has been found, and this can probably be explained by the MeHg exposure having been essentially lower compared with that in e.g. the Finnish studies. In fact, the Swedish studies have actually found a positive relationship between MeHg-exposure and decreased risk of heart attack. This can be interpreted as the protective effects of the n-3 fatty acids (and perhaps also selenium) dominating up to a certain level of intake, beyond which the MeHg-induced negative effects begin to dominate.

The basis for determining whether there is a relationship between MeHg and stroke is extremely limited. Swedish data, based on a population with low MeHg exposure, indicate that there is not a positive relationship between MeHg and the risk of stroke.

There are certain indications that exposure to MeHg during the prenatal stage or in childhood is correlated with increased blood pressure and slight changes in heart rhythm variability. The significance of these findings is unclear, but could have a link to suffering acute cardiac infarction. In Swedish studies of adults, no relationship between exposure to MeHg and blood pressure has been observed, but the exposure levels were low. More studies are needed to clarify this.

Cancer

n-3 fatty acids

The importance of fish consumption and intake of n-3 fatty acids for the incidence of various forms of cancer is unclear. Overall assessments of the results from epidemiological studies show limited or no effects (Hjartåker, 2003; MacLean et al., 2006; Engeset et al., 2006).

Dioxins/PCBs

A number of human populations have been studied in order to identify the relationship between dioxins and cancer, and these have been reviewed by the IARC (1997) and two expert groups within the WHO (Kogevinas, 2000; WHO, 2002). IARC has classified TCDD as a human carcinogen, based on adequate evidence in animal trials and limited evidence in human studies, the latter mainly epidemiological studies based on occupationally-exposed cohorts exposed to TCDD. The epidemiological studies show an increased risk of cancer, all forms of cancer combined, in TCDD-exposed cohorts from the USA (NIOSH), Germany (BASF chemical workers) and Holland. In one of the German studies, a positive dose-response trend was observed. The evidence of a

relationship between specific forms of cancer (e.g. lung cancer, non-Hodgkins lymphoma) and TCDD-exposure was less clear (IARC, 1997).

The WHO's two risk assessments are based on prospective, well executed studies on cohorts from industries in Germany, the USA, Holland and the United Kingdom, on the combined cohort used in the IARC assessment and on the Seveso cohort. It has been established that an association exists between high TCDD exposure and increased risk of dying from cancer and that this relationship probably cannot be explained by confounding, but that this possibility cannot be completely excluded. However, it must be emphasised that the combined relative risk (RR) is only moderately elevated, by a factor of 1.4 in those groups exposed to the highest doses during the longest period. Finally, it should be borne in mind that the general population is exposed to TCDD levels that are two to three orders of magnitude lower than those estimated to be lifetime doses in the occupationally exposed populations and in the Seveso population (Kogevinas, 2000; WHO, 2002).

For cancer risks associated with PCB exposure, there are a number of studies that indicate that occupational exposure to PCBs increases mortality from cancer of various organs, such as stomach and intestine, liver, blood-producing organs and skin (melanoma) (CICAD, 2000). However, these is no clear pattern that points to a certain form of cancer, as many studies are a case of combined exposure and few cases.

A follow-up cancer study of the population exposed to dioxins in conjunction with the Seveso accident was published in 2001 (Bertazzi et al., 2001). During the entire observation period, the combined risk of dying from cancer had not increased. However, in zone B there was an increased risk of dying from certain forms of cancer of lymphatic and blood-producing tissues. When a gender division was made, it was found men had an increased risk of dying from cancer, all forms and specific forms of cancer such as rectal cancer, lung cancer and leukaemia (zone A+B). A specific study of the incidence of breast cancer in the Seveso area gave certain indications of an increased risk with increased TCDD concentration in the blood (Warner et al., 2002).

Swedish cross-sectional studies in which fishing populations on the west and east coast were compared with the general population showed an increased incidence of certain forms of cancer (stomach and skin) in the east coast fishing population (Svensson et al., 1995a). The frequency of multiple myeloma was highest in the east coast fishing population, while the frequency of colon cancer was lower. One explanation can be that the east coast fishing population had a higher intake of oily east coast fish and thus of organic environmental contaminants. However, no measurements of exposure to organic environmental contaminants were carried out in this study. The conclusion of the study was that the increase in stomach and lung cancer could not be linked with any great certainty to exposure to persistent organic compounds, since the fishing population was simultaneously exposed to other potential carcinogens such as arsenic and compounds in smoked fish (Svensson et al., 1995a).

In animal trials, neoplastic changes in the liver can be observed after exposure to dioxins and other structurally closely related compounds. Short-term trials indicate a lack of

direct DNA-damaging effects, but the carcinogenic effects observed could instead be explained by indirect mechanisms comprising control of normal growth and differentiation. In rats, a NO(A)EL value of 10 ng TCDD/kg body weight/day has been calculated regarding tumour development in the liver (Kociba et al., 1978).

Conclusions

There is evidence for classifying dioxins as human carcinogens and the carcinogenic properties of dioxins have also been observed in animal trials. However, it is difficult to use these data to quantify the risk in humans (for example for establishment of TDI). There are many deficiencies in the epidemiological studies as regards e.g. handling of confounding problems and multiexposure. Exposure analyses are also deficient in many cases. Finally, it should be emphasised that the general population is exposed to TCDD levels that are two to three orders of magnitude lower than those estimated to be lifetime doses in the occupationally exposed populations and in the Seveso population, i.e. in those cohorts where a risk increase is reported.

MeHg

The IARC has classified MeHg as a possible carcinogen for humans (class 2B) (IARC, 1993). In a retrospective cohort study, no increased risk of dying from cancer was observed in individuals who had survived the Minamata disaster (see below) compared with age- and gender-matched control individuals from the same city (Tamashiro et al., 1984). In an ecological study, no differences in mortality from cancer were observed, but mortality from e.g. liver cancer was higher in the area with elevated MeHg exposure than in the control area (Tamashiro et al., 1986). However, there are weaknesses in the study, e.g. alcohol consumption and prevalence of hepatitis B infection, factors that can *per s*e lead to liver disease, were higher in the area with high consumption of fish. In addition, an actual measure of MeHg exposure was lacking in those men who were included in the study.

In a further study of mortality from cancer in individuals who had survived the disaster in Minamata, no increased relative risk of mortality was found in these individuals compared with matched control individuals (Kinjo et al., 1996). Survivors of the Minamata disaster ran less risk of dying from stomach cancer than the control group, but had a higher risk of dying from leukaemia. However, the latter estimate is based on five deaths, and the supporting data are therefore very uncertain.

Some animal trials have shown that kidney tumours developed in male mice, but not female mice, at high doses (review: NRC, 2000). However, these doses were so high that renal toxicity was observed and therefore it was concluded that the tumours arise secondarily as a result of damage and with reparation of kidney cells. However, in rats no clear association has been seen between MeHg exposure and development of tumours. Indications that MeHg can act as a tumour promoter are reported in a study on female mice exposed to MeHg and thereafter exposed to urethan (Blakley et al., 1984).

Acute toxicity effects

Dioxins/PCBs

Dioxins and PCB are compounds that are stored in the body for long periods and can give rise to chronic effects (such as cancer) if the exposure has been sufficiently high and prolonged. However, some of the effects of dioxin arise a short time after exposure if it is high. The skin complaint chloracne is such an effect that was observed in 0.6% of the exposed Seveso population, mostly children (Bertazzi et al., 1998). Chloracne was also observed in several of the occupationally exposed cohorts studied (e.g. Suskind & Hertzberg, 1984). However, chloracne cannot be directly linked to body loads of dioxins, and absence of chloracne is not the same as low dioxin concentration in the body (Zober et al., 1997). The condition is reversible, but it can take a long time for complete recovery.

MeHg

Symptoms of acute effects after MeHg exposure were first observed in conjunction with the environmental disasters in Japan and Iraq (Bakir et al., 1973; Harada, 1995). A mutual feature in the victims in Minamata and Iraq was that the nervous system, primarily the central nervous system but also the peripheral, was affected. Paraesthesia (numbness of the hands and feet, pins and needles around the mouth), tremors, dysarthria (speech difficulties), coordination problems, sight and hearing changes and peripheral neuropathy are examples of symptoms. In adults the damage to the brain is limited to certain specific parts. High prenatal exposure resulted in various degrees of damage to the central nervous system, e.g. blindness, deafness, paralysis, hyperactive reflexes, cerebral palsy (CP damage) and delayed mental development.

In Japan and Iraq, it was also found that pregnant women who were exposed and who did not display any symptoms gave birth to babies with damage. It was also observed that the damage to the central nervous system by prenatal exposure differs from the damage from exposure in adults. In the foetus, damage can be seen in the entire brain. The reason for this is unknown, but there are several possible explanations. MeHg disrupts or initiates a number of biochemical processes at cell level (e.g. protein synthesis, oxidative stress, lipid peroxidation and microtubule function). Post-mortem examination of victims from Japan and Iraq found that migration of neurons, i.e. the path of nerve cells out to the cerebral cortex, was disrupted. Such effects have also been observed in *in vitro* studies (reviews: ATSDR, 1999; NRC 2000).

Complex mixtures of environmental pollutants and their combined effect

The Swedish population is exposed to complex mixtures of environmental pollutants in food. In oily fish there are elevated concentrations of a mixture of fat-soluble, poorly degradable compounds, while lean fish, primarily freshwater fish, can contain elevated concentrations of MeHg. Studies of serum levels of PCB and chlorinated pesticides in women and men in Sweden have shown that the concentrations of some of these pollutants co-vary in the body (Glynn et al., 2000; Glynn et al., 2003). In breast milk from Swedish women, there is high co-variation between levels of dioxins and non-dioxin-like PCBs (Glynn et al., 2001). The situation is similar in other countries where there are problems with dioxins and PCB in the environment. This means that lactating women with a low body load of dioxins also have a high probability of having low body loads of non-dioxin-like PCBs and *vice versa*. Against the background of current knowledge, it is not possible to evaluate the consequences of this mixed exposure on health.

In epidemiological studies of the relationship between dioxins and health effects in children and adults who have not been subjected to high occupational exposure, against the background of the problems described above it is not possible to draw conclusions on whether an observed effect is due to dioxin or PCB-exposure, or to some other foreign compound. There are also examples of population groups with relatively high exposure to both PCBs and MeHg, which can create interpretation difficulties when possible relationships between exposure and health effects are being studied (Grandjean et al., 2001b; Stewart et al., 2003). Animal trials have shown that various environmental pollutants interact with each other in the body and this probably also occurs in humans (Chu et al., 2001; Campagna et al., 2002). With the current supporting data, the risks can not be estimated for total exposure to the complex mixtures of environmental pollutants to which humans are exposed via the diet.

Appendix 2. Risk Management

Maximum levels – highest permissible concentrations in commercial food

There is international consensus that the presence of certain organic environmental contaminants such as MeHg in fish can pose a health risk, and therefore within e.g. the EU, agreement has been reached on maximum levels, i.e. the highest permissible concentration of mercury in commercial fish.

For dioxins (PCDD/DF), the joint maximum levels within the EU for animal foods came into force on 1 July 2002 (EG Directive 466/2001; maximum level for fish (muscle meat) and fish products 4 pg WHO-TEQ/g fresh weight). During 2006, dioxin-like PCBs were included in the maximum level determinations and in addition to the previous maximum level, which still applies, there is now also a joint maximum level for dioxins, dibenzofurans and dioxin-like PCBs, which for fish and fish products has been set at 8 pg WHO-TEQ/g fresh weight (EG Directive 199/2006). This directive came into force in November 2006. In this directive, eel has been given a higher total-TEQ maximum level (12 pg WHO-TEQ/g fresh weight), since this species has high concentrations of dioxin-like PCBs in certain areas of the EU.

Sweden and Finland have an exception from the maximum level for dioxins in fish, which means that fish can be sold on the domestic market even if the dioxin concentrations exceed the maximum level. This exception is based on the fact that these countries have dietary advice that consumers are aware of, and that contribute to the total dioxin exposure, despite the high concentrations of dioxins in certain oily Baltic Sea fish caught in the wild, which leads to tolerable intake not being exceeded. The relevant exception has recently been extended to December 2011 (EG Directive 199/2006).

At present the EU has a general maximum level for mercury in fish products of 0.5 mg/kg with the exception of certain fish species (EG Directive 466/2001). For species which due to their form of living often have higher mercury concentrations, the maximum level is 1.0 mg/kg. For Swedish waters, the higher maximum level applies for pike and eel. This Directive is under renegotiation.

Dietary advice on fish in Sweden

The general dietary advice of the National Food Administration is 2-3 portions (120 gram/portion) fish and shellfish per week, with variation between different types (Enghardt Barbieri & Lindvall, 2003). The advice mentions that it is good if one of three fish meals consists of oily fish. Specific dietary advice to limit consumption of certain fish types with elevated concentrations of environmental pollutants was introduced in 1967 and referred primarily to freshwater fish with elevated mercury concentrations. In the same year, blacklisting of fishing waters with high MeHg loads was also introduced (Vår Föda, 1972). Recommendations on limiting the consumption of certain fish have been introduced later, due to contamination with organic environmental toxins such as dioxins and PCBs. The dietary advice was revised with respect to organic environmental toxins in 1995 (Darnerud et al., 1995; Wicklund Glynn et al., 1996) and with respect to MeHg in 1992 in conjunction with the end of blacklisting of fishing waters (SLV FS 1991:25).

The advice was complemented in 2003 and now also comprises large predatory fish species (giant halibut, swordfish, shark, ray and tuna) due to their elevated concentrations of mercury. The advice on oily Baltic fish means that women of childbearing age and girls should restrict their consumption of oily fish from the Baltic Sea (wild salmon, Baltic/North Sea herring, and sea trout), salmon and salmon-trout from Lakes Vänern and Vättern, and alpine char from Lake Vättern to a total of on average one meal per month, while other consumers are recommended to eat an average of one meal per week of these fish. Farmed salmon is not included in this advice. As regards freshwater fish that can contain high mercury concentrations, it is recommended that pregnant and lactating women and women planning to become pregnant avoid predatory fish from freshwater lakes and coastal areas, i.e. pike, perch, pike-perch and burbot, but also giant halibut, swordfish, shark, ray and tuna. However, canned tuna can be consumed without restriction.

The dietary advice is distributed to all antenatal centres in the country and is available in its entirety on the National Food Administration website www.slv.se.

National Food Administration's dietary advice on fish

Fish type	***Pregnant and breastfeeding women and those planning to become pregnant***	***Girls, women of childbearing age***	***Other consumers***	***Motive***
Perch, pike, pike-perch, shark, halibut, ray, swordfish, tuna (fresh/ frozen), eel	Avoid	At most 1 time/week	At most 1 time/week	Methyl mercury
Salmon, sea trout, and herring from the Baltic Sea and Bay of Bothnia	At most 1 time/month	At most 1 time/month	At most 1 time/week	Organochloride compounds, e.g. PCB and dioxins
Salmon and sea mtrout from Lakes Vänern and Vättern	At most 1 time/month	At most 1 time/month	At most 1 time/week	Organochloride compounds, e.g. PCB and dioxins
Char from Lake Vättern	At most 1 time/month	At most 1 time/month	At most 1 time/week	Organochloride compounds, e.g. PCB and dioxins
Liver of cod and burbot	Avoid	Avoid	Refrain from regular consumption	Several environmental pollutants
Smoked and gravad fish (primarily vacuum-packed)	Avoid	No restriction on fish from clean water/farmed fish	No restriction on fish from clean water/farmed fish	Listeria bacteria
Fish for cold-smoking/ gravad fish preparation	Deep freezing for 3-7 days is recommended before cold-smoking/gravad fish preparation			Parasites
Freshwater fish from areas with caesium deposition	0-300 Bq/kg: At normal rate 300-1500 Bq/kg: At most 1 time/week >1500 Bq/kg: At most a few times/year >10000 Bq/kg: Avoid			Radioactive fallout from Chernobyl

Dietary advice on fish in other countries

A number of countries have dietary advice on fish that is based on both nutritional and toxicological evaluations. The Finnish dietary advice recommends that fish be consumed at least twice a week, with variation between different types (Finnish Food Safety Authority, Livsmedelssäkerhetsverket, 2006). Fish that are excepted from the general advice include large (≥ 17 cm) herring and wild salmon. These should be consumed at most 1-2 times per month by children, young people and both women and men of fertile age. According to the Finnish authorities, herring smaller than 17 cm (younger than 4 years) as a rule have dioxin concentrations under the EU maximum level. Pike and other predatory fish from domestic waters can be eaten 1-2 times per month. In addition, it is recommended that pregnant and breastfeeding women refrain from eating pike due to the mercury content. High consumers of predatory fish (large perch, pike-perch and burbot, which can accumulate mercury) should decrease their consumption.

A report from the Danish Fødevaredirektoratet (2003) and dietary advice on the website (Fødevarestyrelsen, Danish Veterinary and Food Administration) state that fish is a healthy food and maintain previous recommendations on consumption of 200-300 grams of fish per week, corresponding to 1-2 main meals per week with variation between lean and oily varieties, plus regular consumption of fish sandwich fillings. The advice is based on the nutritional properties of fish and on data on positive health effects on cardiovascular disease. However, for certain fish and fish products, specific advice is given on restricting or exercising caution in consumption due to the content of environmental pollutants (mercury, dioxin), PAH (smoked and grilled products), vitamin A (cod liver oil), cadmium (bearded mussels), histamines (tuna, mackerel) and algal toxins (oysters). For mercury, the advice given to pregnant and breastfeeding women is to avoid large portions of certain predatory fish (tuna, ray, halibut, oilfish (escolar), swordfish, herring shark, pike, perch and pike-perch) and that the weekly portion should not exceed 100 g (children under 3 years at most 25 g per week). For dioxin, the advice given to women of childbearing age is to limit consumption of large oily fish form the Baltic Sea and Bay of Bothnia (at most one portion, approx. 125 grams, per month). Others can eat Baltic salmon at most two times a month.

In Norway, it is recommended that pregnant and breastfeeding women do not eat fish liver, pike, perch larger than 25 cm, sea trout and char over 1 kilo, shark, swordfish, ray and tuna with the exception of canned tuna (Norwegian Food Safety Authority, Mattilsynet, 2005). Other groups are recommended not to eat these types of fish more often than one time per month on average. There are also a number of pieces of regional dietary advice to limit the intake of PCB and dioxins in particular, but also other environmental pollutants.

At the request of the Norwegian Food Safety Authority, the Norwegian Scientific Committee for Food Safety (VKM) commissioned an evaluation of consumption of fish and shellfish, where the nutritional advantages of such consumption were set in relation to the health risks caused by environmental pollutants and other undesirable compounds in fish and shellfish (VKM, 2005). In Norway, fish consumption is relatively high, approx. 65 g/d, and the relationship between oily and lean fish is approximately 1:2. Among the compounds in fish that have positive effects on health, vitamin D and n-3 fatty acids are mentioned. Fish consumption and marine n-3 fatty acids are considered to be important in pregnancy, for foetal development and to decrease the risk of cardiovascular disease. As regards environmental pollutants, mercury, dioxins and dioxin-like PCBs in particular are regarded as posing a potential risk from consumption of fish and shellfish.

In conclusion, VKM supports a recommendation on higher fish intake in Norway. This applies in particular to those who currently eat little or no fish. VKM sees no health-related problems with consumption of four fish meals per week, of which at most two consist of oily fish. Calculations of mercury intake show that the intake, even in high consumers of fish, lies far below the relevant tolerable intake level. However, for individuals who consume particularly Hg-polluted fish, this can lead to PTWI being exceeded. As regards dioxins and dioxin-like PCBs, consumption of more than two meals of oily fish per week can lead the EU dioxin-TWI of 14 pg TEQ/kg body weight/week being exceeded, which in the first instance does not involve any direct health risks but rather a decrease in the safety margins. Women of fertile age are identified as a risk group, but it is the opinion of VKM that the general recommendation on increased fish consumption will not lead to excessive consumption of oily fish with health risks for foetuses and infants. The dioxin-TEQ intake in the diet of children (2-13 years) will be over the dioxin-TWI in a number of cases, but the contribution from foods other than fish will dominate. VKM wants to see a continued decrease in the concentrations of health-harming compounds in fish and shellfish, while at the same time acknowledging that emission restrictions will only have an effect after a long period. For farmed fish, however, the exposure sources can be controlled within a reasonable time.

A risk-benefit assessment of fish consumption has been carried out in the United Kingdom by the Scientific Committees for Nutrition and Toxicology (SACN/COT, 2004). The report establishes that from a health perspective, British consumers should eat more fish and recommends at least two portions per week, of which one should consist of oily fish. Such consumption would probably have clear positive effects as regards the risk of contracting cardiovascular disease and is also assumed to have positive effects on foetal development. The same general advice also applies for pregnant and breastfeeding women, on condition that certain types of fish are not consumed – these are marlin, swordfish, shark and tuna. It is concluded that there are insufficient data to carry out a quantitative analysis of risks and benefits as regards oily fish and content of organic environmental pollutants. Instead, separate recommendations are given on consumption for girls and women of childbearing age (one to two portions of oily fish per week, in order to keep the intake of dioxins/dioxin-like PCB under a TDI of 2 pg TEQ/kg bodyweight/day), while for women above childbearing age, boys and

men it is 1-4 portions of oily fish per week in order to keep the intake of dioxins/dioxin-like PCB below a reference dose of 8 pg TEQ/kg body weight/day. This reference dose has been calculated by COT and is based on risk assessment for health outcomes other than foetal effects. The authors of the report emphasise that occasional exceeding of the dietary advice is not harmful to health, but that it is long-term high intake than can have harmful effects in risk groups. As regards pregnant and breastfeeding women who have not previously exceeded the recommendations on oily fish, they can increase their consumption of oily fish to 2-3 portion per week during the pregnancy and lactation period without risks to the health of their baby.

The EU Commission has presented general consumption advice to limit exposure to MeHg and that is directed at pregnant or breastfeeding women, women planning a pregnancy and small children (European Commission, 2004). The advice is mainly provided for consumers in countries that are lacking national dietary advice. It recommends at most one portion of 100 g of certain fish species, e.g. pike, and for people eating such fish it is recommended that they avoid consumption of other fish during the week, and that tuna is consumed at most 2 times per week. Restriction of such fish consumption is also recommended for children.

In the EFSA statement on health risks from consumption of wild and farmed fish, the focus is mainly on organic environmental pollutants (dioxins, PCB) and methyl mercury and on n-3 fatty acids in the most important consumption fish within the EU (EFSA, 2005). Herring are also considered. It is concluded that oily fish are an important source of long-chain n-3 fatty acids and that regular consumption of oily fish in particular (1-2 portions per week) is beneficial from a cardiovascular perspective and is suitable for secondary prevention of cardiovascular disease. Fish can also be beneficial for foetal development, but it is not possible to establish an optimal intake. With consumption of fish two times per week for most fish species, it is considered that PTWI for MeHg and dioxins will not be exceeded, although with some exceptions. As regards mercury, it is concluded that frequent consumption of certain large predatory fish, e.g. tuna and pike, makes a considerable contribution. As regards MeHg, it is considered that pregnant women who consume fish two times per week do not risk exceeding the tolerable intake levels provided that they do not eat certain types of tuna more often than once a week. It is also mentioned in this context that e.g. pike often contain high concentrations of MeHg. Against the background of the positive health effects, consumption of oily fish 1-2 times per week is recommended, with the exception of oily fish from the Baltic Sea. Frequent consumption of oily fish such as wild salmon and herring from the Baltic Sea gives a greater risk of TWI for dioxins and dioxin-like PCBs being exceeded, compared with consumption of other oily fish. When it comes to oily Baltic fish, girls are identified in particular as a sensitive group. In addition, it is concluded that there is a lack of accepted methodology for assessing the risks and benefits and therefore it is recommended that tools be developed to enable such balanced qualitative assessments to be carried out. Furthermore, national authorities should be referred to for specific consumption advice.

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