Fish consumption during child bearing age: A quantitative risk–benefit analysis on neurodevelopment

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ABSTRACT

The fish ingredient N3-docosahexaenoic acid 22:6 n-3 (DHA) stimulates brain development. On the other hand methylmercury (MeHg) in fish disturbes the developing central nervous system.

In this Context the IQ score in children is considered as an aggregate measure of *in utero* brain development.

To determine the effect of DHA exposure on prenatal neurodevelopment the maternal DHA intake during pregnancy was compared with its epidemiologically observed effect on the IQ score of children.

For MeHg the maternal intake was converted into its accumulation in the maternal body. The maternal body burden then was compared with its epidemiologically observed relationship with the IQ score.

Taking the MeHg and DHA content of 33 fish species the net effect of these compounds on the IQ score was quantified. For most fish species the adverse effect of MeHg on the IQ score exceeded the beneficial effect of DHA. In the case of long-living predators a negative effect up to 10 points on the IQ score was found.

The results of this study indicate that food interventions aiming at the beneficial effects of fish consumption should focus on fish species with a high DHA content, while avoiding fish species with a high MeHg content.

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1. Introduction

Fish may contain high concentrations of essential long chain n-3 polyunsaturated fatty acids (PUFAs) such as docosahexaenoic acid 22:6 n-3 (DHA). The intake of these nutrients may protect against diseases such as coronary heart disease (CHD). Furthermore DHA is critical for the developing brain *in utero* (Ponce et al., 2000). The health promoting properties of these fatty acids, highly present in fish, therefore may stimulate increased long-term fish consumption during adult life and sensitive periods herein, such as pregnancy. However, fish may also contain compounds with adverse health effects. The neurotoxin methylmercury (MeHg) is a typical example of such a compound: epidemiological studies have revealed a negative association between prenatal exposure to MeHg and cognitive development after birth (Amin-Zaki et al., 1974; Choi et al., 2008; Daniels et al., 2004; Davidson et al., 2008; Harada, 1995; Hibbeln et al., 2007; Myers and Davidson, 2000). Regarding the negative effect of MeHg on the development of the central nervous system, several incidents have indicated that children exposed before birth are most severely affected (Amin-Zaki et al., 1974; Risher et al., 2002).

Indeed, several prospective epidemiological studies on the postnatal cognitive development of children who have been prenatally exposed to a relative high level of MeHg (Faroe Islands (FI) study, the Seychelles Child Development (SCDS) study and the New Zealand (NZ) study) indicate a negative relationship between maternal MeHg intake from fish during pregnancy and the postnatal neurodevelopmental outcome, as measured by the IQ score in children at various ages by means of developmental and cognitive learning tests (Cohen et al., 2005b; Axelrad et al., 2007). Similarly the relationship between maternal DHA intake during pregnancy and postnatal IQ score was quantified (Cohen et al., 2005c).

The fact that fish consumption may reduce the incidence of CHD and provides a key nutrient for *in utero* brain development may be a reason to start a policy to increase fish consumption. At the same

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time, such a policy should avoid an increased neurotoxic risk due to prenatal MeHg exposure.

In order to evaluate the net outcome of such policy on the cognitive development of offspring we quantified the net effect of prenatal exposure to MeHg and DHA on the developing brain after sustained elevated maternal fish consumption.

Given high maternal fish consumption before and during pregnancy the intake of DHA and MeHg was calculated. Given the MeHg intake Physiologically Based PharmacoKinetic (PBPK) modelling was applied to calculate the accumulation of MeHg in the maternal body and its proxy, the concentration in maternal hair.

The DHA intake and the concentration of MeHg in hair then were compared with the epidemiologically observed relationships between these parameters and the postnatal outcome of *in utero* neurodevelopment, i.e. the IQ score in children.

2. Materials and methods

2.1. Fish intake scenario

In this paper an intake of 100 g of a specific fish species per day during the period before and during pregnancy was taken as worst case to determine the net effect between the adverse effect of MeHg and the beneficial effect of DHA exposure on the neurodevelopment of the unborn child and its resulting postnatal IQ score.

The net effect was determined for 33 different fish species. The concentration of MeHg and of DHA in the different fish species was obtained from the extensive data base of Sioen (Sioen et al. 2007a,b) and represents fish species that are for sale on the Belgian market (see Table 1). In converting the absolute fish MeHg and DHA intake to intake per kg bw a maternal weight of 60 kg was assumed.

A scenario of a consumption of 100 g of one species of fish per day is 3–4-fold higher than the fish consumption which is suggested as optimal in reducing CHD disease, i.e. 200 g per week (see above) and is to be considered as a daily fish consumption which is indicative for the maximum attainable effect ("absolute worst case approach"). Furthermore such a high intake allows for the straightforward downscaling of the found effects on the IQ score to the intake of a lesser amount of fish. The reason for this latter effect lies in the fact that, in concordance with epi-

demiological dose–response analyses (NRC, 2000; Cohen et al., 2005a; Axelrad et al., 2007), all relationships between maternal intake and the newborn's IQ were assumed linear. So the calculation of any other (lower) amount of fish intake can be computed easily by multiplying with a constant and the effect of a combination of consumed fish species can be added. For example the IQ change for a daily intake of 50 g of mackerel and 50 g of cod would be to add half the effect of 100 g of mackerel with half the effect of 100 g of cod (for further details, see below).

Choosing a high fish consumption scenario thus guarantees that the effect of any other combination of quantity and species of fish can easily be deduced from the effect levels calculated in this paper. In this context the used fish consumption scenario thus merely serves as a guiding reference for the evaluation of future food interventions which are aimed at increasing the consumption of fish in the general population.

2.2. PBPK model of MeHg

The maternal MeHg intake was converted to the corresponding concentration in the maternal body and its proxy the concentration in the hair, of pregnant women by means of PBPK modelling (Clewell et al., 1999). PBPK modelling was preferred over (apparent) one-compartment modelling as the latter is limited to modelling the long-term "steady state" kinetics of MeHg in the human body (see Supplementary Material 3). PBPK modelling furthermore allows for the incorporation of inter-individual variability in MeHg kinetics in the risk – benefit analyses protocol.

The PBPK model predicts that the amount of MeHg in the maternal body will increase quickly until a constant level, i.e. "steady state", is reached after about 300 days of exposure (for details, see Supplementary Material 1, Fig. 3b). Assuming the beneficial health effects of fish consumption to appear after sustained fish consumption it is reasonable to assume that this will result in sustained exposure to MeHg too. Or, in other words, when a food policy resulting in increased fish consumption is to be successful after a prolonged period of time it likely results in "steady state" MeHg kinetics in pregnant women (assuming women do not change their fish intake at least 300 days before becoming pregnant). In the latter case pregnancy itself is expected to disturb by changes in the mother's body composition, this "steady state". Indeed, as shown in Fig. 1, the PBPK model predicts a rather low increase of 6% of the concentration in the maternal body and consequently also in maternal hair when compared to the non-pregnant. Note that this results indicates that hair concentrations in pregnant women as determined in epidemiological studies may contain an error margin between 0 and (maximally) 6% with regard to the exposure of the unborn. Fig. 1 furthermore shows that, as the methylmercury concentration in the foetal brain closely follows that in maternal hair, the latter indeed is a valid dose metric for the prenatal exposure of the target organ for MeHg neurobehavioral toxicity, i.e. the brain.

The PBPK model was also used to calculate the distribution of the equilibrium concentration of methylmercury in hair of pregnant women taking into account variability in PBPK model parameters (for details, see Supplementary Material 1, Fig. 5). Fig. 2 shows the result of such a simulation for an exposure of 1 μg MeHg/kg-bw/day.

The equilibrium hair concentration depends linearly on the MeHg intake according to equation (1):

$$C_{hair,MeHg} = k \cdot I_{MeHg} \tag{1}$$

Where $C_{hair,MeHg}$ is the concentration in hair in μg/g and I_{MeHg} is the MeHg intake in μg/kg body weight per day. The average k is 14.3 days (2.5th percentile: k is 7.8; 97, 5th percentile: k is 26; see Supplementary Material 1, Fig. 5B)

Table 1
DHA and MeHg concentrations in fish.

Species	Hg (mg/kg)	No. of samples	DHA (g/100 g)	No. of samples
Pike	0.762	19	0.17	65
Swordfish	0.829	954	0.50	6
Sole	0.104	340	0.10	47
Tuna	0.616	1743	0.68	20
Halibut	0.252	44	0.31	54
Perch	0.124	170	0.16	6
Flounder	0.076	321	0.12	8
Catfish, Channel	0.112	107	0.17	7
Bream	0.148	54	0.24	11
Whiting	0.079	257	0.13	6
Carp	0.078	40	0.14	6
Haddock	0.064	195	0.13	11
Plaice	0.051	322	0.13	10
Mackerel, Spanish	0.343	109	0.90	5
Cod	0.069	1910	0.21	42
Vendace	0.077	13	0.26	54
Prawn	0.045	311	0.16	9
Catfish	0.059	93	0.23	10
Hake	0.109	184	0.48	7
Oyster	0.031	7	0.16	4
Saithe	0.047	172	0.26	7
Eel	0.122	1317	0.71	10
Sardine	0.115	430	1.01	205
Red fish	0.023	37	0.32	7
Trout	0.058	85	0.80	63
Anchovy	0.056	129	0.83	7
Salmon, Pacific	0.053	207	0.82	17
Mussels	0.012	369	0.19	13
Herring	0.041	370	0.69	218
Mackerel	0.071	538	1.53	14
Oysters, Pacific	0.011	53	0.29	11

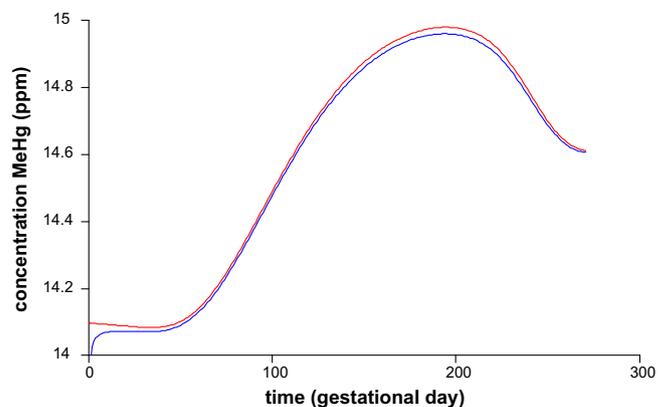The DHA and Hg concentration of the fish were taken from Sioen (2007a,b).

Fig. 1. PBPK simulation of the time-course of the concentration of MeHg in the hair of pregnant women (upper line) and in the foetal brain (lower line). Note that, in order to allow a meaningful comparison, the latter was multiplied by the hair: brain partition coefficient of 83.3 in the simulation. Exposure scenario: 1 μg MeHg/kg-bw/day from fish starting at least 300 days before pregnancy.
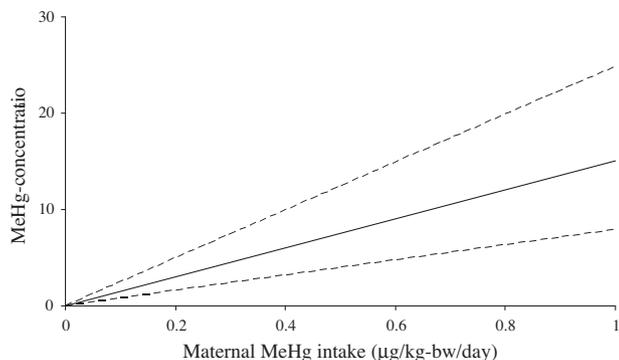
Fig. 2. PBPK simulation of the variability of the maximal concentration of MeHg in hair of pregnant women as a function of the MeHg intake (0–1 μg/kg-bw/day). Solid line: median concentration. Dashed lines: 5th percentile and 95th percentile.

Start of the exposure must be at least 300 days before pregnancy to reach equilibrium at the start of pregnancy.

2.3. Dose–response of MeHg intake, DHA intake and IQ score

Several prospective studies are available in which the postnatal cognitive development is followed of children who have been prenatally exposed to a relative high background level of MeHg (Faroe Islands (FI) study, the Seychelles Child Development (SCDS) study and the New Zealand (NZ) study). The outcome of these studies, which comprised the performance of children on various developmental and cognitive learning tests at various ages, was subjected to a quantitative meta-analysis by Cohen and Axelrad (Cohen et al., 2005b; Axelrad et al., 2007). In this way a quantitative relationship between maternal MeHg intake from fish during pregnancy and neurodevelopmental outcome, as measured by the postnatal IQ score of children, was established. Similarly, based on an extensive literature review, a dose–response relationship between maternal DHA intake during pregnancy and postnatal IQ score was derived (Cohen et al., 2005c). These relationships were used to quantify the positive, negative and net effect of 100 g of fish intake on the IQ score.

The actual quantification of the positive and the negative effects of the fish intake on the IQ score was performed as follows. Cohen et al. (2005a,b) and Axelrad et al. (2007) present the following relationship between maternal hair MeHg concentration and children's IQ loss:

$$\Delta IQ = -c \cdot C_{hair,MeHg} \qquad (2)$$

where $C_{hair,MeHg}$ the MeHg concentration in hair in (μg/g) and c is −0.18 (−0.379 to −0.009) according to Axelrad and −0.7 (0 to −1.5) according to Cohen. Cohen also reports a value of −0.2 in a sensitivity test in which the dose–response from the Faroe Island study is linearised differently. We therefore consider the value of −0.2 of the Cohen study in line with the Axelrad study. So we used for c a triangular distribution with a most likely value (mode) −0.2 and extremes 0 and −1.5 as reported in Cohen et al. (2005a,b). Note that this means an average value for c of −0.56, far greater than the model because the distribution is rather skew.

We combined the relationship mentioned above with the (uncertain) hair concentrations from the PBPK model resulting from MeHg intake. This leads to an (uncertain) IQ-loss of children borne out of mothers who have had a certain level MeHg intake from fish. The combined relationship can be seen in Fig. 3.

Cohen et al. (2005a,b) present the following relationship between maternal DHA intake and children's IQ gain:

$$\Delta IQ = d \cdot I_{DHA} \qquad (3)$$

with d = 1.3 uniformly distributed between 0.8–1.8 and I_{DHA} the maternal DHA intake (g/day).

Similarly, the IQ-gain, including uncertainty, resulting from maternal DHA intake during pregnancy is obtained by combining DHA intake from fish with the relationship between the DHA intake and the IQ-loss of children borne out of these mothers (taking into account the uncertainty in relevant regression coefficients for the relationship between the DHA intake and children's IQ loss as supplied by Cohen et al. (2005a,c) (see Fig. 4).

The quantification incorporated various sources of uncertainty: uncertainty in the accumulation of MeHg in pregnant women (as obtained by Monte Carlo sampling of relevant PBPK parameters) and uncertainty in the conversion of the DHA intake and the accumulated amount of MeHg into the IQ score (as obtained by Monte Carlo sampling of relevant regression coefficients). In this way the increase and the decrease in the IQ score were combined into an uncertainty distribution of the net effect of the fish consumption on IQ.
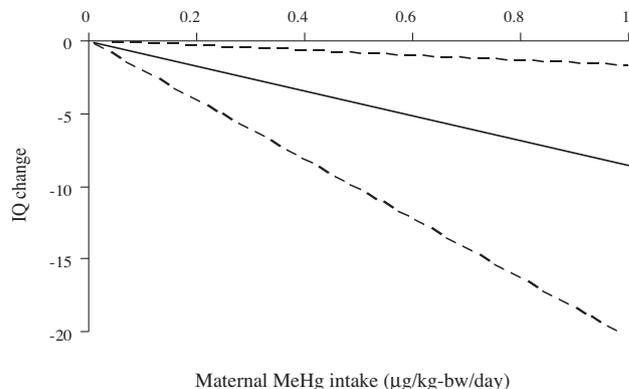

Fig. 3. Variability of the IQ loss of children as a function of the MeHg intake of their mother in the period before and during pregnancy. Regression coefficients: average (solid line): −8.5; 5th percentile: −1.5; 95th percentile: −19.5 (dashed lines).
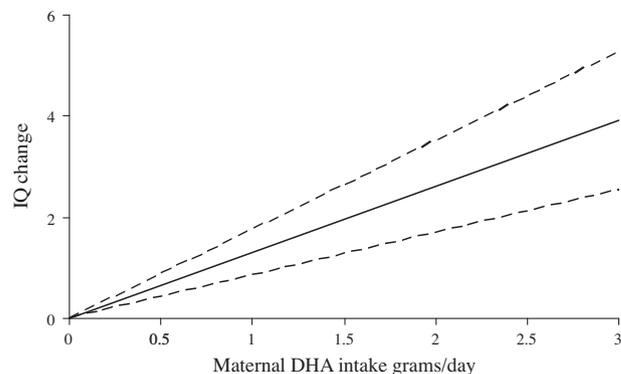

Fig. 4. Variability of the IQ gain of children as a function of the maternal DHA intake during pregnancy. Regression coefficients: average (solid line): 1.3; 5th percentile: 0.85; 95th percentile: 1.74 (dashed lines).

3. Results

Substituting equation (2) into (3) gives the relationship between the children's IQ loss and the maternal MeHg intake with fish, or:

$$\Delta IQ = -c \cdot k \cdot I_{MeHg} \qquad (4)$$

Combining equations (4) and (3) then gives the relationship for net effect of the MeHg and DHA intake with fish and the the children's IQ:

$$\Delta IQ = -c \cdot k \cdot I_{MeHg} + d \cdot I_{DHA} \qquad (5)$$

In this equation the variability in the maternal hair concentration of MeHg was substituted by the equilibrium hair concentration $k \cdot I_{MeHg}$ in pregnant women as simulated by the PBPK model. Regression coefficients d and c were uniformly distributed from 0.8 to 1.8 for DHA and triangularly distributed between −1.5 to 0 with mode −0.2 for MeHg. The MeHg and DHA concentrations in the various fish species were held constant at their nominal value.

Fig. 5 presents the outcome of the application of equation (5) for each of the 33 fish species. Fig. 5 shows that the uncertainty in the simulation is quite large even though the uncertainty that is involved in measuring the concentrations of DHA and MeHg in fish was neglected.

With the exception of some oily fish species such as mackerel (+1 IQ point), herring (+0.3 IQ point), trout (+0.20 IQ point) and salmon (+0.3–1.4 IQ point) the adverse effect of MeHg just exceeded the beneficial effect of DHA. A relatively large net adverse effect on
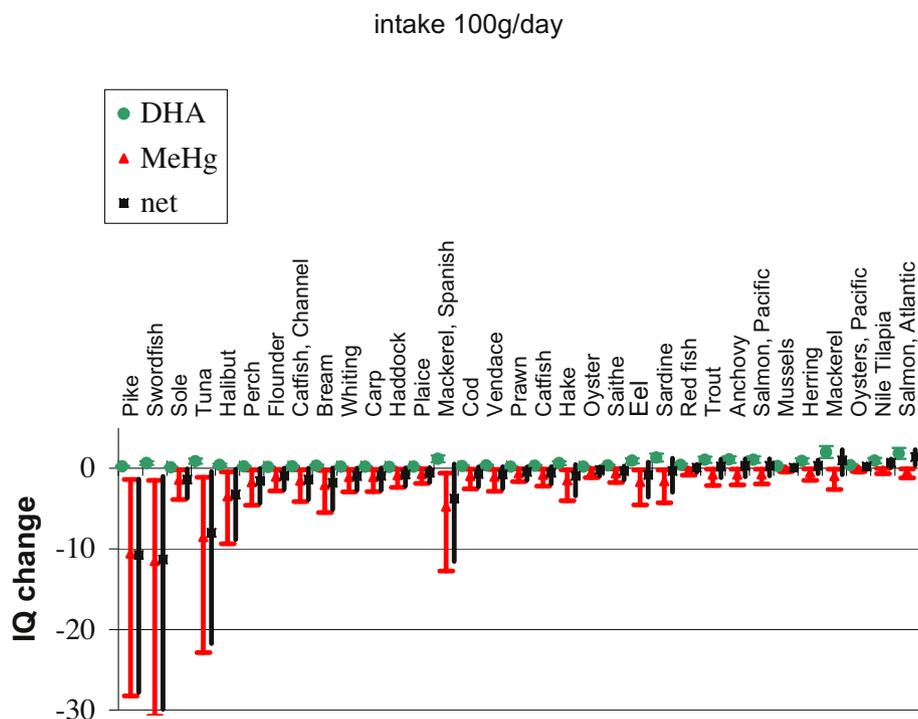
Fig. 5. The effect of the consumption of 100 g of fish on the IQ score of off-spring. DHA (positive effect on IQ, green bars) and MeHg (negative effect, red bars).Black bars: net effect on IQ of the exposure. Indicated variability: 5th percentile and 95th percentile. Data on the level of DHA and MeHG in fish were taken from Sioen et al. (2007a,b).

the IQ score of offspring was found with large long-living predators such as pike (−10 IQ points), swordfish (−11 IQ points) and tuna (−8 IQ points). The consumption of 100 g/day of these fish species during the period preceding and during pregnancy thus is expected to lead to a substantial reduction of the IQ score.

4. Discussion

This study illustrates the effect of increased maternal fish consumption on the neurodevelopment of children: increased fish consumption of mothers before and during pregnancy leads to increased MeHg and DHA intake and, hence, to an increased exposure of the unborn to these compounds. In the case of MeHg this may negatively affect *in utero* brain development, whereas DHA may just stimulate this development. The results of this study show that, given the data of MeHg and DHA concentrations in fish, the negative effect of MeHg outweighs the beneficial effect of DHA for most species of fish (70%).

In total 33 different fish species were investigated. In the case of heavy contaminated species such as pike, swordfish and tuna the simulated effect of the consumption of 100 g/day of these fish species would lead to reduction in the IQ score of children around 10. Note that of the 33 different fish species these three species by far contained the highest MeHg concentration. For example, there is a 20-fold difference between herring and swordfish. For 28 out of the 33 species, maternal consumption of 100 g/day would result in a net reduction less than 2 IQ points. For 10 species (30%) the DHA/MeHg ratio is such that even a small net gain in IQ could be achieved.

This study made use of epidemiologically observed relationships between maternal DHA and MeHg intake before and during pregnancy and the outcome of prenatal neurodevelopment, i.e. the postnatal IQ in children of various ages. In the case of MeHg these data arose from several prospective epidemiological studies on the postnatal cognitive development of children who have been

prenatally exposed to elevated levels of MeHg. These studies are preferred as the starting point for the evaluation of maternal MeHg exposure from food and its outcome on the neurodevelopment of the unborn child (NRC, 2000).

To evaluate the effect of maternal MeHg and DHA exposure on prenatal neurodevelopment a rather high fish intake scenario of 100 g per day was applied. This worst case approach is defendable as background MeHg and DHA exposure typically apply to changes in IQ score which are clinically undetectable at the individual level and are only of importance when aggregated to the level of the whole population. For example, on the scale of the entire US population, the expected effect of a 17% decrease in fish consumption (3.2 g/day at a baseline level of 18.7 g/day) only led to a gain of 0.025 IQ points per child (Cohen et al., 2005a).

Furthermore, when compared with the background fish consumption the food interventions evaluated so far were, however, quite modest and clearly did not maximize their beneficial effects, i.e. a reduction in CHD/stroke mortality in the case of increased fish consumption. To obtain the latter objective a significant increase of the daily fish consumption may be needed. Mozaffarian and Rimm (2006) report that 250 mg/day of EPA and DHA is a reasonable target, which corresponds to at least 200 g of oily fish per week. This may indeed lead to the intended result, i.e. a reduction in the incidence of CHD, however at the possible expense of an increased neurotoxic risk for the unborn due to an increased prenatal MeHg exposure resulting from the increased fish consumption of its mother. The evaluation of the latter effect therefore needs the quantification of the clearly elevated maternal MeHg intake before and during pregnancy, its accumulation in the maternal body (including the exposure of the unborn) and the induced neurotoxicity in the unborn resulting from the latter exposure.

The calculated IQ effect of MeHg and DHA is based on the meta-analysis of Cohen and Axelrad. The MeHg regression coefficients vary between 0 and −1.5. A coefficient of 0 stems from the outcome of the SCDC study (no effect MeHg on IQ) and −1.5 with

the FI studie (MeHg negatively associated with IQ) (Cohen et al., 2005b). In fact, this variation illustrates the (considerable) inter-study uncertainty which exists in the quantification of the neurotoxic effect of prenatal MeHg exposure. For this reason the regression coefficients used in the Monte-Carlo simulation shown in Fig. 5 were drawn from the interval [0; −1.5]. Consequently, this leads to a rather wide variation of the simulated effect on the IQ scores. Furthermore, this large uncertainty interval and the very skew triangular distribution that we assumed causes the average effect of MeHg to be much larger than when we would have assumed less uncertainty.

Extra fish consumption reduces the incidence of CHD death e.g. Mozaffarian and Rimm (2006). This finding may be a reason to start a policy to increase fish consumption. At the same time, such a policy should avoid an increased neurotoxic risk due to prenatal MeHg exposure during pregnancy. As shown above, given current MeHg concentrations in fish, a policy that aims at reducing the incidence of CHD has the potential to lead to an unwanted accumulation of MeHg in women of childbearing age, resulting in a lower IQ score in their children. In this context it, however, should be kept in mind that the latter conclusion is based on a fish intake scenario (100 g/day) which grossly exceeds the current fish intake in most countries. For example, in The Netherlands the current fish intake on average amounts 1 portion of 41–122 g fish per week (6–17 g/day), whereas in Spain this may be twice as high (www.sea-foodplus.org). Nevertheless, even a with a fish consumption of 100 g per day *most* fish species would only have *small* effects on the IQ of newborns, meaning that in practice a food intervention campaign aiming at a sustained increase of fish consumption will only in rare lead to adverse effects on IQ. Nevertheless, advising women that are pregnant or aim to become pregnant in the near future to abstain from eating fish known (from monitoring campaigns, US EPA, 2003) to be heavily polluted with fish (such as swordfish and pike depicted Table 1) is defendable.

Alternatively, in order to be absolutely sure that no adverse effects of increased fish consumption occurs, it might be considered to advise women to abstain from eating some fish species (Oken et al., 2003), such as swordfish during a well defined period preceding pregnancy but to advise them to eat fish species such as herring an salmon which have a beneficial effect on IQ. These oily species also have a larger effect on the benefits of reducing CHD incidence. The establishment of a "waiting period", i.e. a period preceding pregnancy in which the consumption of polluted fish is avoided, is defendable. During such a period the level of MeHg in the female body which has been build up during the previous period may decrease again to an accepted low level. Such a waiting period has been calculated with the aid of the PBPK model. Starting with a background level of 0.2 μg MeHg/g hair (representative for the general population) and a maximum level of 9.5 μg MeHg/g hair as occurring after long-term fish consumption of heavily polluted fish (representative for relative high levels in the FI, SCDC and NZ studies), a waiting period of maximally 334 days was calculated. In practice this means that women should avoid polluted fish consumption during a period of 1 year preceding pregnancy as well as during pregnancy itself.

5. Conclusion

The concern for IQ decrease in newborns due to maternal fish consumption applies to the situation in which women consume large amounts of MeHg contaminated fish with low DHA content (tuna, swordfish, pike). On the other hand DHA containing fish like salmon, mackerel, herring and trout usually have a low MeHg level. Interventions aiming on a reduction of the incidence of CHD through encouragement of fish consumption therefore should focus on fish species with a high DHA content and a low MeHg con-

tent. This will prevent the accumulation of MeHg in the body of women of childbearing age which poses an unacceptable neurotoxic risk to the unborn child.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgement

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