



**Food and Agriculture
Organization of the
United Nations**



**World Health
Organization**

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

Rome, Italy, 25 - 29 January 2010

HEALTH RISKS ASSOCIATED WITH FISH CONSUMPTION

FOCUS ON METHYLMERCURY, DIOXINS AND DIOXIN-LIKE PCBS

Lucio G. Costa

**Professor, Department of Occupational and Health Sciences
University of Washington, Seattle, USA**

&

Vittorio Fattori

Nutrition and Consumer Protection Division, FAO, Rome, Italy

TABLE OF CONTENTS

1	INTRODUCTION	4
1.1	Objective and Scope of the paper	4
2	CONTAMINANTS IN FISH	4
3	INTERNATIONAL ADVISORIES	6
3.1	Mercury	6
4	MERCURY	8
4.1	Mercury in the environment	8
4.1.1	<i>The environmental cycle of mercury</i>	8
4.1.2	<i>Main sources of mercury release into environment</i>	9
4.1.3	<i>Main food sources</i>	9
4.2	Methylmercury (MeHg)	16
4.2.1	<i>Toxicokinetics</i>	16
4.3	Health effects of methylmercury	17
4.3.1	<i>Neurological effects</i>	17
4.3.2	<i>Reproductive Outcomes</i>	17
4.3.3	<i>Immune System Effects</i>	18
4.3.4	<i>Cardiovascular Effects</i>	18
4.3.5	<i>Developmental Neurotoxicity</i>	18
4.4	Recent epidemiological studies	21
4.4.1	<i>Cardiovascular endpoints</i>	21
4.4.2	<i>Neurological and developmental studies</i>	22
4.5	Recent toxicological research	25
4.5.1	<i>Interactions between PCBs and MeHg</i>	25
5	DIOXINS AND DIOXIN-LIKE PCBs	26
5.1	Sources in the environment	26
5.2	Main food sources	26
5.3	Health effects of dioxins and dioxin-like PCBs	27
5.3.1	<i>Toxicity in experimental animals</i>	27
5.3.2	<i>Toxicity in humans</i>	29
5.4	Recent epidemiological studies in various countries	36
6	EXPOSURE TO METHYLMERCURY AND DIOXINS/PCBs THROUGH FISH	42

6.1	Worldwide Overview	42
6.1.1	<i>Europe</i>	42
6.1.2	<i>North America</i>	48
6.1.3	<i>Central and South America</i>	49
6.1.4	<i>Asia</i>	49
6.1.5	<i>Africa</i>	52
6.1.6	<i>Oceania</i>	53
7	ABBREVIATIONS AND GLOSSARY	54
8	REFERENCES.....	56
	APPENDIX 1	81
	APPENDIX 2	86
	REFERENCES (APPENDICES 1 and 2).....	89

SUMMARY

This report examines the existing literature on the health implications arising from the exposure to mercury, dioxins and dioxin-like PCBs through fish consumption. Some general and basic information on how these contaminants are released into the environment and enter the food chain are discussed. The report reviews recent advances in the understanding of the toxicity of mercury, dioxins and dioxin-like PCBs, with an emphasis on epidemiological studies, and on potential mechanisms underlying adverse health effects. The occurrence of these contaminants in fish and seafood in several countries is also presented. Mercury, found in some fish meat primarily as methylmercury, is a known developmental neurotoxicant, and exposure is also associated with cardiovascular disease. Dioxins and dioxin-like PCBs are concentrated in fish fat, and exposure has been associated with a range of adverse health effects, ranging from immunotoxicity, developmental neurotoxicity, and cancer. The risks of contaminant exposure through fish are not distributed evenly across the population, and some subgroups are potentially more vulnerable to risks than others.

I. INTRODUCTION

A. OBJECTIVE AND SCOPE OF THE PAPER

In recent years, the evolving science and debate concerning the benefits and risks from consuming fish has resulted in confusion as to how much, or even if, fish should be consumed and by whom. International and national food safety agencies have recognized the need to provide useful, clear and relevant information to populations that are concerned about making the healthiest choices when eating fish. This includes fish consumption prior to or during pregnancy and breastfeeding, or when serving fish to young children. Fish consumption is an integral component of a balanced diet, providing a healthy source of dietary protein and high in nutrients such as n-3 (omega-3) fatty acids. There is evidence of beneficial effects of fish consumption on coronary heart disease, stroke, age-related macular degeneration, growth and development, but on the other hand, under some circumstances, fish can also contribute significantly to the dietary exposure to some contaminants. The health benefits and risks vary according to the fish species, size, cultivation as well as amount and means of consumption. While there are a number of potential contaminants of concern in fish, methyl mercury, dioxins and dioxin-like PCBs are the subject of this report.

II. CONTAMINANTS IN FISH

Fish may accumulate contaminants, such as methyl mercury (MeHg), dioxins and polychlorinated biphenyls (PCBs), brominated flame retardants, chlorinated pesticides, and organotin compounds, from the environment. Concentrations of these contaminants in fish vary with the nature of the contaminant, the type of fish and the habitat from which it comes. Fat-soluble contaminants such as dioxins and dioxin-like PCBs are found in fatty fish such as salmon and herring. In contrast, MeHg levels are not related to the fat content of the fish but, because of its bio-accumulation in the food chain, higher amounts are found in large predators at the apex of the food chain, such as swordfish and tuna. High consumers of such apical predators

(especially bluefin or albacore tuna and swordfish) may exceed the provisionally tolerable weekly intake (PTWI) for MeHg, while those consuming a high quantity of fatty fish may exceed the PTWI for dioxins and dioxin-like PCBs. Additional dietary sources of the fat soluble contaminants, such as high meat intake, may also cause certain individuals to exceed the PTWI for dioxins and dioxin-like PCBs, regardless of their level of fish consumption. Therefore, replacing fish with meat will not inevitably lead to decreased dietary exposure to these contaminants.

The beneficial effects of fish consumption are perhaps greatest during development, which is also the period of greatest susceptibility to the adverse effects of MeHg and dioxin-like PCBs. Exposure during this life stage usually results from the total amount of contaminant in the mother's body. While it is possible for a woman to decrease her body burden of MeHg by decreasing intake in the months preceding and during pregnancy, this is not possible for dioxins and dioxin-like PCBs because it would take many years.

A direct comparison of contaminant levels in fish is complicated by the variation that is caused by the age of the fish, the geographic origin and the season in which the fish is harvested or caught. In the wild, older fish which are generally larger, accumulate higher levels of contaminants over a longer period than their younger, smaller peers in the same population. Contaminant levels are also dependent on the specific tissue sampled and the time of the year. For example, cod are very fatty in spring and summer months, when plankton and/or prey levels are high, and most of this fat is stored in the liver. In winter they have lower levels of liver lipid. Salmon, on the other hand, store most fat in the abdominal peritoneal lipid tissue, the intermyotomal fascia and particularly in the dermis of the skin, not in the liver. Other oily fish, such as mackerel and tuna, are likely to store fat in skeletal muscle.

It is generally accepted that most contaminants in fish derive predominantly from their diet, although uptake also occurs via the gills, and levels of bioaccumulative contaminants are higher in fish that are higher in the food chain. Whilst it is not possible to control the diet of wild fish, the levels of contaminants, and of some nutrients, in farmed fish may be modified by altering their feed. Fish meal and fish oil, are the most important sources of contamination of farmed fish feed with dioxin-like compounds; it has been established that fish oil and fish meal contribute up to 98% of these contaminants in the diets of carnivorous fish (EFSA, 2005). Data (EC SCAN, 2000) indicate that fish oil and fish meal from European production contain higher levels of dioxin-like PCBs than fish oil and fish meal of South East Pacific origin. Hites *et al.*, (2004) and Foran *et al.*, (2005a), showed that the concentration of these contaminants in feed purchased from Europe were significantly higher than those in feed purchased from North and South America and this may reflect higher contaminant concentrations in the fish that are the raw material for fish meal and oil from the industrialized waters of Europe's North Atlantic as compared to that from the waters of North and South America.

Replacement of fish products with vegetable protein and oils in fish feed or decontamination procedures may be a possible means of reducing some contaminant levels. However, modification of the fish oil inclusion rate may change the fatty acid composition and in particular reduce the n-3 levels in farmed fish. Between 25 and 90 % of the fish meal in fish feed can be replaced by plant proteins (Lim and Klesius, 2004) depending on the target fish species, but plant feedstuffs have lower nutrient concentration, lower digestibility and occurrence of certain natural constituents, such as inhibitors of proteolytic enzymes, isoflavones or glucosinolates (Mambrini *et al.*, 1999; Burel *et al.*, 2000).

Farmed fish tend to have higher whole body lipid levels than their wild counterparts, but their fatty acid content can be influenced by the lipid composition of the feed to resemble that of

wild fish. However, even if the relative n-3 fatty acid content of farmed fish tends to be lower than that of wild fish, the amount provided per portion is likely to be the same due to the higher fat content (EFSA, 2005). Available data indicate that there are no consistent differences in contaminant levels between wild and farmed fish: results from Hites *et al.*, (2004), indicate that farmed salmon, particularly from Europe, had higher levels of dioxins than wild-caught Pacific salmon, but in some other cases (e.g. wild herring from the Baltic Sea) contaminant levels may be higher in wild-caught fish (EFSA, 2005).

III. INTERNATIONAL ADVISORIES

A. MERCURY

In 2000, an expert committee—the National Research Council (NRC) committee—was charged to evaluate, on the basis of the new available data on MeHg-induced health effects, the appropriateness of the U.S. Environmental Protection Agency (EPA)'s reference dose (RfD) for MeHg i.e., 0.1 ug/kg of body weight (bw)/day, derived in 1995 from the Iraqi acute poisoning data. To date, the RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime. The NRC panel compared, for various neurobehavioral endpoints tested in 5- to 7-year-old children, the BMDs and their associated benchmark dose lower limits (BMDLs) expressed in equivalent terms across three major epidemiological studies (Faroe Islands, Seychelles and New Zealand). The committee suggested using an RfD of 0.1 ug/kg bw/day that is identical to the one set in 1995 (EPA, 2001).

The evaluation of the epidemiological studies by other regulatory agencies has led to dissimilar estimations of safe levels for MeHg ingestion (Table 1). Conceptually, the EPA's RfD is equivalent to the Minimal Risk Level (MRL) of the Agency for Toxic Substances and Disease Registry (ATSDR), the Acceptable Daily Intake (ADI) of the U.S. Food and Drug Administration (FDA), and the Tolerable Daily Intake (TDI) of the Food and Agriculture Organization/World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA) and of the Food Safety Commission (FSC) in Japan.

The acceptable MeHg intake levels indicated by these agencies, though not identical are remarkably close, with reduced uncertainty factors ranging from 4 to 10, due to the large quantity of reliable exposure data obtained from studies of the most sensitive human groups. All agencies share the view that MeHg has the potential to damage the human nervous system, particularly in the developing organism. The EPA's RfD is one fifth of the intake guidelines (0.47 ug/kg bw/day) originally set by the WHO. In 2003, JECFA re-evaluated previous risk assessments for MeHg and recommended reducing the Provisional Tolerable Weekly Intake (PTWI) to 1.6 ug/kg bw (0.23 ug/kg bw/day) because of growing evidence of health risks from Hg to pregnant women and children. JECFA used a composite value, based on both the Faroes and Seychelles studies, assuming 14 ppm Hg in maternal hair as the critical dose and applying a total uncertainty factor of 6.4 to account for variability (JECFA, 2003). The PTWI is the amount of a substance that can be consumed weekly over an entire lifetime without appreciable risk to health and is an endpoint used for food contaminants such as heavy metals with cumulative properties. Its value represents permissible human weekly exposure, protecting the most susceptible part of the population, to those contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods. In the case of methylmercury, the developing foetus is considered to be the most sensitive subgroup, and neurodevelopment the most sensitive outcome.

On request of the Japanese Government, in 2005 the FSC issued the report “Food Safety Risk Assessment Related to Methylmercury in Seafood” advising that: “The high risk group is fetuses, the tolerable intake is 2 ug/kg bw/week; the TWI covers both pregnant and potentially pregnant women”. The assessment was similar to that of JECFA, but it clearly defined pregnant women as the target population to apply TWI, and the uncertainty factor of 4 was smaller than JECFAs. The TWI was calculated from the mean value (11 ppm) of the two hair Hg levels, corresponding to the BMDL (10 ppm) in the Faroes study and the NOAEL (12 ppm) in the Seychelles study (Food Safety Commission, 2005).

ATSDR’s MRL for MeHg (0.3 ug/kg bw/day) was based primarily on the results of the studies in the Seychelles and is modified to account for the results of the Faroe Islands study (ATSDR, 1999). The ATSDR evaluation included an uncertainty factor of 3 for variability of pharmacokinetics and pharmacodynamics in the population. An additional 1.5 was added to account for possible less sensitive neurological domain testing used in the Seychelles study for a total uncertainty factor of 4.5.

Table 1. MeHg acceptable intake levels established by national and international agencies

Agency (year)	Study location	Critical dose (µg/kg bw/day)	Uncertainty factor	Acceptable level (µg/kg bw/day)
EPA (2001)	Faroe Islands	1.08	10	0.1
ATSDR (1999)	Seychelles	1.3	4.5	0.3
	Faroe Islands			
JECFA (2003)	Seychelles	1.5	6.4	0.23
	Faroe Islands			
FSC, Japan	Seychelles	1.17	4	0.29
	Faroe Islands			

Sources: NRC (2000); US EPA (2001); JECFA (2003); Food Safety Commission, Japan (2005)

Because fish consumption dominates the pathway for exposure to methylmercury for most human populations, many governments provide dietary advice to limit consumption of fish where mercury levels are elevated. WHO/FAO recommends a maximum of 0.5 mg MeHg/kg in non-predatory fish and 1 mg MeHg /kg in predatory fish. The US FDA has set an action level of 1 mg MeHg/kg in fish, shellfish, and aquatic animals. The European Community allows 0.5 mg mercury/kg (wet weight) in fishery products (with some exceptions). Japan allows up to 0.4 mg total mercury per kg (or 0.3 ppm methylmercury) in fish.

3.2 Dioxins

In 2001 the World Health Organization (WHO) established a tolerable intake for dioxin of 2 pg TCDD/kg/body weight (bw) per day (WHO, 2001), and this was extended to include dioxin-like PCBs and expressed over a longer time period because of the long half-lives in the human body. The EU Scientific Committee on Food (SCF) established a Provisional Tolerable Weekly Intake (PTWI) of 14pg TEQ/kg/bw/week and the Joint FAO/WHO Expert Committee on Food Additives (JECFA), established a Provisional Tolerable Monthly Intake of 70 pg TEQ/kg/bw (WHO, 2001) (see Table 2).

Table 2

Comparison of tolerable intake levels for dioxin and dioxin-like PCBs derived by international Agencies

Agency or organization (year)	Tolerable intake value (TEQ pg/kg day)
ASTDR* (1998)	1
EPA (2000)	0.001-0.01
SCF (2001)	2 (14 pg/kg week)
WHO/FAO JECFA (2001)	2.3 (70 pg/kg month)

*(Agency for Toxic Substances and Disease Registry)

The difference between the EPA and other agencies evaluations of dioxin and dioxin-like PCB toxicity data is mostly because of a more conservative view of the margin of exposure needed to ensure safety.

IV. MERCURY

A. MERCURY IN THE ENVIRONMENT

The environmental cycle of mercury

Mercury exists in the environment as a result of natural and human activities. Most of the mercury in water, soil, sediments, or plants and animals is in the form of ionic mercury salts (such as mercuric chloride) or organic forms of mercury (such as MeHg). Mercury is transformed in the environment by biotic and abiotic oxidation and reduction, bioconversion of inorganic and organic forms, and photolysis of organomercurials. Inorganic mercury can be methylated by microorganisms indigenous to soils, fresh water, and salt water. This process is mediated by various microbial populations under both aerobic and anaerobic conditions. Sulphur-reducing bacteria are responsible for most of the mercury methylation in the environment (Gilmour and Henry, 1991), with anaerobic conditions favouring their activity (Regnell and Tunlid, 1991). Yeasts, such as *Candida albicans* and *Saccharomyces cerevisiae*, whose growth is favored by low pH conditions, are able to methylate mercury and are also able to reduce ionic mercury to elemental mercury (Yannai *et al.*, 1991). Volatile elemental mercury may be formed through the demethylation of methylmercury or the reduction of inorganic mercury, with anaerobic conditions again favouring the demethylation of the methylmercury (Barkay *et al.*, 1989; Regnell and Tunlid, 1991).

Methylation is a key process in the transformation of inorganic Hg to MeHg that bioaccumulates in food webs. Although Hg methylation has been studied in depth in coastal and open-ocean environments, studies of tropical and polar regions and deep ocean basins are limited. Potential regions of methylation in marine ecosystems-coastal are low-oxygen waters and deep ocean

sediments (Kraepiel *et al.*, 2003). Current research suggests that net MeHg production in coastal marine sediments is one of the more important sources and thus a potential source for MeHg in marine fish (Hammerschmidt and Fitzgerald, 2004; Sunderland *et al.*, 2006).

Main sources of mercury release into environment

Mercury is released in the environment by both natural processes (volcanic activity and weathering of rocks containing mercury) and anthropogenic sources. Mercury ore is found in all classes of rock, including limestone, calcareous shales, sandstone, serpentine, chert, andesite, basalt, and rhyolite (Gavis and Ferguson, 1972). Mercury associated with soils can be directly washed into surface waters during rain events. Surface runoff is an important mechanism for transporting mercury from soil into surface waters, particularly in soils with high humic content (Meili, 1991).

Mercury may also be released to surface waters in effluents from a number of industrial processes, including mining operations and ore processing, metallurgy and electroplating, chemical manufacturing, ink manufacturing, pulp and paper mills, leather tanning, pharmaceutical production, and textile manufacture (Dean *et al.*, 1972; EPA, 1971). Additional anthropogenic releases of mercury to soil are expected as a result of the disposal of industrial and domestic solid waste products (thermometers, electrical switches, and batteries) to landfills.

Main food sources

Once deposited, the chemical form of mercury can change (through the above mentioned methylation process) into MeHg, which is soluble, mobile, and quickly enters the aquatic food chain. This form of mercury is accumulated to a greater extent in biological tissues than inorganic forms of mercury (Riisgard and Hansen, 1990), and constitutes over 90% of the total mercury detected in fish muscle, with no detection of inorganic or dimethylmercury (Grieb *et al.*, 1990; Bloom, 1992).

MeHg is particularly hazardous because it biomagnifies in food webs, especially the aquatic food web (such as in fish species higher in the food chain), and various studies indicate that anthropogenic releases of mercury from industrial and combustion sources contribute to the levels of methylmercury in fish. In surface waters it rapidly accumulates in aquatic organisms, and its concentrations in carnivorous fish (pike, shark, and swordfish) at the top of both freshwater and marine food chains are biomagnified on the order of 10,000-100,000-fold the concentrations found in ambient waters (Callahan *et al.*, 1979; EPA, 1984; WHO, 1990). It has also been shown that methylmercury can be ingested by aquatic organisms lower in the food chain, such as yellow perch, which in turn are consumed by piscivorous fish higher in the food chain (Cope *et al.*, 1990; Wiener *et al.*, 1990).

Typical mercury concentrations in large carnivorous freshwater fish (pike), large marine fish (swordfish, shark, and tuna) and fish-consuming mammals (e.g., seals and toothed whales) (UNEP, 2002) have been found to exceed 1 µg/g (EPA, 1984; Fairey *et al.*, 1997; FDA, 1998; Hellou *et al.*, 1992; Hueter *et al.*, 1995; Storelli *et al.*, 2002;), with mercury content being positively correlated with the age of the fish (Gutenmann *et al.* 1992; Hueter *et al.* 1995). The biomagnification of MeHg has been demonstrated by the elevated levels found in piscivorous fish compared with fish at lower levels of the food chain (Jackson, 1991; Watras and Bloom, 1992). Watras and Bloom (1992) reported that biomagnification of methylmercury seems to be a result of two processes: the higher affinity of inorganic mercury in lower trophic level organisms and the high affinity of MeHg in fish.

Fish appear to accumulate MeHg from both food sources and the water column, and this bioaccumulation is influenced by the pH of the water, with a greater bioaccumulation seen in waters with lower pH (Ponce and Bloom, 1991). Mercury concentrations in fish have also been negatively correlated with other water quality factors, such as oxygen content (Wren, 1992). Also contributing to MeHg concentrations in fish are existing background levels, which may consist of mercury from natural sources, as well as historic anthropogenic mercury that has been re-emitted from the oceans or soils (UNEP, 2002). High MeHg concentration has also been observed in fish at lower levels in the food web, most probably due to higher background levels of mercury in the environment.

Although fish and seafood are the predominant sources of MeHg in the diets of humans and wildlife, a few reports of other sources exist. Rice cultivated in areas contaminated with mercury can contain relatively high levels of MeHg (Horvat *et al.*, 2003). MeHg has also been reported in organ meats of terrestrial animals (Ysart *et al.*, 2000), as well as in chicken and pork, probably as a result of the use of fish meal as livestock feed (Lindberg *et al.*, 2004). Some communities also have higher MeHg exposure because of the consumption of fish-eating marine mammals (Grandjean *et al.*, 1995; Van Oostdam *et al.*, 2005).

The relationship between the ecosystem fate of MeHg in freshwater and marine systems remains poorly understood, and little is known about the effects of ecosystem variability on human exposure. The intake of mercury depends not only on the level of mercury in fish, but also the amount consumed and frequency. Moderate consumption of a variety of fish is not likely to result in exposures of concern. However, people who consume higher amounts of contaminated fish or marine mammals may be highly exposed to methylmercury and therefore could be at risk (UNEP, 2002).

MeHg contamination poses a particular challenge to public health because this toxicant is mainly contained in fish, a highly nutritious food, with known benefits for human health. Moreover, fish is culturally vital for many communities and constitutes an important global commodity. Although we often refer to “fish” in a generic way, all fish do not have similar amounts of mercury. The concentrations of total mercury vary widely across fish and shellfish species, and some examples are given in Table 3. Many factors influence mercury levels in fish including age, girth, weight, length of the fish, and characteristics of the water body (e.g., local contamination, pH, reduction-oxidation potential, and other factors). Because mercury biomagnifies in the aquatic food web, fish higher on the food web (or of higher trophic level) tend to have higher levels of mercury. Hence, large predatory fish such as king mackerel, pike, shark, swordfish, walleye, barracuda, large tuna, scabbard, and marlin, as well as some marine mammals, such as seals and toothed whales, contain the highest concentrations (Storelli *et al.*, 2003). Older predatory fish exhibit higher mercury levels than fish that are smaller, younger and/or lower in the food-chain. About 90% of the total mercury in these predatory fish species is assumed to be methylmercury. However, the percentage of methylmercury to total mercury may be quite variable, and can be as low as 30% in certain non-predatory fish. Concentrations of MeHg within each fish species also vary, increasing with fish length, weight, age and trophic level (Garcia and Carignan, 2005). Therefore, estimates of fish consumption rates and patterns for the general population and various subgroups must include as detailed information as possible regarding fish species that are consumed. Because MeHg is associated primarily with muscle tissue in the body of a fish, rather than with fatty deposits, trimming and skinning of mercury-contaminated fish does not reduce the mercury content of the fillet portion, and its bonds to proteins, as well as to free amino acids, that are components of muscle tissues, are not removed by any cooking or cleaning processes.

Although in general, MeHg accumulates in fish through the food chain, consumption of farmed fish can also lead to MeHg exposure, in part, because of the presence of MeHg in feed (Choi and Cech, 1998). Some studies have shown no significant difference in MeHg levels in farmed vs. wild salmon, although concentrations in both cases are relatively low (Easton *et al.*, 2002; Foran *et al.*, 2004). In other studies farmed fish, particularly salmon and trout, mercury levels tend to be relatively low (FSA, 2002). These lower concentrations can be attributed to low mercury levels in the diet and also to the fact that farmed fish are usually harvested at a young age, and aquacultured fish are not usually the large predatory types of fish that accumulate MeHg over time by eating other fish containing MeHg. In addition, the chemical characteristics of pond aquaculture (high pH and high content of suspended organic compounds) reduce MeHg bioavailability.

Table 3

Range and mean total mercury concentrations \pm standard deviation in different commercial fresh fish from several regions, with mean length and weight data where available.

Seafood sample	Species	Region	n	Mean length (cm)	Mean weight (kg)	Range Hg concentration (mg/kg)	Mean Hg + SD (mg/kg)	Reference
Albacore tuna	<i>Thunus alalunga</i>	Fiji Islands	31	72.7	21.3	0.03 - 1.01	0.34 + 0.22	Kumar <i>et al.</i> ,2008
Yellowfin tuna	<i>Thunus albacore</i>	Fiji Islands	24	71.3	15.2	< 0.02 - 0.40	0.11 + 0.11	Kumar <i>et al.</i> ,2008
Skipjack tuna	<i>Katsuwana s pelamis</i>	Fiji Islands	12	45.7	2.4	< 0.02 - 0.16	0.06 + 0.04	Kumar <i>et al.</i> ,2008
Marlin	<i>Tetrapturus audax/ Mokaira mazara</i>	Fiji Islands	5	167.6	67.4	0.45 - 5.60	1.76 + 1.94	Kumar <i>et al.</i> ,2008
Reef fish		Fiji Islands	5	17.2	0.1	< 0.02 - 0.04	0.04 + 0.01	Kumar <i>et al.</i> ,2008
Barracuda	<i>Sphyræna sp</i>	Fiji Islands	4	61.3	1.3	0.18 - 0.38	0.26 + 0.07	Kumar <i>et al.</i> ,2008
Bokkem	<i>Trachurus trachurus</i>	Adriatic sea	100	32.7	0.36	ND - 1.87	0.23 + 0.47	Storelli <i>et al.</i> 2003
Gilt sardine	<i>Sardinella aurita</i>	Adriatic sea	150	18.8	0.03	ND - 0.30	0.09 + 0.07	Storelli <i>et al.</i> 2003
Pilchard	<i>Sardina pilchardus</i>	Adriatic sea	300	15.9	0.03	ND - 0.40	0.13 + 0.14	Storelli <i>et al.</i> 2003
Sprat	<i>Sprattus sprattus</i>	Adriatic sea	70	12.9	0.03	ND - 0.14	0.06 + 0.05	Storelli <i>et al.</i> 2003
Pandora	<i>Pagellus erythinus</i>	Adriatic sea	170	14.9	0.06	ND - 0.70	0.22 + 0.19	Storelli <i>et al.</i> 2003
Four spotted megrim	<i>Lepidorhombus bosci</i>	Adriatic sea	180	24.9	0.11	0.14 - 0.69	0.35 + 0.19	Storelli <i>et al.</i> 2003
Megrim	<i>L. whiffjagons</i>	Adriatic sea	150	29.6	0.12	0.09 - 1.17	0.39 + 0.45	Storelli <i>et al.</i> 2003
Red fish	<i>Helicolenus dactylopterus</i>	Adriatic sea	220	21.8	0.10	0.11 - 0.84	0.42 + 0.20	Storelli <i>et al.</i> 2003
Striped mullet	<i>Mullus barbatus</i>	Adriatic sea	270	16.5	0.07	ND - 1.74	0.39 + 0.47	Storelli <i>et al.</i> 2003

Skate	Starry ray	Adriatic sea	120	44.0	0.41	0.09 - 1.78	0.73 + 0.54	Storelli <i>et al.</i> 2003
Forkbeard	Phycis blennoides	Adriatic sea	330	18.9	0.05	0.16 - 0.57	0.36 + 0.14	Storelli <i>et al.</i> 2003
Goldline	Sarpa salpa	Adriatic sea	140	26.7	0.31	0.06 - 0.16	0.08 + 0.05	Storelli <i>et al.</i> 2003
Frost fish	Lepidopus caudatus	Adriatic sea	300	70.2	0.37	0.09 - 1.61	0.61 + 0.38	Storelli <i>et al.</i> 2003
Angler fish	Lophius budegassa	Adriatic sea	200	57.0	0.87	0.19 - 1.77	0.76 + 0.46	Storelli <i>et al.</i> 2003
Picarel	Spicara flexuosa	Adriatic sea	180	15.9	0.02	0.09 - 0.60	0.20 + 0.13	Storelli <i>et al.</i> 2003
Tuna	Thunnus thynnus	Japanese markets	58			0.36 - 5.25	1.11	Nakagawa <i>et al.</i> 1997
Bonito	katsuwonus pelamis	Japanese markets	18			0.12 - 0.41	0.25	Nakagawa <i>et al.</i> 1997
Yellow tail	Seriola dorsalis	Japonese markets	8			0.06 - 0.76	0.26	Nakagawa <i>et al.</i> 1997
Seabass	Seriola purpuraseens	Japonese markets	6			0.04 - 0.37	0.20	Nakagawa <i>et al.</i> 1997
Anchovies		USA markets	40			ND - 0.34	0.04	US FDA 2006
Butterfish	Pampus argenteus	USA markets	89			ND - 0.36	0.06	US FDA 2006
Catfish	Ictalurus sp	USA markets	23			ND - 0.31	0.05 + 0.08	US FDA 2006
Cod	Gadus morhua	USA markets	39			ND - 0.42	0.10 + 0.09	US FDA 2006
Croaker Atlantic	Micropogonias undulatus	USA markets	35			0.01 - 0.15	0.07 + 0.04	US FDA 2006
Herring	Alosa sapidissima	USA markets	38			ND - 0.14	0.04	US FDA 2006
Mackerel Atlantic	Scomber scombrus	USA markets	80			0.02 - 0.16	0.05	US FDA 2006
Mackerel chub	Scomber japonicus	USA markets	30			0.03 - 0.19	0.09	US FDA 2006
Mackerel King	Scomberomorus cavalla	USA markets	213			0.23 - 1.67	0.73	US FDA 2006
Mackerel Spanish	Scomberomorus sierra	USA markets	109			0.05 - 1.56	0.32	US FDA 2006
Marlin	Makaira nigricans/ Tetrapturus audrax	USA markets	16			0.10 - 0.92	0.49 + 0.24	US FDA 2006

Mullet	Mugil sp	USA markets	191			ND - 0.13	0.05	US FDA 2006
Pollock	Pollachius virens	USA markets	62			ND - 0.78	0.04 + 0.10	US FDA 2006
Salmon*	Several species	USA markets	34			ND - 0.19	0.01 + 0.04	US FDA 2006
Sardine		USA markets	29			0.004 - 0.04	0.02 + 0.01	US FDA 2006
Shark	Carcharhinus limbatus	USA markets	351			ND - 4.54	0.99 + 0.63	US FDA 2006
Swordfish	Xiphias gladius	USA markets	618			ND - 3.22	0.98 + 0.51	US FDA 2006
Tilefish	Caulolatilus princeps	USA markets	60			0.65 - 3.73	1.45	US FDA 2006
Trout (freshwater)	Oncorhynchus mykiss	USA markets	34			ND - 0.68	0.07 + 0.14	US FDA 2006
Tuna (canned, light skipjack)	Katsuwonus pelamis	USA markets	347			ND - 0.85	0.12 + 0.12	US FDA 2006
Tuna (canned, albacore)	Thunnus alalunga	USA markets	399			ND - 0.85	0.35 + 0.13	US FDA 2006
Tuna (fresh/frozen)	Several species	USA markets	228			ND - 1.30	0.38 + 0.27	US FDA 2006

Note: * Only methylmercury was analysed; n = number of samples; ND = mercury

In addition to fish, marine mammals and shellfish may also represent a source of mercury. Exposure can be significant in populations consuming meat (muscle and organs) from marine mammals, such as seals and whales. The kidney and liver of marine mammals in particular can have extremely high levels of mercury (Table 4).

Table 4

Range and mean total mercury concentrations + standard deviation in different mammals from several regions.

Mammal		Origin	Muscle	Liver	Kidney	Muktuk ^a	Reference
Beluga whale	Delphinapterus leucas	Canadian Arctic	0.13 - 8.35 (305)	4.10 - 43.8 ^b	0.16 - 20.7 (535)	0.19 - 1.92 (176)	Lockhart <i>et al.</i> , 2005
Narwhal	Monodon monoceros	Canadian Arctic	0.51 - 1.20 (20)			0.32 - 0.85 (20)	Wagemann and Kozłowska, 2005
Harp seal	Phagophilus groenlandicus	Greenland Sea	0.04 - 0.31 (25)	0.08 - 3.3 (25)	0.14 - 0.68 (25)		Brunborg <i>et al.</i> , 2006
Hooded seal	Cystophora cristata	Greenland Sea	0.08 - 0.31 (25)	0.004 - 0.13 (25)	1.00 - 4.40 (25)		Brunborg <i>et al.</i> , 2006
Pilot whale	Globicephala macrorhynchus	Japan coastal area	5.38 - 13.8 (4)	390 - 422 (2)			Endo <i>et al.</i> , 2004

Risso's dolphin	Grampus griseus	Japan coastal area	9.09 - 9.21 (2)	30.2 - 645 (7)	7.30 - 28.8 (4)		Endo <i>et al.</i> , 2004
Striped/Bottle-nose/ Common dolphins	Stenella coeruleoalba/Tursiops truncatus/Delphinus delphis	Japan coastal area	1.43 - 63.4 (12)	7.6 - 1980 (11)	7.85 - 153 (10)		Endo <i>et al.</i> , 2004
Baird's beaked whale	Berardius bairdii	Japan coastal area	1.71 - 5.30 (4)				Endo <i>et al.</i> , 2004
Minke whale	Balaenoptera spp ^c	Japan coastal area	0.03 - 0.12	0.12 (1)	0.01 (1)		Endo <i>et al.</i> , 2004

Note: ^a skin (considered as a sought-after food by the Inuit); ^b range of mean concentrations; ^c caught in Antarctic or Northern Pacific

With regard to shellfish (crustaceans and molluscs), popular seafood in some countries, relatively low levels of mercury have been reported (Burger *et al.*, 2005; SACN, 2004), and MeHg represents in general less than 60% of total mercury concentrations. In the United Kingdom, for example, it has been shown that dietary intakes of mercury did not represent any known health risk even to high level shellfish consumers (SACN, 2004). However, mercury concentration in shellfish collected from polluted areas can be elevated, and diets combining high shellfish and fish consumption can lead to high mercury and methylmercury exposure.

Although most studies identified a clear association between the quantity and the frequency of fish consumption and mercury exposure, there is considerable inter individual and inter-group variability in the relation between the amount or the frequency of fish consumption and the levels of biomarker of MeHg exposure. Additionally, those who eat mainly carnivorous fish and/or fish-eating mammals have relatively higher levels of mercury compared with those who eat mainly non carnivorous fish (Van Oostdam *et al.*, 2005; Dolbec *et al.*, 2001; Johnsson *et al.*, 2004; Muckle *et al.*, 2001). Independent of the MeHg concentration, the frequency of fish consumption is also an important factor in this variability.

To characterize local dietary habits of a given population living in a particular area, it is important that fish consumption information includes descriptive information on the consumption of locally caught fish and other fish (such as market-based fish imported to the area). For locally caught fish and market-based fish (such as canned, fresh, and frozen fish species shipped to the area from other parts of the country or from other countries), the information questionnaire should take into account species, frequency of the meals (over the short and long term), and portion sizes, as well as information regarding temporal patterns of consumption throughout the year (to the extent feasible). For locally caught fish, additional information should be collected, including the size and location of the fishing population using specific water bodies.

Because biomarkers reflect the weighted average of exposure over time, short-term reporting of fish consumption may not correspond with a longer-term average of MeHg exposure. Under some circumstances, episodic exposures can result in large bolus doses of MeHg. Bolus doses

can arise, for example, from the infrequent consumption of fish or fish-eating mammals with high concentrations of MeHg. Given practical limitations in sampling frequency, as well as the nature of some of the biomarkers themselves, bolus doses during putative discrete windows of sensitivity in fetal development may not be fully revealed by biomarkers of exposure.

B. METHYLMERCURY (MEHG)

Toxicokinetics

a) ADME

Organic mercury compounds like MeHg are more readily absorbed by the oral route than inorganic mercury compounds. Following ingestion, MeHg is rapidly and extensively absorbed (about 95 %) through the gastrointestinal tract. Once absorbed, MeHg can be converted into inorganic mercury in tissues, specifically the divalent cation (Hg^{+2}) (Dunn and Clarkson, 1980). Several investigators have reported high levels of inorganic mercury in tissues and faeces after methylmercury exposure (Turner *et al.*, 1975).

Distribution of organic mercury involves complexes with proteins in the body. MeHg associates with proteins by amino acids containing thiols because of the high affinity of the methylmercuric cation (CH_3Hg^+) for the sulphhydryl groups (SH-) (Aschner and Aschner, 1990). Complexes of MeHg with cysteine or glutathione have been identified in blood, liver, and bile (Aschner and Aschner, 1990). The transport of MeHg to the brain appears to be closely linked to thiol-containing amino acids (Aschner and Clarkson, 1988). The MeHg cation can bind to the thiol group of the amino acid cysteine, forming a complex with a chemical structure similar to that of the essential amino acid methionine (Clarkson, 1995). In such a manner, MeHg can cross the blood-brain barrier "disguised" as an amino acid via a carrier-mediated system, and so transport is not solely the result of MeHg's lipid solubility. The uptake of MeHg by the brain is inhibited by the presence of other amino acids such as leucine, methionine, phenylalanine, and other large neutral amino acids (Clarkson, 1995; Kanai and Endou, 2003; Sakamoto *et al.*, 2004).

In humans, the elimination of metallic mercury occurs through the urine, faeces, and expired air, while inorganic mercury is excreted in the urine and faeces, with a body burden half-life of approximately 1-2 months (Clarkson, 1989). Excretion of organic mercury is predominantly thought to occur through the fecal (biliary) route in humans, with less than one-third of the total mercury excretion occurring through the urine, following oral and inhalation exposure (Norseth and Clarkson, 1970). In humans, nearly all of the total mercury in the faeces after organic mercury administration is in the inorganic form. MeHg is also excreted in the breast milk of humans, rats, and guinea pigs (Sundberg and Oskarsson, 1992; Yoshida *et al.*, 1992).

b) Mother → foetus

One area where toxicokinetic data are of particular importance is the MeHg transfer from the mother to the foetus across the placenta. MeHg has been shown to be actively transferred via neutral amino acid carriers during gestation (Sakamoto *et al.*, 2001). Although maternal and cord blood Hg concentrations are highly correlated, cord blood MeHg is consistently higher than the corresponding maternal concentration, with an average ratio of about 1.7 (Morrisette *et al.*, 2004; Stern and Smith, 2003; Sakamoto *et al.*, 2004). As a result, when MeHg in adult women's blood is biomonitoring as a surrogate for potential foetal exposure, the corresponding foetal level will be, on average, 70% higher than maternal blood and up to three times higher at the 95th percentile. The maternal body burden of MeHg tends to decrease during gestation consistent with hemodilution and a transfer of a portion of the maternal body burden to the foetus (Morrisette *et al.*, 2004).

c) **Mother → newborn**

Neonatal and infant exposure to MeHg may occur through intake of breast milk. However, milk has a lower level of MeHg than plasma, and is enriched in inorganic Hg relative to the whole blood (Oskarsson *et al.*, 1996). Thus, lactational exposure to MeHg is reduced compared with what would be expected on the basis of maternal blood MeHg. Human and animal studies showed that, after birth, there is a decline in MeHg levels, reaching 40–50% at 2–3 months of age (Bjornberg *et al.*, 2005). During this period, infant body weight increases about 1.5–2 times. Consequently, the rapid increase in body volume and the limited MeHg transfer appear to explain the dilution of MeHg in infants during breast feeding.

C. HEALTH EFFECTS OF METHYLMERCURY

Neurological effects

Most of what is known about the clinical signs, symptoms and neurological effects of methylmercury has been learned from studies of pollution incidents in Japan and Iraq. The first reported widespread outbreak of neurological disorders associated with the ingestion of methylmercury-contaminated fish occurred in the late 1950s in the Minamata area of Japan (Kutsuna, 1968). The neurological syndrome was characterized by a long list of symptoms including prickling, tingling sensation in the extremities (paresthesia), impaired peripheral vision, hearing, taste, and smell, slurred speech, unsteadiness of gait and limbs, muscle weakness, irritability, memory loss, depression, and sleeping difficulties (Kutsuna, 1968; Tsubaki and Takahashi, 1986). Elevated concentrations of methylmercury were observed in the hair and brains of victims. Children exposed in utero to high levels of MeHg presented cerebral palsy, mental retardation, movement and coordination disorders, dysarthria, and sensory impairments. The neuropathological lesions associated with Congenital Minamata Disease (mercury poisoning) were diffuse, occurring throughout the brain. In individuals exposed only in adulthood, the lesions were highly focal, clustering in regions that matched clinical presentation (e.g., motor disorders = precentral gyrus and cerebellum; constriction of visual fields = calcarine fissure of occipital cortex).

Epidemics of similar neurological disorders were reported in Iraq in 1971–72 (Bakir *et al.*, 1973) as the result of eating flour made from seed grain treated with ethylmercury p-toluene sulphonanilide. Affected individuals had an inability to walk, cerebellar ataxia, speech difficulties, paraplegia, spasticity, abnormal reflexes, restriction of visual fields or blindness, tremors, paresthesia, insomnia, confusion, hallucinations, excitement, and loss of consciousness.

Neurotoxic effects seen both in the Minamata and Iraqi poisonings have been associated with neuronal degeneration and glial proliferation in the cortical and cerebellar gray matter and basal ganglia (Al-Saleem *et al.*, 1976), derangement of basic developmental processes such as neuronal migration (Choi *et al.*, 1978; Matsumoto *et al.*, 1965) and neuronal cell division (Sager *et al.*, 1983). In the brain, Purkinje, basket, and stellate cells were severely affected, while granule cells were variably affected. Sural nerves removed from two women with neurotoxicity associated with the Minamata incident also showed evidence of peripheral nerve degeneration and regeneration (Miyakawa *et al.*, 1976).

Reproductive Outcomes

The effect of MeHg on the sex ratio of offspring at birth and stillbirth in Minamata City, Japan, in the 1950s and 1960s, including the period when MeHg pollution was most severe, showed decreases in male birth in offspring in the overall city population, as well as among fishing families (Sakamoto *et al.*, 2001; Itai *et al.*, 2004). An increase in the proportion of male stillborn

foetuses raises the possibility that increased susceptibility of male foetuses to death in utero could explain the altered sex ratio.

Immune System Effects

Inorganic mercury was shown to suppress immune functions and to induce autoimmunity in multiple species (Silbergeld *et al.*, 2005). Both MeHg and inorganic Hg were shown to produce an autoimmune response, as well as an immunosuppressive effect in several strains of genetically susceptible mice (Haggqvist *et al.*, 2005). However, data on the immune effects of MeHg in general are scarce, and research is required in this area.

Cardiovascular Effects

In recent years, more attention has been given also to other possible adverse effects of MeHg exposure, for example its contribution to cardio vascular disease (CVD). This attention to mercury implications in the cardiovascular system stems predominantly from initial epidemiological findings from Finland where high mercury content in hair was associated with an increased progression of atherosclerosis and risk of CVD (Salonen *et al.*, 1995; 2000). Subsequent research has confirmed these findings (Virtanen *et al.*, 2005; Guallar *et al.*, 2002), and these adverse effects on CVD have been observed at MeHg levels much lower than those associated with neurotoxicity.

MeHg is a risk factor for cardiovascular disease through a variety of mechanisms potentially involving pro-oxidant effects via the generation of radical species and the inactivation of cellular antioxidant systems such as glutathione peroxidase and catalase (Guallar *et al.*, 2002). There is evidence for lipid peroxidation and elevations of oxidized low density lipoprotein in association with MeHg exposure (Andersen and Andersen, 1993; Salonen *et al.*, 1995). Mechanistic studies indicate that MeHg can exert toxic effects on the vascular endothelium by depletion of sulphhydryls, increased oxidative stress and activation of phospholipases (Hagele *et al.*, 2007; Mazerik *et al.*, 2007). Oral dosing of rats with methylmercury at a daily rate of 0.5 mg/kg for 9 months yielded a persistent pressor effect (Wakita, 1987). Human overdose with organic or inorganic mercury has also produced a variety of adverse effects on the heart and blood pressure, and occupational exposure to inorganic mercury has been associated with hypertension and non-ischemic heart disease (ATSDR, 1999; Boffetta *et al.*, 2001).

Developmental Neurotoxicity

The brain is the main target tissue for MeHg and the unique susceptibility of the developing CNS has long been known (NRC, 2000). The public health concerns associated with developmental MeHg exposure have indeed resulted in extensive research.

a) Why is the developing brain so sensitive to MeHg?

The CNS is particularly sensitive to alterations of the microenvironment during early development, when there are windows of susceptibility to adverse interference that are not present in the mature brain. Alterations in environmental conditions during development produce long-lasting and often permanent changes in the structure and function of the brain that reflect altered expression of key genes involved in neuronal development and plasticity (Colvis *et al.*, 2005). Such conditions include sensory or social stimuli, maternal care, stress but also drug treatments and toxic compounds (Ansorge *et al.*, 2007). The consequences of early exposure to chemicals that are specifically harmful to the brain (neurotoxic agents), can be very subtle and may be evident only after a prolonged latency (For extensive review on "silent toxicity" see Reuhl, 1991; Costa *et al.*, 2004). Evidence is growing that in utero or early postnatal

exposure to toxicants, can lead later in life to severe behavioral abnormalities, even if how aging exactly triggers activation of these silent changes is at present unknown.

CNS development encompasses a tightly regulated temporal and spatial sequence of events (proliferation, migration, synaptogenesis, selective programmed cell death, myelination), and even a short-term impairment in this cascade may cause irreversible neurotoxicity if the tissue cannot compensate for the damage. The routes of exposure to toxicants during development are rather unique (e.g., transplacental in foetus, via breast milk in nursing infants, hand-to-mouth in early childhood) and have no parallel among adults. Moreover, on a body-weight basis children eat and drink more than average adults, and thus they are potentially more heavily exposed to food contaminants than grown-up individuals (Landrigan *et al.*, 2004). Toxicokinetic factors vary during development, between pre- and post-natal life and even during the course of gestation. Children's metabolic pathways, especially in foetal life and in the first months after birth, are immature (Ginsberg *et al.*, 2004) as is the blood-brain barrier.

b) *Symptoms and effects*

The symptoms observed in offspring of mothers exposed to MeHg are primarily neurological in origin and, as mentioned above, have ranged from delays in motor and verbal development to severe brain damage. Subtle changes, such as small changes in intelligence or learning capacity have been tested in populations with low-level, chronic exposure to mercury in the diet (Davidson *et al.*, 1998; Grandjean *et al.*, 1997, 1998). Findings of developmental neurotoxicity, following high level exposure to prenatal MeHg, raised the question of whether children whose mothers consumed fish contaminated with background levels during pregnancy are at an increased risk of impaired neurological function. To address these concerns, a number of epidemiological studies of neurobehavioral development in children have been conducted in fish and seafood consuming populations (see Section 4.4.2).

The three longitudinal, largest and most carefully done studies were carried out in New Zealand (Crump *et al.*, 1998), the Seychelles islands (Davidson *et al.*, 1998; Myers *et al.*, 2003) and the Faroe Islands (Grandjean *et al.*, 1997). Whereas adverse effects have been unequivocally demonstrated in poisoning incidents, the implications of the exposure to low levels of MeHg, such as those occurring in fish-eating populations, are still controversial. In the longitudinal study conducted by Grandjean *et al.*, (1997) of children in the Faroe Islands exposure to MeHg largely resulted from ingestion of whale meat. Evaluations at 7 years of age found 9 of 20 measures with mercury-associated deficits on multiple regression analysis. They reported adverse associations in the domains of language, attention, memory, and to a lesser extent visuospatial and motor functions. However, the longitudinal study of children in the Seychelles pre- and postnatally exposed to MeHg from fish consumption found no adverse associations through 66 months of age (Davidson *et al.*, 1998). Differences between testing methods, source, and measurement of exposure, concomitant exposures, lifestyle, and culture of the populations or statistical methods could account for the seemingly inconsistent findings between the studies.

Animal studies show a broad range of harmful consequences after in utero exposure to MeHg, from increased rates of intrauterine death, delayed developmental growth, and altered brain cellular arrangement to more subtle effects, such as delayed reflexive behavior, impairment of locomotor activity and motor coordination or cognitive dysfunctions, depending on the duration and level of exposure at different developmental stages (Doré *et al.*, 2001; Baraldi *et al.*, 2002; Daré *et al.*, 2003; Goulet *et al.*, 2003; Carratu' *et al.*, 2006).

c) *Mechanisms of Neurotoxicity*

High-affinity binding of the divalent mercuric ion to thiol or sulphhydryl groups of proteins is believed to be a major mechanism for the biological activity of mercury. Because proteins containing sulphhydryl groups occur in both extracellular and intracellular membranes and organelles, and because most sulphhydryl groups play an integral part in the structure or function of most proteins, the precise target(s) for mercury is not easily determined. Possibilities include the inactivation of various enzymes, structural proteins, or transport processes (Bulger, 1986), or alteration of cell membrane permeability by the formation of mercaptides (Sahaphong and Trump, 1971). Binding may also occur to other sites that are less favoured than sulphhydryl groups, like amine, carboxyl groups. A variety of mercury-induced alterations have been investigated, including increased oxidative stress, disruption of microtubule formation, increased permeability of the blood-brain barrier, disruption of protein synthesis, disruption of DNA replication and DNA polymerase activity, impairment of synaptic transmission, membrane disruption, and disruption in calcium homeostasis. These alterations may be acting singly or in combination.

Major molecular mechanisms of MeHg neurotoxicity include inhibition of protein and macromolecular synthesis, mitochondrial dysfunction, defective calcium and ion flux, disruption of neurotransmitter homeostasis, initiation of oxidative stress injury, microtubule disaggregation, and post-translational phosphorylation (for extensive review see Johansson *et al.*, 2007). The diffuse injury associated with prenatal exposure is attributable to the ability of MeHg to arrest mitotic cells in metaphase, disrupting the exquisitely choreographed processes of cell proliferation, differentiation, and migration. The result is a brain in which there are reduced cortical cell densities, islands of heterotopic neurons in cerebral and cerebellar white matter, anomalous cytoarchitecture, disturbance in laminar pattern of cerebral cortex, absence of granule and Purkinje cells in the cerebellum, incomplete myelination in the hypoplastic corpus callosum, glial proliferation (“bizarre astrocytes in the white matter”), and limited gyral differentiation (Johansson *et al.*, 2007; Choi, 1989).

While MeHg can directly cause damage to neurons, numerous studies have established a prominent role for astrocytes in mediating MeHg neurotoxicity (Gotz *et al.*, 2002). The evidence includes observations that MeHg preferentially accumulates in astrocytes (Aschner, 1996) and inhibits uptake systems for glutamate and cysteine transport, both of which will compromise glutathione (GSH) synthesis and redox status in astrocytes (Allen *et al.*, 2001; Shanker and Aschner, 2001, 2003; Shanker *et al.*, 2001). Furthermore, MeHg causes the activation of cytosolic phospholipase A2 (cPLA2), leading to arachidonic acid release and further inhibition of glutamate transporters and neuronal dysfunction (Aschner, 2000; Aschner and Syversen, 2005). These studies suggest that mercurial neurotoxicity is at least, in part, mediated by excess extracellular glutamate concentrations.

Inactivation of Na^+/K^+ -ATPase by mercury could cause partial membrane depolarization allowing excessive Ca^{2+} entry into neurons with resultant toxic events similar to excitotoxicity and be implicated in the pathological abnormalities of neurodegenerative diseases (Xie and Cai, 2003; Yu, 2003). MeHg was found to significantly inhibit Na^+/K^+ -ATPase activity and to cause cellular or organic dysfunction (Chuu *et al.*, 2001a, b; 2007). Reactive oxygen species (ROS)-induced damages were also associated with the inhibition of Na^+/K^+ -ATPase activity in mammals, and prevention of the inhibition of this enzyme by antioxidants has also been reported (Rodrigo *et al.*, 2007). Other studies have indicated that MeHg could produce toxic effects by oxidative stress and cause the alteration in cellular functions, eventually resulting in cell death and pathological injury which are accompanied by a decrease of antioxidant enzymes (Chen *et al.*, 2006). Cultured neurons (Mundy and Freudrich, 2000) and glia (Shanker *et al.*, 2003) exposed to MeHg and brain synaptosomes prepared from animals injected with MeHg (Ali *et al.*, 1992),

demonstrate increased ROS production. In addition, an increase in ROS has been observed in mitochondria isolated from MeHg-injected rat brains, isolated rat brain mitochondria exposed to MeHg in vitro (Myhre and Fonnum, 2001) and mitochondria from Hg- and glutamate-exposed astrocytes and neurons. Evidence suggests that MeHg exposure causes production of ROS, depletion of ATP, excessive accumulation of calcium (Ca^{2+}) and a decrease in mitochondrial membrane potential in mitochondria from the nervous (Limke and Atchison, 2002) and immune (Shenker *et al.*, 1998) systems. Excessive ROS production, leading to a decrease of mitochondrial membrane potential may also induce the oxidation of membrane polyunsaturated fatty acids, yielding a multitude of lipid peroxidation products. A study by Yin *et al.*, (2007) has further demonstrated that MeHg exposure is associated with increased mitochondrial membrane permeability, alterations in glutamine/glutamate cycling, increased ROS formation and consequent oxidative injury leading to cellular dysfunction and cell death.

D. RECENT EPIDEMIOLOGICAL STUDIES

Cardiovascular endpoints

Epidemiological evidence is generally supportive of an association between MeHg body burden in the general public, primarily from fish consumption, and cardiovascular disease (Stern, 2005). A prospective study of 1014 Finnish men found that those in the highest quintile of MeHg exposure (hair mercury > 2.81 ppm) had an accelerated thickening of the carotid artery, an indication of atherosclerosis (Salonen *et al.*, 2000). Several studies provided evidence of increased cardiovascular mortality in men in relation to hair or toenail mercury (Guallar *et al.*, 2002; Rissanen *et al.*, 2000; Salonen *et al.*, 1995; Virtanen *et al.*, 2005). In a case control study spanning eight European countries and Israel, 684 men with myocardial infarction were found to have significantly greater toenail mercury than the 724 matched controls (Guallar *et al.*, 2002). An earlier study of 1833 Finnish men followed prospectively showed a doubling of risk for myocardial infarction in the highest tertile of exposure (hair mercury > 2 ppm) (Salonen *et al.*, 1995). A follow-up of this eastern Finland population continued to show a heightened risk of coronary events due to MeHg which was able to offset the positive influence of omega-3 fatty acids (Virtanen *et al.*, 2005).

However, several other studies failed to find a consistent association between mercury body burden and cardiovascular outcomes (Ahlquist *et al.*, 1999; Hallgren *et al.*, 2001; Yoshizawa *et al.*, 2002). A study of 1462 Swedish women did not find an association between serum mercury and stroke, but this study was focused primarily on mercury exposure via amalgam fillings (Ahlquist *et al.*, 1999). This appears to have been a significant source based upon the strong correlations between serum mercury and number of fillings. There was no assessment of fish ingestion or attempt to factor out the benefit of fish oils on the endpoints measured. In another Swedish study, this time involving 78 men and women with myocardial infarction and 124 controls, mercury was found to be correlated to myocardial infarction risk (Hallgren *et al.*, 2001). However, the mercury body burden in this population was much lower than in the Finnish studies, possibly too low to have an adverse effect on its own. Overall, this study did not have sufficient power to detect an independent effect of MeHg on myocardial infarction, especially given the low exposures to MeHg in this population.

A large prospective study of US health professionals collected toenail mercury data from 33,737 men, of whom 470 had a myocardial infarction during the course of follow-up (Yoshizawa *et al.*, 2002). The overall analysis showed no difference in risk of myocardial infarction across the quintiles of toenail mercury, but also in contrast to other studies, there was no demonstrable benefit from fish ingestion. The majority of subjects were dentists and they were overrepresented in the highest exposure groups. The authors reported a positive but non-

significant association of mercury with coronary heart disease in a sub-analysis that excluded dentists. This may indicate that MeHg from fish ingestion has a greater influence on cardiovascular risk than inorganic mercury from dental amalgams. While speculative, this would help explain the negative findings in the Swedish women's study described above (Ahlquist *et al.*, 1999). Overall, mechanistic evidence and results of animal toxicology, human clinical toxicology and epidemiology studies support the notion that MeHg can be a risk factor for cardiovascular disease. The strongest epidemiological study in this regard is that of Guallar *et al.*, (2002) in that it provided separate dose response functions for MeHg risk and omega-3 fatty acids benefit for the same cardiovascular endpoint.

A recent study by Valera *et al.* (2009) found that environmental mercury exposure in Nunavik Inuit adults (Northern Quebec, Canada) was associated with increased blood pressure and pulse rate. Furthermore, Lim *et al.* (2009) reported that in a Korean community, low dose mercury (average hair concentration 0.83 ug/g) was associated with altered cardiac autonomic activity, possibly through an action of mercury on parasympathetic functions.

Neurological and developmental studies

As mentioned above the three major epidemiological studies that have received significant attention are those in the Faroe Islands (Grandjean, 1997), Seychelles (Myers *et al.*, 2005b), and New Zealand (Kjellstrom *et al.*, 1986). The study in the Faroe Islands commenced in 1986 with a cohort of newborn infants, who were tested at ages 12 months, 7 years, and 14 years. In the Seychelles, a first study commenced in 1987 with a sample of newborn infants who were followed up at age 5 weeks, 66 months, and 108 months. A subsequent study commenced in the Seychelles in 1989 with a sample of newborns who were followed up at ages 6.5 months, 19 months, 29 months, 66 months, and 108 months.

Both the Seychelles and Faroe studies involved populations that had a high per capita consumption of fish (Davidson *et al.*, 1998; Grandjean *et al.*, 1997). A variety of outcome measures were used that included neurological examination, developmental rating scales, neuropsychological tests, and attainment tests. A strong variation occurred between studies in terms of the tests used for children of the same age group, and with the exception of the Seychelles studies, information on testing procedures provided in the published reports was rather limited and therefore difficult to evaluate. All studies reported control of some potential effect modifiers such as socioeconomic status, ethnicity, and parental IQ, but the particular factors selected for inclusion varied between studies. All studies used multivariate analysis techniques.

In the Faroe Islands, a major source of MeHg for the population, besides fish, is episodic consumption of pilot whale meat, a traditional food containing, on average, significantly higher concentrations of MeHg than the local fish. The whaling in the Faroe Islands is a non-commercial whaling conducted at the community level, and approved by the International Whaling Commission. The average annual catch of pilot whales over the years is 850. Meat and blubber of pilot whales are stored in freezers, or traditionally salted and dried in the open air, or cooked. The mean mercury levels of pilot whales and cod captured around the Faroe Islands in early 1990 were 3.3µg/g (approximately half was MeHg) and 0.07µg/g (mostly MeHg), respectively (Grandjean *et al.*, 1992). According to this study, the mean consumption by adults was 12g/day for whale meat and 72g/day for fish meat, and the mean mercury intake was estimated at approximately 36µg/day. In addition, blubber was the main source of PCB intake.

During 1986–1987, a Faroese cohort of more than 1000 singleton births was assembled and children were followed up for 14 years to evaluate exposure parameters and a series of physiological endpoints based on a detailed neurobehavioral examination. Unexpectedly, at 12

months of age, early milestone development (i.e., sitting, creeping and standing) was associated with higher hair Hg concentrations (Grandjean *et al.*, 1995). At age 7 years, decrements in attention, language, verbal memory and, to a lesser extent, in motor speed and visual-spatial function, and delays in brainstem auditory-evoked potentials were associated with prenatal MeHg exposure (previously determined from Hg concentrations in cord blood and maternal hair; Grandjean *et al.*, 1997). A follow-up of these children at 14 years of age still indicated deficits in motor, attention and verbal tests, delayed brainstem auditory-evoked potentials as well as MeHg-associated alterations of cardiac autonomic activity (Murata *et al.*, 2004; Debes *et al.*, 2006).

The Seychelles Child Development Study (SCDS) was designed to study the developmental effects of prenatal MeHg exposure in a fish-eating population. A number of social, dietary and economic factors make the Seychelles Islands an optimum environment for studying the effects of prenatal exposure to MeHg arising from fish consumption. In the Seychelles, the population's diet is based on deep sea and reef fish. Inhabitants do not eat marine mammals.

Two birth cohort longitudinal studies, referred to as the pilot and the main study, have been performed each including more than 700 mother-child pairs. The pilot study on children aged 5–109 weeks did not find any significant association of maternal hair levels (median concentration: 6.6 ppm; range: 0.59–36.4) with the overall neurological examination, increased muscle tone or deep tendon reflexes (Myers *et al.*, 1995 a, b, c; Davidson *et al.*, 2000). The main study, which had several additional covariates and expanded endpoints, did not detect any significant adverse outcome in children regardless of the age of testing (Myers *et al.*, 2003; Davidson *et al.*, 1998, 2000, 2006). Rather, the test performance of both cohorts was even enhanced, in some instances. Such positive effects have been hypothesized to derive from the intake of beneficial factors present in fish, such as omega-3 fatty acids (Davidson *et al.*, 2000). However, while the Seychelles is still overall a negative (without effects) study, some evidence has recently been found suggestive of a latent MeHg effect (Davidson *et al.*, 2006).

In New Zealand, a group of children whose mothers had eaten at least three fish/seafood meals per week during pregnancy was studied (Kjellstrom *et al.*, 1986, 1989). The fish species consumed were mainly shark with average MeHg levels above 2 ppm, reaching even 4 ppm (Kjellstrom *et al.*, 1986; Clarkson and Magos, 2006). At age 4, a higher prevalence of abnormal results in the Denver Developmental Screening Test (DDST) was detected in highly exposed children (i.e., maternal hair Hg >6 ppm; Kjellstrom *et al.*, 1986). At age 6, poorer scores on full-scale IQ, language development, visual-spatial and gross motor skills were associated with maternal hair Hg concentrations in the range of 13–15 ppm (Crump *et al.*, 1998; Kjellstrom *et al.*, 1989).

In the Amazon Basin, mercury contamination of fish has been recognized as a problem affecting many of the indigenous people who live along the tributaries and rely on fish as a major source of protein. Mercury has been released during gold mining operations, but the largest sources of mercury may be deforestation and damming of rivers, which makes naturally occurring mercury in the soil accessible to biomethylation by aquatic organisms. Extensive studies have been conducted in the Amazon on mercury exposure and neurobehavioral effects. Using segmental hair analysis, Dolbec *et al.*, (2001) were able to document that hair mercury levels among Amerindian women varied with the season. During the wet season when herbivorous fish predominated in the diet, levels were lower than in the dry season, when herbivores made up <50% of the diet. In a cross-sectional study, Dolbec *et al.*, (2000) studied neurobehavioral performance of 84 residents along the Rio Tapajos, using hair mercury as their exposure metric. The mean percentage of meals containing fish was 62%, and the median hair mercury was 9 ppm (almost 95% was organic mercury). There was a negative correlation between hair mercury

and neurobehavioral performance, particularly in fine motor coordination, and the relationship was stronger than with blood mercury, indicating the benefits of using hair levels that track exposure over a period of months. However, only 8–16% of the variance in performance was explained by the hair Hg.

The study by Steuerwald *et al.*, (2000) reported that examination of children at 2 weeks of age showed that those with higher prenatal exposures had slightly lower overall neurologic scores, although there was no discernible pattern of suboptimal findings. Similarly, McKeown-Eyssen *et al.*, (1983) carried out neurologic examinations on Cree Indian children between 12 and 30 months of age and found an association between MeHg exposure and the prevalence of abnormal muscle tone reflexes in males only. The authors noted the mildness of the abnormality, which they considered to be of doubtful clinical significance.

Cordier *et al.*, (2002), in a study of children 9 to 12 years of age, found an association between scores on one test and MeHg exposure, but this did not appear in separate analysis of the highest exposure subgroup. Moreover, results from one test showed a positive association with MeHg exposure. An ongoing study of a birth cohort in Massachusetts shows an association of MeHg exposure with neurodevelopmental effects at lower levels of exposure than in prior studies (Oken *et al.*, 2005; Oken *et al.*, 2008).

a) Patterns of exposure

Temporal exposure patterns during pregnancy may be relevant in relation to susceptibility “windows” of the foetal brain to MeHg. Because developmental stages occur in temporally distinct time frames across the various brain regions, MeHg may induce different regional effects depending on the timing of exposure. MeHg adverse effects on the developing brain have been proposed to be more a function of episodic high-level (peak) exposures than of average (continuous) exposures over the course of pregnancy (Clarkson and Magos, 2006).

Different patterns of exposure between the Faroes and Seychelles may be part of the explanation for different results reported in the two studies. The pattern of in utero exposure to MeHg (frequency, source, amount) differed in the Seychelles and Faroese populations with lower MeHg concentrations in the seafood consumed on a daily basis in the Seychelles (0.3 ppm in ocean fish) and peak episodic exposure to MeHg in the Faroe Island population when eating pilot whale (1.6 ppm, less than once per month, on the average, with additional intermittent snacks of dried whale). Because of this differing Hg content, the bolus dose of MeHg reaching the brain after food consumption was estimated to be about 10 times higher in the Faroe Islands (and New Zealand) inhabitants, than in the population from the Seychelles (Clarkson and Magos, 2006). Nonetheless, the 12 fish meals/week reported in the Seychelles cannot be easily compared with the three fish dinners/week in the Faroe Islands, in that the types of fish eaten and their Hg concentrations differ (NRC, 2000). In the Faroes Hg exposure assessment relied on both umbilical cord blood and maternal hair analyses, while only the latter biomarker was used in the Seychelles. Cord blood Hg, which is assumed to reflect exposure during the last half of the 3rd trimester of pregnancy, was a better predictor of MeHg effects in Faroese children than hair Hg levels. In the Seychelles, only 9-cm-long hair samples reflecting average Hg exposure during pregnancy were collected, while Faroese hair samples of various lengths were analyzed, some 3 cm (reflecting late 2nd and 3rd trimester) and some 9 cm (presumably reflecting the entire pregnancy).

The inconsistency in the results of these epidemiological studies where there were some positive and some negative findings, stresses the idea of giving additional consideration in future research to resolve the uncertainties surrounding exposure assessment and outcome measurement, as both elements varied between studies. Outcome assessment would benefit

from the development of theoretically based measures of specific aspects of cognitive functioning to replace the relatively crude measures of attainment and IQ currently employed in most studies. This would assist in the development of classic longitudinal studies by allowing repeated assessment over the full age range and providing data that are more readily interpretable and comparable between studies.

E. RECENT TOXICOLOGICAL RESEARCH

Interactions between PCBs and MeHg

Exposure to dioxins and dioxin-like PCBs can occur simultaneously with MeHg since these contaminants are found in similar food sources, especially fish, seafood, and marine mammals (Easton *et al.*, 2002). Assessing the combined effect of chemicals is extremely complex and often unpredictable; thus all possible effects resulting from interactions need to be considered when assessing risk from exposure to chemicals. These effects include: additivity, where agents are no more and no less effective in combination than they are separately; synergism, where the effectiveness of agents is increased when in combination; potentiation, where the increased effect of a toxic compound acts concurrently with a non-toxic compound; and finally, antagonism, where the effectiveness of agents is decreased when in combination. Though some recent studies suggest there may be cause for concern about the effects of combined exposure to PCBs and MeHg, the results are still contrasting. Interactive effects of PCBs and MeHg have been reported on neuronal calcium regulation and dopamine function in vitro (Bemis and Seegal 1999, 2000), and an additive effect of exposure to the two chemicals in vivo on the rotating rod, a cerebellar motor task has been reported (Roegge *et al.*, 2004). In contrast, there was no evidence of an interaction between the two chemicals on a spatial learning task (Widholm *et al.* 2004). Apparent interactive effects of PCBs and MeHg have also been observed in epidemiological studies (Grandjean *et al.*, 2001; Stewart *et al.*, 2003).

Johansson *et al.*, (2006), investigated possible interactive effects of PCBs and MeHg in AtT20 pituitary cells. Their analysis of data from simultaneous exposures to moderately cytotoxic doses of MeHg and PCB 126 suggested slightly synergistic effects of the toxicants. PCB and MeHg co-exposure effects seem to be dose-dependent, and concomitant exposures to doses that were not cytotoxic by themselves did not induce significant effects on apoptosis or necrosis in the AtT20 cells. A study by Coccini *et al.*, (2007), aimed at evaluating the effects of gestational and lactational exposure to low doses of MeHg and a dioxin-like PCB congener (PCB126), alone and in combination, on muscarinic receptors (MR) in selected brain areas of weanling and pubertal rat pups. There was no evidence of overt toxicity in the dams and pups from any of the treated groups, except for the female pups in the PCB126 + MeHg treated group. MR density was not affected at post natal day (PND) 21 by MeHg or PCB126 administered alone. However, in the co-exposed group, female pups showed a decrease (15%) in MR density. In another study by Costa *et al.*,(2007), binary combinations of MeHg and PCB126 were tested in PC12 rat pheochromocytoma cells and in 1321N1 human astrocytoma cells, to investigate possible interactions between these chemicals. A purely additive effect was found, indicative of a lack of interaction.

V. DIOXINS AND DIOXIN-LIKE PCBs

A. SOURCES IN THE ENVIRONMENT

In this background paper, the term “dioxins” is used to designate the polychlorinated dibenzo-p-dioxins (PCDDs), the polychlorinated dibenzofurans (PCDFs) and the coplanar (“dioxin-like”) polychlorinated biphenyls (PCBs), since these classes of compounds show similar types of toxicity. PCBs mixtures not containing dioxin-like congeners are not considered.

PCDDs and PCDFs are mainly by-products of industrial processes (such as metallurgical processing, bleaching of paper pulp, and the manufacturing of some herbicides and pesticides) but can also result from natural processes like volcanic eruptions and forest fires. Waste incineration, particularly if combustion is incomplete, is among the largest contributor to the release of PCDDs and PCDFs into the environment.

PCBs have been produced commercially for decades starting about in 1920, by direct chlorination of biphenyl. They were produced as mixtures characterized by their chlorine content (e.g. Aroclor, Clophen, Fenclor, or Kanechlor. Due to their unique physical and chemical properties such as non-flammability, stability, high boiling point, low heat conductivity and high dielectric constants, PCBs have been widely used in a wide scale of applications, such as coatings, inks, flame retardants and paints, but the major uses were in electronic appliances, heat transfer systems, and hydraulic fluids, lubricants and dielectric fluids in transformers and capacitors, as well as in a variety of other industrial applications (Afghan and Chau 1989).

Because of the persistent nature of PCBs in the environment many countries decided in the 1970s to ban the use of PCBs in open applications. They may still be in use in closed systems such as capacitors and transformers. However, this use will decrease over time. Today, waste disposal, both of household and industrial waste, is the major source of PCB emissions into the environment.

In general, PCBs are relatively insoluble in water, and the solubility decreases with increased chlorination, while they are freely soluble in non polar organic solvents and biological lipids. PCBs are highly persistent and accumulate within food chains. Among the 209 individual PCB congeners that are theoretically possible, only some of them have a chemical structure similar to dioxin TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), and exhibit toxicological effects mainly, but not only, mediated by activation of the aryl hydrocarbon receptor (Ah receptor), and are thus called dioxin-like PCBs. These congeners, lead to toxicological effects on liver, immune function, reproduction and behaviour similar to those caused by dioxin (TCDD). Dioxin and dioxin-like PCBs can disrupt the endocrine system so that they are called “endocrine disruptors”. These compounds are thought to interfere with thyroid hormone (TH) homeostasis by displacement of hormones from serum transport proteins, altering deiodinase activity and increasing thyroid hormone catabolism via glucuronidation (Hood and Klaassen, 2000).

B. MAIN FOOD SOURCES

Human exposure to dioxin and dioxin-like PCBs is primarily through the diet, with estimates of over 90% of body burden derived from dietary sources and with meat and dairy products as the largest contributors (Charnley and Doull, 2005). These contaminants are also present in fish. However, depending on national or regional food habits and traditions, the actual intake of these chemicals, and the relative intake from different food groups, may vary considerably.

C. HEALTH EFFECTS OF DIOXINS AND DIOXIN-LIKE PCBS

As early as the 1930s, occupational exposure to dioxins and PCBs was reported to cause some acute health effects, such as chloracne, in humans. Workplace exposure limits were established in the early 1940s, and for decades workers continued to manufacture and use PCBs safely. It was not until the late 1960s and afterwards that concern over PCBs in the environment began to rise.

Two significant events involving direct over-exposure of humans to dioxins and PCBs from contaminated foods served to firmly cement the perception of PCBs as environmental health risks in the public's eye. The first of these poisonings occurred in Japan in 1968 (Yusho) and a second similar episode occurred in Taiwan in 1979 (Yu-Cheng). In both cases, rice oil that had been contaminated with thermally degraded PCB-containing heat transfer fluid from leaky equipment during processing was ingested, and many of the individuals consuming the oil (including children) became ill. Afterwards several studies evaluated the consequences of PCB exposure to humans, and it has been shown how dioxins and dioxin-like PCBs caused a variety of adverse health effects. These include cancer and a number of serious non-cancer health effects on the immune system, reproductive system, nervous system, endocrine system and others. The available literature indicates that dioxin-like compounds may induce a wide spectrum of biological responses at the biochemical, cellular and tissue level. Even though the main focus of initial attention on the health effects of dioxin concerned cancer, recent toxicological investigations have focused also on non-cancer effects.

Toxicity in experimental animals

Acute toxicity after exposure to dioxins shows considerable variation among species, with LD50 values ranging from 1 ug/kg bw in the guinea pig to >1000 ug/kg bw in the hamster. Rats and non-human primates have an intermediate sensitivity. Death follows a characteristic wasting syndrome in which animals mobilize their body fat and muscle mass. Atrophy of the thymus is a characteristic effect of exposure to dioxin. In the rat, acute doses greater than 1 ug/kg bw are required to cause thymic atrophy. Atrophy of the spleen is slightly less sensitive and does not occur in all species. The adult testis and ovary have similar sensitivity to that of the spleen (EC Scientific Committee on Food (SCF), 2001).

Liver hyperplasia, fatty infiltration, and necrosis have been observed in a number of species. Liver toxicity is associated with increased serum transaminases and dehydrogenases, and impaired biliary clearance. Altered lipid metabolism results in elevated serum triglycerides and cholesterol, as well as decreased serum glucose levels. Accumulation of porphyrins and proliferative responses are seen at relatively high doses of dioxins (SCF, 2001).

In chicken, the heart and the entire cardiovascular system appear to be very sensitive targets for dioxins, resulting in oedema. Recent studies have demonstrated that the heart is also a target in mammals (EPA, 2006; Lund *et al.*, 2003). The gastrointestinal tract undergoes hyperplasia after toxic doses of dioxins in several species, such as non-human primates. Monkeys also respond to dioxins with squamous metaplasia of the meibomian glands on the eyelids, and the ceruminous glands lining the ear canal (SCF, 2001).

The immune system is also a target for dioxin toxicity in multiple animal species; these chemicals cause suppression of both cell-mediated and humoral immunity. In adult animals, these effects have generally been seen at doses that are also associated with thymic atrophy and other overt signs of toxicity. Perinatal exposure of experimental animals to dioxins resulted in suppression of primary T cell immune functions, with suppression persisting into adulthood.

This suggests that perinatal development is a critical and sensitive period for TCDD-induced immunotoxicity (SCF, 2001; EPA, 2003).

Reproductive effects have been documented in multiple animal species. High doses are associated with infertility and foetal loss. Adverse developmental effects of dioxins, e.g. growth retardation, thymic and splenic atrophy, haemorrhage, and oedemas have been observed in fetuses and neonates of many species. Structural malformations, i.e. hydronephrosis and cleft palate, have been induced in mice. Prenatal doses of dioxins also accelerated tooth eruption in mice and impaired dentine and enamel formation in continuously growing rat incisors (SCF, 2001).

Prenatal exposure to dioxins results in permanent adverse effects on the developing reproductive, immune, and nervous systems of both male and female offspring in rats (reviewed by Larsen, 2006). Male pups demonstrated delayed puberty, altered mating behaviour, and decreased sperm counts. Female pups showed genital malformation consisting of vaginal threads and cleft phallus. These effects were all caused by in utero exposure at gestation day 15 (GD15). A series of studies comparing the magnitude of effects of dosing pregnant rats at various time-points during the gestation period has indicated that the maternal/foetal tissue concentration at the critical window of sensitivity (day 15-16 of gestation) is the key dose metric. Neurobehavioral effects of prenatal exposure to dioxins in rats resulted in changes in locomotor activity and rearing behaviour, deficits in learning, and hearing deficits in the offspring (SCF, 2001; Fattori, 2007). The offspring of rhesus monkey dams with a chronic dietary intake of approximately 0.15 ng/kg bw per day for a total of 4 years had deficits in object learning. Subtle effects on the developing immune system, such as changes in cell surface markers and a permanent suppression of delayed-type hypersensitivity in the offspring have been observed after prenatal doses lower than those inducing atrophy of the thymus in both mice and rats.

The effects of PCBs at the genetic level have been widely investigated (for an extensive review see Shields, 2006). Overwhelming evidence shows that the PCBs are not mutagenic. DNA binding has been reported, although a specific nucleotide adduct has not been identified (Pereg *et al.*, 2002).

The target organ for PCB tumorigenicity in animals is the liver and pathological criteria indicate that the potency of the mixture of PCBs depends on the chlorination, and not all exposures should be considered equivalent. There are, however, many pathological dissimilarities between experimental animal tumors induced by PCBs and human liver cancer. In spite of the morphological appearance of cancer in animals, these lesions do not otherwise display malignant behavior. It should be noted that some methods in animal studies reduce the reliability of extrapolating to human cancer risk, such as exposures that are substantially higher than potential human exposure.

Laboratory animal studies also show that PCBs can act as modifying agents following exposure to known carcinogens, acting as both tumor promoters and inhibitors. On one hand, PCBs have been shown to promote hepatocellular tumors and preneoplastic lesions following ingestion of N-nitrosamines and azo dyes; lung and colon tumors following exposure to N-nitrosamines and 1-nitropyrene; and mammary tumors following exposure to 7,12-dimethylbenz(a)anthracene. In contrast, PCBs inhibit tumorigenesis when animals are treated before carcinogen exposure. Because of this complexity, and the fact that PCBs are not multiorgan initiators, these promotion studies cannot be used to defend the hypothesis that PCBs are a multiorgan carcinogen.

Extensive research over the past quarter century has demonstrated that all major toxic effects of dioxin-like chemicals are mediated by their binding to a soluble intracellular protein, the aryl hydrocarbon receptor (AhR). The AhR's normal function is to regulate transcription of multiple genes that are important in development, physiological function and adaptive responses to xenobiotic chemicals. Dioxin-like chemicals appear to exert their toxicity by deregulating expression of key genes that are under control of the AH receptor. Although the role of AhR in the toxic and biological effects produced by dioxins is well documented, the exact biochemical events and responsible gene products responsible for the adverse effects of these chemicals still remain to be elucidated. Denison and Nagy (2003), reviewed the intracellular mechanisms evoked by AhR activation.

Toxicity in humans

Information on toxic effects of dioxins and PCBs in humans is available from studies of people exposed occupationally, by consumption of contaminated rice oil in Japan (the Yusho incident) and Taiwan (the Yu-Cheng incident), by consumption of contaminated fish and other food products of animal origin, and via general environmental exposures. Health effects that have been associated with exposure to PCBs in humans include alterations in respiratory apparatus, cardiovascular, gastrointestinal, haematological, musculoskeletal systems; liver, thyroid, renal effects; dermal and ocular changes; immunological alterations; reproductive toxicity, genotoxic effects, cancer and neurodevelopmental changes (Van Oostadam *et al.*, 2005; Zoeller *et al.*, 2000; Hennig *et al.*, 2005; Chiu *et al.*, 2004; Miller *et al.*, 2004). In these studies, exposure to PCBs has been reported to result in respiratory tract symptoms, such as cough and tightness of the chest, gastrointestinal effects including anorexia, weight loss, nausea, vomiting, and abdominal pain, mild liver effects, and effects on the skin and eyes, such as chloracne, skin rashes, and eye irritation.

a) Cancer

There are >40 human studies of dioxins and dioxin-like PCB exposure and cancer risk, including individuals with high occupational exposures over long periods of time (i.e., capacitor and transformer workers), evidenced by very high blood levels and histories of PCB-related skin effects. Multiple follow-ups of some cohorts have been undertaken.

Rusiecki *et al.*, (2004), assessed a hospital-based case control study of 266 cases and 347 benign breast disease controls to examine the association of blood serum and adipose tissue concentrations of PCBs with breast cancer but found no clear associations between any of the tumor subtypes and total PCBs. McElroy *et al.*, (2004) examined the association between sport-caught Great Lake fish consumption and breast cancer incidence as part of an ongoing population-based case-control study in that area. They reported that frequency of sport-caught fish consumption was not associated with breast cancer risk, though there might be an increased breast cancer risk for subgroups of women who were young and/or premenopausal. Muscat *et al.*, (2003) reported that among 223 women from New York, the concentration of PCBs was correlated with baseline age and body mass index, but not with cancer stage. The highest PCB concentrations were associated with an increased risk of tumour recurrence.

Prince *et al.*, (2006) examined mortality in a cohort of electrical capacitor manufacturing workers highly exposed to PCBs and re-examined the increased risks for mortality from cancers of the liver and rectum previously observed in the same cohort. Mortality from biliary passage, liver and gall bladder cancer was significantly elevated, but mortality from rectal cancer was not. Among women, mortality from intestinal cancer and from "other diseases of the nervous system and sense organs", which include Parkinson's disease and amyotrophic lateral sclerosis, were elevated. Mortality was elevated for myeloma, particularly among workers employed for

10 years or more. No linear associations between mortality and duration of employment were observed for the cancers of interest. The small numbers of deaths from liver and intestinal cancers, myeloma and nervous system diseases coupled with the lack of an exposure-response relationship with duration of employment, preclude drawing definitive conclusions regarding PCB exposure and these causes of death. In a follow up study by the same authors (Prince *et al.*, 2006b), mortality from melanoma, and rectal, breast, and brain cancers were neither in excess nor associated with cumulative exposure to dioxins and dioxin-like PCBs. Mortality was not elevated for liver cancer, but increased with cumulative exposure. Among men, stomach cancer mortality was elevated and increased with cumulative exposure. Among women, intestinal cancer mortality was elevated, especially in higher cumulative exposure categories, but without a clear trend. Prostate cancer mortality, which was not elevated, increased with cumulative exposure. This study corroborates previous studies showing increased liver cancer mortality, but the authors could not clearly associate rectal, stomach, and intestinal cancers with PCB exposure. This was the first PCB cohort showing a strong exposure–response relationship for prostate cancer mortality.

Ruder *et al.*, (2006) updated mortality through 1998, adding 14 years of follow-up to a cohort study (Sinks *et al.*, 1992) among workers exposed to PCBs in an electrical capacitor manufacturing plant in Indiana. The primary purpose of the study was to investigate the increased risks for brain cancer and malignant melanoma, originally observed in the cohort followed through 1984. Overall mortality was found to be reduced. Non-Hodgkin lymphoma mortality was elevated, and melanoma remained in excess. Brain cancer mortality increased with exposure, and among those working ≥ 90 days, both melanoma and brain cancer were elevated, especially for women. Verkasalo *et al.*, (2004) investigated cancer risk in people living near the River Kymijoki, in southern Finland, heavily polluted with polychlorinated dioxins, which may pose a health threat to local residents, especially farmers. A total of 14,242 cases of cancer was diagnosed among the study cohort between 1981 and 2000. The incidence of total cancer in all residents was very similar to the general population risk. Similarly, when studied by sex, age, or time period, the risk for total cancer differed no more than 3% from the general population risk. There was a subtle increase in the risk for total cancer in those living < 20.0 km and decreases in those living farther away from the Gulf of Finland. Statistically significant risk increases were observed for skin cancers. The incidence of total cancer in farmers living in the study area did not differ statistically significantly from the incidence in all farmers in the country.

Raaschou-Nielsen *et al.*, (2005) conducted the largest prospective study to examine the association between PCBs and organic chlorinated pesticides and breast cancer in postmenopausal women in Denmark, and the first prospective study to use stored adipose tissue in the exposure assessment. They found no risk patterns or statistically significant results for the sum of PCBs or any of the PCB congeners in relation to either all breast cancers or estrogen receptor positive breast cancer. The final results did not indicate that higher organochlorine body levels increased the risk of breast cancer in postmenopausal women. The interpretation of the inverse association for estrogen receptor–negative breast cancer still remains unclear.

Pavuk *et al.*, (2004) reported the results of two studies conducted in the Michalovce district of eastern Slovakia. In a cross-sectional study, they measured serum PCB levels in the general population of the Michalovce district and compared these to levels from a district in eastern Slovakia with expected background PCBs exposure (Svidnik). In a companion ecological study, they determined the cancer incidence over a 10-year period (1985–1994) in each of these two districts, using the eastern Slovakia population as the standard population to calculate standardized incidence ratios. The age-adjusted geometric mean for PCBs was statistically significantly higher in subjects from the Michalovce district for both sexes: 3327.6 versus 1331.4

ng/g of lipid in males, 2751.8 versus 992.2 ng/g of lipid in females. In the ecological study, among males from Michalovce (exposed), but not Svidnik (unexposed), there was an excess of cancer of the tongue, stomach, lung, testis, and kidney, and lower than expected incidence of prostate cancer; in contrast, there was an excess of peritoneal and laryngeal cancer in Svidnik not observed in Michalovce. Among females from Michalovce, but not Svidnik, there was an excess of cancer of the lip, stomach, and lung; in contrast, there was an excess of kidney and thyroid cancer in Svidnik not observed in Michalovce. As conclusion, the authors claimed that high environmental exposure to PCBs in the Michalovce district might be associated with higher rates of certain cancers, particularly stomach and lung cancer.

There are several occupational groups where the all-cause cancer mortality has been found not to be increased and, in some cases, decreased for individual cancers (Kimbrough *et al.*, 2003; Mallin *et al.*, 2004; Ruder *et al.*, 2006). Taken together, these reports fail to show consistently increased death rates either for all causes of death, cancer deaths, or any individual cause of death, when compared with the expected number for the general population. Commonly, cohort studies investigating multiple cancer rates, find a statistically significant positive association with a particular cancer, at a rate of 5 associations per 100 examined, because of a multiple comparison issue. Thus, in the evaluation of causality, both consistency and dose-response relationships must be shown.

The largest study assessing risks related to PCB exposure to date was published by Kimbrough *et al.*, (2003). There were 7,075 PCB-exposed capacitor workers studied with 235,984 person-years of observation and 1,654 deaths. The workers were studied in a number of different ways, providing evidence of internal consistency. The study found no associations with cancer and all cancer-combined mortality was actually decreased. This study had the most power and used a 3-month entry criteria that is more relevant for causation assessment compared with most of the other studies that included workers with shorter work times. Other advantages of this study were that it had excellent follow-up, uncontested use of large amounts of PCBs in the two plants, and classification of exposure-potential by job.

Schwarz and Appel, (2005) summarized some of the mechanistic aspects underlying the carcinogenic effects of dioxins, furans, and dioxin-like PCBs. TCDD and the other polyhalogenated dibenzodioxins, dibenzofuranes, and dioxin-like PCBs are not directly genotoxic. Most researchers therefore agree that the carcinogenicity of these agents is mediated via sustained aryl hydrocarbon receptor (AhR) signalling, leading to tumor promotion. It has recently been shown that hepatocarcinogenesis is enhanced in transgenic mice harbouring a constitutively active AhR mutant, which demonstrates the oncogenic potential of the activated AhR (Moennikes *et al.*, 2004).

Any quantitative estimation of risk associated with current dioxin and PCB exposure levels requires low dose extrapolation of experimental data. When interpreting results from animal toxicity studies for purposes of assessing human relevance, one must consider a number of important factors, such as major physiological and metabolic differences between the laboratory animals used in testing and humans; variation within the human population, including differences in age, sex, and individual susceptibility; and the very large doses of the agent administered to laboratory animals. Toxicology tests are specifically designed to detect and elicit adverse effects, and for this reason, high dose levels, unrealistic for humans, are employed. These doses invariably exceed the level of realistic human exposures, often by hundreds to thousands of times. Some cancer classification schemes are not reflective of the true risk to humans because of the vast difference in exposures between laboratory animals and humans.

Thus, while PCBs can cause tumors in laboratory animals, the relevant questions are at what dose level and under what types of exposure conditions (animals are exposed daily for their lifetimes) and whether these conditions realistically reflect human environmental exposures. In a recent noteworthy action, the EPA lowered the cancer slope factor for PCBs, meaning that EPA now considers the carcinogenic potential to be lower than previously thought, a decision based on additional testing of those congeners originally assessed for carcinogenicity (US Environmental Protection Agency, 2003).

b) *Diabetes*

Some studies have investigated associations between dioxins and diabetes. Lee *et al.*, (2006) studied the association of dioxins with diabetes in the 1999–2002 National Health and Nutrition Examination Survey (NHANES) and found a strong dose–response relationship. The results of Everett *et al.*, (2007) were similar to those of Fierens *et al.*, (2003), who found an association of coplanar PCBs with diabetes among 115 men and 142 women in Belgium. In the study by Everett *et al.*, (2007), dioxin-like PCBs were significantly associated with undiagnosed diabetes. Longnecker (2006), suggested an association between PCBs and diabetes found in a prospective study (Vasiliu *et al.*, 2006) was due to differences in metabolism and excretion.

c) *Endocrine System*

Over the past decade there has been an increasing focus on the effects of environmental contaminants on human endocrine systems, with increasing evidence from animal and in vitro studies, that the thyroid is vulnerable to endocrine-disrupting effects. Chemicals may interfere with thyroid homeostasis through many mechanisms of action (at the receptor level, in binding to transport proteins, in cellular uptake mechanisms or in modifying the metabolism of thyroid hormones (THs)). Several chemicals have a high degree of structural resemblance to the THs thyroxine (T4) and triiodothyronine (T3), and therefore interfere with binding of THs to receptors or transport proteins.

Among the wide range of health effects induced by dioxins and dioxin like-PCBs, their action on the endocrine system is of particular interest. Concern that the thyroid hormone system may be important in dioxin-like PCB mechanisms of toxicity stems mainly from two important types of observations: a) extensively corroborated findings in experimental animals reported that exposure to PCBs in utero and/or during early development (through breast milk) can deplete levels of circulating thyroid hormone in the foetus or neonate, which may effectively give rise to a hypothyroid state during development. b) the recognition of the importance of thyroid hormones in normal development of the brain, as evident from neurodevelopmental disorders and deficits associated with hypothyroidism. The latter are typified by iodine deficiency (endemic cretinism), which can produce a wide range of neurodevelopmental deficits, including auditory, motor, and intellectual deficits.

Subclinical hypothyroidism in adults is often diagnosed only by chance because of subtle symptoms, but on the other hand growth and development in foetal life and childhood is highly dependent on normal levels of THs. Particularly during gestation, normal levels of THs are crucial for the development of the central nervous system. This critical phase may be vulnerable to even subtle effects of synthetic chemicals on foetal and maternal TH levels. Such developmental deficiencies may not be identifiable until later in life (Morreale de Escobar *et al.*, 2004). PCBs, especially the hydroxylated metabolites, have a high degree of structural resemblance to T4. The effect of PCB exposure on peripheral TH levels is well documented by studies in laboratory animals. One of the most consistent findings is that PCB exposure decreases the levels of circulating THs, especially T4 (van der Plas *et al.*, 2001; Hallgren *et al.*, 2001; Hallgren and Darnerud, 2002). Histopathological changes of the thyroid, indicative of

hyperactivity, were found after PCB exposure (Hallgren and Darnerud, 2002; Kilic *et al.*, 2005; Fattori, 2007), and there is substantial evidence that perinatal PCB exposure decreases THs in animal models (Meerts *et al.*, 2002, 2004; Donahue *et al.*, 2004).

Multiple studies of PCB exposure and effects have been carried out in human populations, the majority of which raised concern that environmental levels of PCBs may alter thyroid homeostasis. In adults, adolescents and children from highly PCB-exposed areas the concentration of PCB in blood samples correlated negatively to levels of circulating peripheral THs (Hagmar *et al.*, 2001; Persky *et al.*, 2001), few studies demonstrated a positive correlation between PCB exposure and TSH, and other studies found no associations (Hagmar *et al.*, 2001b; Bloom *et al.*, 2003). The thyroid volume is another endpoint for thyroid function, which is rarely used in human toxicological studies. In adults from a PCB-polluted area the thyroid volume, assessed by ultrasound, was found to be significantly larger than in 'non-exposed' subjects. The highest thyroid volumes were clustered among 5% of subjects with PCB levels above 10 000 ng/g lipids (Langer *et al.*, 2003).

Halogenated aromatic hydrocarbons (dioxins and PCBs) may compete with binding to the TH receptors and transport proteins like transthyretin (TTR), possibly interfering with TH transport and metabolism (Meerts *et al.*, 2002; Purkey *et al.*, 2004). Metabolites and derivatives of PCBs, had remarkably stronger binding affinity than their parent compounds, indicating an important role for hydroxylation and halogenation in thyroid toxicity. TTR is the major TH transport protein in the human brain, presumably playing an essential role in the determination of T4 levels in the extracellular compartment, which is independent of the T4 homeostasis in the body. Furthermore, TTR may mediate the delivery of T4 across the blood–brain barrier and the maternal to foetal transport through the placenta. Thus, dioxin- like compounds bound to TTR may be transported to the foetal compartment and foetal brain, and be able to decrease foetal brain T4 levels (Ulbrich and Stahlmann, 2004). Dioxin- like PCBs can change TH-stimulated gene transcription, but it is still not clear through which mechanisms these changes are induced. PCBs alter the expression of TH-responsive genes by inhibiting the binding of T3 to the thyroid receptor (TR) (Kitamura *et al.*, 2005). Oligodendrocyte development and myelination are under TH control, as well as the extension of Purkinje cell dendrites, which is essential for normal neuronal circuit formation (synaptogenesis) and subsequent behavioral functions. In a study of perinatal exposure, dioxin-like PCBs affected the development of white matter in rat pups by mimicking some, but not all, of the effects of hypothyroidism on white matter, indicating that PCBs may partly affect the neurological development through thyroid disruption (Sharlin *et al.*, 2006).

d) *Developmental Neurotoxicity*

One in every six children has a developmental disability and in most cases these disabilities affect the nervous system (Grandjean and Landrigan, 2006). The most common neurodevelopmental disorders include learning disabilities, sensory deficits, developmental delays, and cerebral palsy. Some experts have reported that the prevalence of certain neuro developmental disorders - autism and attention deficit and hyperactivity disorder (ADHD), in particular- might be increasing. Evidence has been accumulating over several decades that industrial chemicals can cause neurodevelopmental damage and that subclinical stages of these disorders might be common. Genetic, environmental, and social factors interacting in complex ways are important determinants of cognitive development and behavior. None alone is sufficient to explain populationwide increases in neurodevelopmental abnormalities.

Dioxin-like PCBs also reduce circulating thyroxine concentrations and could selectively damage the cerebellum, via a thyroid hormone dependent mechanism. Thyroid hormones are important for brain development (Zoeller *et al.*, 2002), and in particular, for cerebellar development for

various reasons, including the late developmental timeline of the cerebellum compared to other brain regions (Rodier, 1980), its high expression of thyroid hormone receptors (Koibuchi *et al.*, 2003), and its sensitivity of gene expression to alterations in thyroid hormone status (Koibuchi *et al.*, 2003). Moreover, although the cerebellum is traditionally assigned the role of balance and coordination of voluntary movement, it is now believed that it may play a much larger integrative role in the CNS than previously believed, including cognitive functions and locomotor activity control (Roegge *et al.*, 2006). This makes this specific brain region absolutely relevant for understanding pathologies like Attention Deficit Hyperactivity Disorder (ADHD) and autism among others. A number of studies have suggested that perinatal perturbation of thyroid function by food contaminants, such as dioxin-like PCBs, is one of the environmental risk factors for ADHD (Jacobson and Jacobson, 2003; Kimura-Kuroda *et al.*, 2007; Fattori, 2007).

It is important to note that recent toxicological research on dioxins has focused on deleterious effects that may not become clinically evident for some months, or even several years, after exposure. This makes the establishment of causal relationships between chemical exposure and adverse neurological effects difficult to pinpoint. Recent studies are in fact emerging showing how exposure to a toxic stimulus can cause "imprinting," a process by which early environmental factors may permanently alter the gene expression profile of an organism (for extensive review see Costa *et al.*, 2004). The consequences of such imprinting might not manifest themselves until adulthood. This period during which the individual may manifest no evidence of toxicity is referred to as a silent period. Silent toxicity can be defined as persistent morphological and/or biochemical injury that remains clinically unapparent unless unmasked by experimental or natural processes. Silent toxicity has been compared to the process of carcinogenesis, where chemical exposure and cellular damage occurs years, if not decades, before clinical manifestations of the disease are apparent. In fact, the identification of perturbations of developmental processes by environmental contaminants has led the recognition that a developmental insult can initiate a cascade of alterations that may not be detected structurally or functionally until much later in life. These effects may be manifested at a time much removed from the critical developmental window when the exposure occurred. The developmental effects may be manifested as persistent deficits, developmental delays, or transient deficits. Developmental delays and transient deficits in these developmental processes and ontogeny of function may have more insidious consequences later in life. These two types of effects may result from the continued growth and differentiation of the nervous system resulting in apparent compensation.

Many possible hypotheses have been proposed to explain the delay between exposure and clinical expression of neurotoxic injury. One possibility is that toxic exposure results in lethal injury to a subpopulation of neuronal cells, but the total number of cells lost is insufficient to immediately compromise functions, owing to a reserve provided by surviving cells. The deficit would only be unmasked by exogenous influences (stress, disease, additional chemical exposure) or by the natural aging process. A second possibility is that toxic exposure may result in sublethal injury to neural elements, which leads to progressive, incremental loss of function. The organism will initially compensate for the mild deficit, but the functional reserve and plasticity of the brain would, with time, be overcome, and loss of function would appear. Such apparent recovery can in fact be reversed during aging, when the compensatory ability of the nervous system may be significantly reduced. However exactly how aging triggers activation of these silent genetic changes is at present unknown.

The concept of silent damage and the hypotheses on possible underlying mechanisms may also find a place in developmental toxicity. The concept that adult disease may have a foetal origin has been introduced by David Barker and is known as the Barker hypothesis (Godfrey and

Barker, 2001). Exposure to environmental agents may cause damage or alter developmental programming, whose resulting functional deficits become apparent only later in life.

e) Parkinson's disease

Epidemiological studies have established a role of the environment in the etiology of Parkinson's disease (PD), and although specific environmental contaminants that contribute to the incidence of PD have yet to be identified, recent studies have implicated dioxins exposure as a possible risk factor. A recent mortality study of 17,000 workers occupationally exposed to PCBs revealed an increased incidence of PD in female subjects (Steenland *et al.*, 2006). PCB exposure is known to pose numerous toxic effects in the central nervous system, resulting in motor and cognitive deficits (reviewed by Faroon *et al.*, 2001), and a common finding, among others, has been a significant reduction of brain dopamine (DA) levels following exposure to PCBs. Several *in vitro* studies have demonstrated that individual congeners, congener mixtures, as well as extracts from PCB-contaminated Great Lakes fish produce a reduction in DA. While the mechanism of DA reduction is unclear, it has been postulated, based on cell culture experiments, that decreased DA levels are a result of inhibition of two enzymes involved in the synthesis of DA (tyrosine hydroxylase (TH) and L-aromatic acid decarboxylase (L-AADC)). Richardson and Miller (2004) have reported a significant decrease in striatal DA following high-dose, acute exposure of rodents to Aroclor 1016, 1254, or 1260. In addition, Seegal (2003) has reported decreases in DA in the striatum of non human primates, as well as loss of dopaminergic cells in the substantia nigra, both of which are hallmark features of PD.

To date, studies with PCBs have focused on loss of striatal DA or nigral DA neurons as the toxicological end points. Recent studies have additionally shown that PCBs affect the dopamine transporters (DATs), important in the handling and packaging of DA (Gainetdinov and Caron, 2003; Richardson and Miller, 2004). DA that has been released into the synapse following neurotransmission is removed through reuptake into the presynaptic terminal by the DAT. The recycled and newly synthesized DA is transported into vesicles by the vesicular monoamine transporter 2 (VMAT2), where it is made available for release. Several studies have determined the importance of DAT and VMAT2 in maintaining proper homeostasis of the DA system. Recently, Caudle *et al.*, (2006), utilized an environmentally relevant exposure to PCBs to identify early signs of damage to the DA system. These authors used a dosing regimen, which resulted in PCB levels similar to those found in human brain samples, and did not cause overt degeneration to the DA system, as shown by a lack of change in striatal DA levels or tyrosine hydroxylase levels. However, they did observe a dramatic dose-dependent decrease in striatal dopamine transporter (DAT) levels. The observed reductions appear to be specific to the DAT populations located in the striatum, as no change was observed in other dopaminergic brain regions or to other neurotransmitter transporters present in the striatum. These changes demonstrated a marked disruption of nigrostriatal DA function in the absence of overt toxicity and may represent an early event in PCB-induced DA neuron degeneration. Caudle *et al.*, (2006) proposed that the prolonged inhibition of VMAT2 and DAT by PCBs leads to altered DA compartmentalization and thereby increased oxidative damage. This was followed by downregulation of DAT, and to a lesser extent, VMAT2. Together, these changes decreased the recycling of DA, which over time should result in reduced striatal DA content. The prolonged disruption of DA homeostasis was likely to increase the vulnerability of the DA neuron and ultimately result in a higher degree of cell death. These data provided a plausible mechanism by which PCBs damage the nigrostriatal DA system and lead to an increased incidence of PD.

Oxidative stress (OS) has been hypothesized as a contributing factor in the development of several neurodegenerative conditions, including Parkinson's disease (Gao *et al.*, 2003; He *et al.*, 2003; Sherer *et al.*, 2003). Since the role played by reactive oxygen species (ROS) in PCBs-

induced neurotoxicity remains unclear, Lee and Opanashuk, 2004, tested the hypothesis that PCB exposure compromises dopamine neurons by stimulating ROS production. In this study, the direct toxicity and oxidative stress response following PCB exposure were examined. They evaluated these effects both in MN9D dopamine cells and primary mesencephalic cultures. PCBs induced a time- and concentration-dependent increase in ROS production, which preceded cytotoxicity. Whereas intracellular glutathione (GSH) depletion exacerbated the effects of PCBs, antioxidant pretreatment attenuated ROS production and cell death. Coincident alterations in antioxidant defence enzymes also accompanied ROS production. Furthermore, PCBs produced concentration-dependent reductions in intracellular dopamine levels and elevated dopamine turnover leading to the conclusion that sub lethal PCB concentrations activate an oxidative stress-related pathway, which potentially disrupts dopamine neuron function.

D. RECENT EPIDEMIOLOGICAL STUDIES IN VARIOUS COUNTRIES

United States. Native American communities are believed to be at high risk of dioxin exposure, since their tradition and culture emphasize the interdependence of humans and the environment and favors consumption of local fish and waterfowl. Fitzgerald *et al.*, (2004), examined how dietary, occupational, and residential exposures to dioxins and dioxin-like PCBs impacted the concentration of these chemicals in the serum of pregnant Mohawk women at Akwesasne, a Native American community. The results indicated a significant decline in local fish consumption from an annual mean of 31.3 meals more than 1 year prior to pregnancy to an annualized mean of 11.7 meals during pregnancy. This change was reported as result of the advisories issued against consumption of local fish by pregnant and nursing women of childbearing age. The geometric mean concentration of total PCBs in the serum was 1.2 ppb, a level that is similar to that in other studies of women with no unusual exposures to PCBs, suggesting that the consumption of other local foodstuffs, occupation, residential soil, and ambient air were not significantly contributing to serum PCB concentrations in this population. Three years later, the same authors presented a study conducted to address the question of how fish consumption, occupation, and outdoor air affected serum dioxin-like PCB concentrations and congener patterns among men from the same Native American population (Fitzgerald *et al.*, 2007). The results indicated that serum PCB concentrations were positively associated with cumulative lifetime exposures to PCBs from local fish consumption and occupation. The same authors (Fitzgerald *et al.*, 2007b) also assessed the impact of dietary and residential exposure on dioxins and related compounds body burdens among older men and women living along contaminated portions of the upper Hudson River. This study was part of an ongoing project designed to evaluate the neuropsychological effects of PCBs. The focus was upon older persons because PCBs may exacerbate the neurodegenerative processes associated with aging (Schantz *et al.*, 1999, 2001). Serum PCB concentrations increased with cumulative lifetime exposure to PCBs from Hudson River fish consumption.

Karmaus and Zhun (2004) identified 168 offspring born after 1968, with maternal exposure to PCBs. Birth weight of the offspring from mothers who had the highest PCB levels ($\geq 25 \mu\text{g/L}$) significantly reduced by approximately 500 g, adding to the body of evidence that high maternal serum PCBs concentration may reduce the birth weight in offspring. In another study by Buck *et al.*, (2003), 2,716 infants born to participants of the New York State Angler Cohort Study were studied with respect to duration of maternal consumption of contaminated fish from Lake Ontario and gestational age and birth size. No adverse effects were found. Weisskopf *et al.*, (2005) examined whether foetal exposure to PCBs and dichlorodiphenyl dichloroethylene (DDE) by way of maternal Great Lakes fish consumption was a risk factor for decreased birth weight.

They found that fish-consuming mothers had higher serum PCBs and DDE concentrations, but only increased DDE was associated with lower birth weight.

A study by Choi *et al.*, (2006) was undertaken to assess whether residential proximity to PCB contaminated site or consumption of locally produced foods were associated with higher cord serum PCB levels among infants of mothers living near the New Bedford Harbor in southeastern Massachusetts, an area highly contaminated with PCBs as a result of waste disposal from local industry from the 1940s until 1977. Maternal consumption of meat and local dairy products was associated with higher PCB levels. Infants born later in the study had lower PCB levels, likely due to temporal declines in exposure and site remediation in 1994–1995.

Canada. Dellaire *et al.*, (2002) described the time trends of organochlorines, including PCBs, in umbilical cord plasma of newborns from the lower north shore of the St. Lawrence River (Québec, Canada). The results showed a steady decrease of the mean concentrations for all groups of contaminants between 1993 and 2000.

Several Canadian epidemiological studies investigated the Inuit populations, as their diet is mainly based on fish. It is well known that Inuit children suffer from a high incidence of respiratory infections, and many authors have identified high rates of ear infections and lower respiratory tract infections in Inuit populations (Banerji *et al.*, 2001; Curns *et al.*, 2002; Holman *et al.*, 2001; Koch *et al.*, 2002). To clarify the possible link between prenatal exposure to dioxins and infections in this population, Dellaire and colleagues have reported results of dioxins and PCB concentrations in umbilical cord blood and incidence rate of acute respiratory tract infections in Inuit children (Dewailly *et al.*, 2000; Dellaire *et al.*, 2004; Dellaire *et al.*, 2006). In a cohort of 98 breast-fed infants < 1 year of age recruited in 1989–1990, the authors first observed that infants with higher perinatal exposure to PCBs through breast-feeding had a higher prevalence of recurrent otitis media compared with that of infants in the lowest exposure group (Dewailly *et al.*, 2000). In a second cohort of 199 infants < 1 year of age, they found that the incidence rates of ear infections and lower respiratory tract infections were positively associated with dioxin-like compounds concentration in maternal blood (Dellaire *et al.*, 2004). In the third study, a cohort of 343 preschool children of Nunavik born between 1993 and 1996 was studied to identify an association between prenatal exposure to PCBs and rate of acute respiratory infections during the first 5 years of life (Dellaire *et al.*, 2006). The authors reviewed the medical charts of 343 children from 0 to 5 years of age and evaluated the associations between PCB concentrations in umbilical cord plasma and the incidence rates of acute otitis media and of upper and lower respiratory tract infections. They found that, on a lipid basis, the geometric mean concentration of the sum of PCBs in cord blood was 323.5 µg/kg.

In 1995, Ayotte and co-workers initiated an Inuit Cohort Study to investigate adverse neurodevelopmental effects induced by developmental PCB exposure in Inuit infants from Nunavik. For cultural and economic reasons, the Inuit from Nunavik (Arctic Québec, Canada) rely heavily on marine foods for their subsistence, and their high consumption of sea mammal fat (in particular, ringed seal and beluga), made Inuit women display a mean total PCBs concentration in breast milk exceeding that of southern Québec women by a factor of seven. Ayotte's article of 2003 (Ayotte *et al.*, 2003) was the third in a series reporting results from this epidemiological study. To assess prenatal exposure in this study, the authors measured concentrations of 14 PCB congeners and 11 chlorinated pesticides in maternal plasma, umbilical cord plasma, and breast milk samples. Postnatal exposure was evaluated by quantifying PCBs in plasma samples from 6-month-old infants. PCB congeners were detected in more than 70% of maternal and infant biological samples. The highest concentrations were found in breast milk, followed by maternal plasma, cord plasma, and infant plasma. Mean PCB plasma lipid concentration in infants who

were breast-fed for more than 3 months was 4.3-fold greater and 6.6-fold greater, respectively, than those of infants who were breast-fed for 3 months or less and never breast-fed infants.

To provide more data on the long term consequences of exposure to environmental contaminants on neuromotor functions in children, Despres *et al.*, (2005) set out to investigate neuromotor effects in preschool Inuit children exposed to some environmental neurotoxicants including PCBs. They evaluated neurological status, reaction time, alternating and pointing arm movements and balance in different conditions. In this cohort of preschool-aged Inuit children, the authors did not find any adverse effects of prenatal exposure to PCBs on the neurological status, gross motor functions or pre-clinical motor signs assessed (tremor, sway oscillations, reaction time, alternating and pointing movements). Previously, Chen and Hsu, (1994), working with a group of 7- to 12-year old children born to PCB poisoned Taiwanese mothers, reported no anomalies with the standard neurological examination, but soft neurological signs, such as mirror movements, poor finger-thumb opposition and choreiform movements were observed with increased PCB exposure. In the Despres *et al.*, (2005), cohort, finger-thumb opposition was not assessed but mirror movements were measured in alternating movements, and choreiform movements would have been detected with tremor tests. They did not find any such adverse effects with prenatal exposure to PCBs and chlorinated pesticides. Taiwanese children were exposed to much higher PCB concentrations than those in the Inuit cohort. The only significant association with exposure to PCBs was observed in larger transversal sway oscillations in balance condition. Despres *et al.*, (2005), concluded that no adverse effects were observed on either gross motor function or neurological status in preschool Inuit children exposed to environmental contaminants such as PCBs through consumption of traditional foods.

The Netherlands. Soechitram *et al.*, (2004) conducted a study with the objective of assessing PCB levels in mothers and children at birth and to determine the transplacental transfer of PCBs. PCB concentrations in maternal plasma ranged from 2 to 293 ng/g lipid, while in cord plasma they ranged from 1 to 277 ng/g lipid, approximately 30% of the levels found in the mother. These results indicate that PCB levels in the Netherlands seem to have declined very little in the past 10 years.

A cohort study by Vreugdenhil *et al.*, (2002), evaluated the effects of perinatal exposure to environmental levels of PCBs and dioxins on childhood play behavior and whether the effects showed gender differences. Higher prenatal exposure to PCBs was associated with less masculinized play behavior in boys and with more masculinized play behavior in girls. Effects of prenatal exposure to dioxins were seen on feminine play behavior. In boys as well as in girls, higher prenatal dioxin levels were associated with more feminized play behavior. Childhood play behavior shows marked sex differences and is likely to be influenced by the prenatal steroid hormone environment. The authors suggested that these results might indicate behavioral effects of steroid hormone imbalances early in development, related to prenatal exposure to PCBs and dioxins, their metabolites, and/or related compounds.

Weisglas-Kuperus *et al.*, (2004) reported on the immunological effects of perinatal environmental exposure to PCBs and dioxins in Dutch children from pre-school to school age. To examine whether PCBs and dioxins were associated with immune changes in healthy Dutch preschool children and if such effects persisted into later childhood, the authors investigated perinatal exposure to these chemicals in 167 Dutch children of school age. A higher postnatal PCB exposure was associated with a higher prevalence of recurrent middle ear infections and a higher prenatal PCB exposure with less shortness of breath (with wheeze), as assessed by parent questionnaire. These data indicate that, subtle health effects may occur from environmental levels of these man-made chemicals.

Belgium. At the end of May 1999, Belgium was the scene of a major food crisis due to the contamination of animal feed with about 40–50 kg of PCBs and almost 1 g of PCDDs and PCDFs. The aim of the study by Debacker *et al.*, (2007), was to investigate whether the contamination had caused significant changes in the plasma PCDD/Fs levels of people, who agreed to donate a second blood sample after the 1999 PCB/Dioxin incident. Results showed that the total plasma dioxins level had significantly decreased between 1998 and 2000 (geometric mean: from 445 to 417 pg/g fat), but on the contrary, two PCDF congeners exhibited a slight but significant increase: 2,3,4,7,8-PeCDF increased from 14.5 pg/g fat in 1998 to 17.9 pg/g fat in 2000 whereas 1,2,3,7,8-PeCDF increased from 0.004 to 0.006 pg/g fat. The other congener concentrations remained unchanged between 1998 and 2000. However, no change in total toxicity was observed between 1998 and 2000: it amounted to 22.9 pg TEQ/g fat in 1998 (range: 0.3–93.2 pg TEQ/g fat) and to 23.1 pg TEQ/g fat in 2000 (range: 2.0–74.0 pg EQ/g fat). The authors concluded that, the 1999 PCB/dioxins incident was traceable in the plasma profiles (rise of the two specific PCDF congeners), but comparison of the results for both years indicated that the changes were too small to cause an adverse public health effect.

Slovakia. The effects of long-term exposure to PCBs on developmental dental defects of deciduous and permanent teeth in children were evaluated in eastern Slovakia, where PCBs from a chemical plant contaminated the surrounding district. Jan *et al.*, (2007) found that the proportion of teeth with different types and extensions of developmental enamel defects correlated with serum PCB concentration. The proportion of deciduous teeth affected with enamel defects was significantly higher in higher exposed children, according to their serum PCB concentration. The proportion of permanent teeth affected with any enamel defect was significantly higher in higher exposed children. Furthermore, the extent of the enamel defects was also greater.

In the former Czechoslovakia, an outbreak of occupational poisonings by dioxins occurred between 1965 and 1968 in a chemical plant, where herbicides based on 2,3,5-trichlorophenoxyacetic acid were produced. About 350 workers were exposed, 80 of whom became ill. In 1968, the plant was closed. This cohort has been under surveillance and a recent follow-up was performed in 2003–4, about 35 years after exposure (Urban *et al.*, 2007). They reported the results of the examinations targeted at the nervous system with the aim of contributing to the discussion on whether or not dioxins could induce any damage to the nervous system. The estimated mean concentration of dioxins at the time of exposure was about 5000 pg/g of plasma fat. Only 15 subjects from the original cohort remained available for the recent follow-up in 2004. All were men, mean age 60 years. The 2004 mean dioxins plasma concentration was 128 pg/g. Nine patients showed clinical signs of polyneuropathy: diminished sensation to touch and pain in a stocking-glove distribution, diminished vibration sense, bilaterally diminished or lost ankle and/or knee jerks. Neurasthenic syndrome (cephalea, fatiguability, emotional lability, memory disturbances, etc.) was present in eight patients. The authors found significant correlations between the plasma concentration of dioxins and the number of errors in the Category Test (new problem solving, concept formation, judgment, and abstract reasoning), which is a part of the Halstead–Reitan Neuropsychological Battery, as well as the percentage of non-perseverative errors in the Wisconsin Card Sorting Test. Additionally, visual-evoked potential was abnormal in five cases, electroencephalography showed a low-voltage record in four cases, and nerve conduction studies were abnormal in three patients. This nerve abnormality corresponded to a polyneuropathic pattern with a slowing of conduction velocity on the sural nerve. All three patients showed clinical signs of polyneuropathy as well.

Urban *et al.*, (2007) concluded that: in the group of persons with severe and protracted exposure to dioxins about 35 years ago, a high plasma concentration could still be found. Both clinical and neurophysiological examinations showed abnormalities compatible with a mild toxic

encephalopathy and/or polyneuropathy. The results of this, as well as of previous studies on the same group, supported the hypothesis that dioxins can induce chronic damage to both peripheral and central nervous systems.

Germany. In the South German Federal State of Baden-Wuerttemberg, an environmental health surveillance system was established in 1992/1993, and results were recently presented by Link *et al.*, (2007). The aim of the survey was the detection of regional differences and the identification of time trends concerning the body burden, as well as health effects caused by environmental factors, including dioxins. Four study regions (two larger cities, one small city, and one rural area) were designated in order to get information about the body burden of persistent chemicals (toxic metals and chlorinated compounds) in children and about lung function, frequency of respiratory diseases, and allergies. From 1993 to 2003, blood concentrations of dioxins compounds decreased 2 to 4-fold. Slightly lower concentrations could be seen in children from the municipal population of Mannheim compared to other regions. Breast feeding was associated with considerably higher concentrations of PCBs and most other chlorinated compounds. Static and dynamic lung function parameters showed no differences between the investigated areas. No time trend was observed in the prevalence of respiratory diseases and allergies, except for pertussis, which showed a decrease in 2002/2003, probably due to an increase of vaccination rates. In addition, the prevalence of atopic sensitization against aero allergenes remained unchanged at about 35% during the observation period. Overall, these results showed that the reduction of chlorinated compounds in industrial and traffic emissions during the last decades has resulted in a reduction of children's body burden of many of these compounds.

Italy. The Seveso accident of 1976 exposed a large population to dioxin, and resulted, mostly among children, in one of the largest ever-reported outbreaks of chloracne, the typical skin disorder due to halogenated-hydrocarbon compounds. Approximately 20 years after the accident, Baccarelli *et al.*, (2005), designed a case-control study to collect exposure, epidemiological and clinical data to investigate the association between dioxins and chloracne. They reported data on (a) the health status of chloracne subjects and controls from the same area; (b) possible determinants of individual's dioxin levels and susceptibility to dioxin dermatotoxicity; and (c) dioxin-chloracne dose-response relationship and the effect of age on dioxin disposition. Current plasma dioxins ranged from background levels to more than 10 ppt in 78 of the 293 subjects with adequate plasma samples. Proximity of primary residence to the site of the accident was a strong determinant of elevated dioxin levels. Women had higher plasma levels than men, and occurrence of elevated levels increased with increasing body mass index. Similarly, subjects who had eaten home-grown poultry or livestock had higher odds of elevated plasma dioxin. Subjects who had direct experience of the accident (i.e. saw or smelt the toxic cloud, heard the explosion, experienced eye/throat irritation or itching of the skin), and those who recalled the details of the accident (e.g. they could correctly remember the date and or the time of the accident) had higher dioxin plasma levels in the analyses adjusted by age and sex. On the other hand, lower plasma levels were found among residents of the study area who were reported to have been on vacation at the date of the accident. Elevated plasma dioxins were associated with chloracne, with the risk being higher in subjects younger than 8 years at the time of the accident and, contrary to previous hypotheses, did not increase at onset of puberty or in teenage. Baccarelli *et al.*, (2005), concluded that, 20 years after the Seveso accident, dioxin levels were still elevated in exposed individuals, particularly in females, in subjects who had eaten home-grown animals, and in individuals of older age, higher body mass index and residence near the accident site. Plasma dioxin levels were strongly associated with chloracne. This association was modified by age and pigmentation characteristics, possibly reflecting an increased sensitivity to chloracnegenic factors or differential dioxin clearance. Dioxin toxicity in chloracne subjects appeared to be confined to the acute dermatotoxic effects.

Zambon *et al.*, (2007), evaluated the risk of sarcoma in relation to the environmental pollution caused by dioxins emitted by waste incinerators and industrial sources of airborne dioxin. The study population lived in a part of the Province of Venice, where a population-based cancer registry (Veneto Tumour Registry) has been active since 1987. The results of this research clearly showed a significant increase in the risk of sarcoma, correlated both with the level and the length of environmentally modelled exposure to dioxin-like substances. In fact, the risk of developing a sarcoma was 3.3 times higher among subjects of both sexes, with the longest exposure period and the highest exposure level. A significant excess of risk was also observed in women and for both sexes for cancers of the connective and other soft tissues,.

Japan. In a recent study, Nagayama *et al.*, (2007), examined the effects of prenatal exposure to PCDDs, PCDFs, dioxin-like PCBs and their main metabolites on the incidence of congenital hypothyroidism (cretinism). Concentrations of these organochlorine compounds in the breast milk of mothers, which were considered as the indicator of prenatal exposures, were around two times higher in the cretinism group than in the normal group.

Five years after the outbreak of Yusho, a follow-up survey of dioxin concentrations in the blood of patients was begun. Recently, Todaka *et al.*, (2007) measured the concentrations of PCDDs, PCDFs, and dioxin-like PCBs in blood collected from 279 Yusho patients living in Japan, 92 Yusho-suspected persons living in Japan in 2002, along with 127 normal controls living in Fukuoka Prefecture, whose ages were similar to those of the Yusho patients, and compared the concentrations of these compounds among the groups. The total TEQ concentrations of these chemicals in the blood of Yusho patients and Yusho-suspected persons were 161.4 and 51.2 pg TEQ/g lipid, respectively, and these concentrations were 3.5 and 1.1 times higher than those in normal controls, respectively. In Yusho patients, PCDFs contributed about 65% to the total TEQ concentration. These findings indicated that Yusho patients even now, more than 34 years after the outbreak of Yusho, have much higher concentrations of dioxins in their blood than do unaffected persons.

Taiwan. In 1979, the Yucheng (oil-disease in Chinese) incident occurred in central Taiwan, involving approximately 2000 victims, due to ingestion of rice oil contaminated with dioxins Tsai *et al.*, (2007) compared the 24-year overall and disease-specific mortality in Yucheng people who were highly exposed to dioxins with that of the background population in Taiwan. Increased mortality due to chronic liver disease and cirrhosis was found 13 years after exposure, but not increase in cancer mortality (Yu *et al.*, 1997). In the 2007 follow-up (Tsai *et al.*, 2007), there was a significant elevation of mortality for diseases of the digestive system and two thirds of these deaths were due to chronic liver disease and cirrhosis. Such increase in mortality was most prominent in men. Mortality of systemic lupus erythematosus was increased significantly in Yucheng females. The authors concluded that, the 24-year follow-up of the mortality in the Yucheng population showed an early increase in liver mortality in men, and a delayed increase in systemic lupus erythematosus mortality in women.

The effects of PCBs/PCDFs and related compounds on sexual maturation, endocrine and reproductive functions in females have been studied in post-pubescent females from the Yucheng cohort, who were exposed in utero to dioxins. Yang *et al.*, (2005) tested the hypothesis that in utero exposure to these chemicals alters sexual maturation, endocrine, and reproductive function. Forty-eight young female adolescents, 27 Yucheng and 21 unexposed, participated in the study. Yucheng girls reported shorter mean duration of bleeding per cycle than the unexposed and the difference was significant. There was a higher rate of irregular menstrual cycle in the exposed girls, serum levels of estradiol and follicle stimulating hormone (FSH) were higher in exposed girls as compared to controls.

VI. EXPOSURE TO METHYLMERCURY AND DIOXINS/PCBs THROUGH FISH

A. WORLDWIDE OVERVIEW

Europe

Baltic Sea. The Baltic Sea is characterized by high levels of a number of pollutants in biota and sediments. Industrial activities in the past, together with the long retention time of the water might be important factors. Available data show that concentrations of hazardous substances such as dioxins and PCBs have declined in Baltic fish over the past three decades. This decreasing trend has, however, become less obvious in many areas and during the last decade no further decrease was observed. A study by Isoaari *et al.* (2006) reported that the highest PCDD/F concentrations in Baltic Sea fish were measured in salmon, river lamprey and herring. The highest concentration of all the investigated samples, 17.7 pg TEQ/g fw (41.6 pg/g fw of PCDD/Fs), was analysed from herrings larger than 21 cm (mean age 8.5 years), caught from the Bothnian Bay in spring. The same fatty fish species that carried the greatest PCDD/F load were also the most contaminated with PCBs. The dioxin concentrations in salmon, river lamprey and herring were of particular concern, because they mostly exceeded the EU's maximum permissible level. There are many different strains of Baltic herring that migrate and feed in different areas of the Baltic Sea. There are also strains that migrate to and from the North Sea area. These differences in strain, behaviour and feeding area are part of the explanation for the great variation in concentration of persistent organic contaminants found in Baltic herring. On average, the total TEQ from dioxin-like PCBs in Baltic herring is about 3.5 times that in herring that are not from the Baltic Sea. In Baltic salmon, on average, the total TEQ from dioxin-like PCBs in wild salmon is about 5 times that of farmed salmon. As a result there is a greater potential for consumers to exceed the PTWI if they eat herring or wild salmon from the Baltic more than once a week.

The contaminant levels of dioxins, dioxin-like PCBs have been determined in relation to various fishing grounds of the Baltic Sea (Karl and Ruoff, 2007). Sampling covered an area from the Skagerrak to the coast of Latvia. The data were compared with herring from fishing grounds in the North Sea and west of the British Isles. Very low dioxin concentrations of 0.199 ng TEQ/kg ww were found in herring from fishing grounds around St. Kilda west of the British Isles, while contamination of herring from the central North Sea of comparable size and caught at the same time was substantially higher. The dioxins content of 0.842 ng/kg ww was comparable to the dioxins levels found in herring fillets from the Skagerrak and the Kattegatt. Concentrations of dioxins in herring caught at the coast of Mecklenburg and in the area of Rugen up to 1.841 ng/kg ww were found, but they remained under the current EU-limit of 4 ng TEQ/kg ww. The more the fishing grounds moved to the eastern Baltic area, the higher dioxin levels were found. In some cases the EU-limit was exceeded. The highest level of 6.972 ng TEQ/kg ww was found in herring fillets off the coast of Latvia. Additional information for some of the countries bordering the Baltic Sea is given below.

Belgium. Baeyens *et al.*, (2007) investigated dioxin and dioxin-like PCB levels in fish and fish products and their impact on the population in Belgium. The average PCDD/Fs content of the fish species (eel, red gurnard, and sole) collected in 2002 amounts to 64 pg/g fat, with a range from 3.5 to 205 pg TEQ/ g fat. The highest concentrations were found in sole sampled in the plume of the Scheldt Estuary on the Belgian coastal area, while the lowest was for eel obtained from a fish farm. In the 2004–2006 samples, the dioxin-like content (sum of the PCDD/Fs +

dioxin-like PCB fractions) was assessed in fresh muscle tissue. The fish species showing the lowest activity were shark, ray, sole, and whiting, while the highest levels were observed in shrimps and turbot. The average dioxin-like content (averaging the 16 species) amounted to 1.18 pgTEQ/ g wet weight. The intake of PCDD/Fs via fish amounted to 41 pg TEQ/ day and of PCDD/Fs + dioxin-like PCBs to 71 pg TEQ/ day. For PCDD/ Fs + dioxin-like PCBs, fish consumption represents 47% of total intake (total daily intake is 151 pg TEQ) meat and meat products 33%, milk and dairy products the remainder.

Czech Republic. Houserová *et al.*, (2007) determined total mercury and MeHg in muscle tissues of common carp, grass carp, northern pike, goldfish common tench, and perch. Tissue of predatory fish contained significantly higher contents of total mercury non predatory fish. High content of total mercury was found in the common tench (0.32 ± 0.13 mg/kg dry matter), while the lowest content of total mercury was found in the grass carp. MeHg levels ranged from 65.1% to 87.9% of total mercury.

Estonia. It appears that dioxin concentrations are lower in muscle than in the other tissues and organs (Isosauri *et al.* 2006; Amrhein *et al.* 1999; Simm *et al.* 2006). These differences are because the average concentration of lipids in fish exceeds the values in the muscle due to intraperitoneal fat (Vuorinen *et al.* 2002). It has already been reported that the dioxin level of older fish is often higher than in the younger fish (Kiviranta *et al.* 2003; Roots and Zitko.2006). For fish older than five years the EU limit value of 4 pg (WHO-TEQ/g fw) can be met or exceeded (Kiviranta *et al.* 2003). From this point of view it is important to monitor fish of less than five years. Research by Pandelova *et al.*, (2008) has confirmed that for herring from the Gulf of Finland there is a correlation between the PCDD/F content and the age of the fish. Baltic herring of age 4.5-5 years collected in 1999 from the Gulf of Finland contained two to four-fold higher concentrations than the same fish from the same region in 2002 and 2003. The PCDD/F concentration of 4.10 pg (WHO-TEQ/g fw) for herring from the Gulf of Finland in 2003 are the highest measured values nowadays and are critical with respect to the limit established by the EU. Another interesting finding is that about two-fold lower PCDD/F concentrations in 2004 and 2005 are measured for the younger (2 - 2,5 years) herring collected from the Gulf of Riga , compared to same species caught in 2002. The Estonians have attempted to determine the impact of gender on the dioxin level of juvenile Baltic herring and sprat, but found no correlation (Pandelova *et al.*, 2008).

Finland. Voigt (2001) found a concentration of mercury in big perch from the Finland coastal waters of 0.22 mg/kg. Kiviranta *et al.*, (2004) reported a market basket study on dietary intake of PCDD/Fs, and PCBs in Finland. The maximum concentration of the sum of PCDD/Fs was detected in fish, while the lowest concentration occurred in milk products. The fish basket also showed the highest concentrations of PCBs. The contribution of fish to daily intake was overwhelming. Fish accounted for 71% of the dioxin TEQ intake while the contribution to the PCB TEQs was around 80%. In this study the Finnish daily intake of dioxins TEQ per body weight (bw) was 1.5 pg/kg bw. Kiviranta *et al.* (2003) determined that there was no significant sex-related difference in PCDD/F or PCB concentrations found in herring from the Gulf of Finland and the Gulf of Bothnia (investigations 1993/4 and 1999). Similarly there were no significant differences in the concentrations between the catch areas in the both Gulfs. The fat percentage of herring in the Gulf of Finland was significantly lower than in the Gulf of Bothnia, which accounted for higher dioxin concentrations in the latter area. There was no significant difference in weight, length and condition factor of the herring between the catch areas. Possible heavier exposure to some of PCDD/F and dl-PCBs in the Gulf of Bothnia and/or differences in feeding habits of large herring might explain their higher concentrations of dioxins in the fat. Herring feed mainly on zooplankton, but the older herring have a diet that also contains crustaceans and small fish. Total WHO-TEQ in old herring reached a value of 34 pg/g fw in the Gulf of Finland,

and 50 pg/g fw in the Gulf of Bothnia. The contribution of PCDD/F and dl-PCBs to the total TEQ was equal in both catch areas.

France. Sirot *et al.*, (2008) assessed seafood consumption and MeHg levels in four French coastal areas. Predator fish contained the highest levels of MeHg, while the lowest MeHg levels was in anchovies. Octopus and fresh crab also has high MeHg levels. Average intake of MeHg was 1.33 ± 1.19 ug MeHg/kg body weight (bw)/week (wk) for adult males and 1.56 ± 1.19 ugMeHg/kg bw/wk for adult females. Fish contributing most to MeHg intake were tuna (19.2%), cod (7.18%), ling, sole, and hake (about 5% each). Fish generally accounted for more than 75% of the MeHg intake, and consumption of all seafood by frequent consumers contributed for 94% (tuna being the main contributor with an average of 18.1%).

Tard *et al.*, (2007) reported PCDD/F and dioxin-like PCB levels in the French diet. Fish and fish products were the most contaminated food products, irrespective of whether they were wild or farmed, from the sea or freshwater. In 2000, total exposure to dioxins and furans in the French population was estimated at 1.31 pg TEQ/ kg bw/ day. In 2005 it was 0.53 pg TEQ/kg/ body weight (bw)/ day. This indicates a 60% reduction in five years. In 2000, the highest contributing food groups were dairy products (40.5% of the total exposure) and seafood products (24.4%). In 2005, the order was reversed. Animal products (including fish) were still major contributors with 85% of total exposure, but fish products were now the leading contributor (almost 45% of total ingestion). Dietary intake of dioxins and dioxin-like PCBs for adults was estimated at 1.8 pg TEQ/kg/bw/day. Contributions to total intake of PCDD/Fs+ dioxin-like PCBs were ranked for the seven food groups with the greatest contribution for adults coming from fish products (48%), whereas for children it came from dairy products (43%). For others products, contributions were the same for adults and children: meat products represented 8% of total intake, vegetables accounted for 5–6%, fats for 4–5% and eggs for 2–3%.

Germany. Schweinsberg (2003) summarized studies conducted in Germany on mercury in fish and its health effects and discussed the consequences for protection of human health from this particular mercury exposure. The highest values were found in tuna, halibut and eel, while lower values were detected in rainbow trout and carp.

Karl *et al.*, (2002) analyzed the contents of PCDD/Fs of 184 pooled samples of 20 marine fish and fishery products (canned fish) from the German market. Dioxin concentrations in herring, based on wet weight (ww), ranged from 0.317 to 3.163 ng TEQ/kg ww, showing a clear dependency on the fishing area. Considering a daily fish intake in Germany of about 20 g, the estimated daily intake of dioxins via fish was 6.2 pg TEQs per person or 0.089 pg/kg body weight, respectively.

Italy. Storelli *et al.*, (2002) provided data on total and organic mercury concentrations in muscle tissue of several fish species. The highest levels of total mercury, ranging from 1.30 to 5.16 mg/kg wet weight (mean 3.14 mg/kg wet weight), were detected in ghost shark.

A study by Miniero *et al.*, (2005) indicated the northern part of the Adriatic Sea as one of the most polluted sites. In particular the Venice lagoon had high concentrations of PCBs and other persistent organic pollutants (POPs) due to a many old large industrial settlements in the area (Porto Marghera) and the city of Venice, both of which released their wastes into lagoon waters through industrial and urban effluents. Other studies measured concentrations of PCBs in clams, mussel, lobster, red mullet, cuttlefish, squid, anchovy, sardine and mackerel from two sites of the Italian coast of the Adriatic Sea. The maximum PCB levels were in mackerel (20.8), followed by red mullet (18.0) and anchovy (17.5), while the lowest levels were detected in cuttlefish (0.73) and squid (2.4).

The Netherlands. Data on occurrence of dioxins and dioxin-like in food products consumed in the Netherlands were collected by Baars *et al.*, (2004). Average concentrations of dioxins and dioxin-like PCBs in fish were higher than in meat products. The highest value was found in fatty fish (3158 pg/kg product). The average concentrations of PCBs in fish, as well as the concentrations of dioxins, were higher than in meat products. The highest average concentration was found in fatty fish (31.8 ng/kg product).

Norway. Julshamn *et al.* (2006) presented the results of a monitoring programme of contaminant levels in fish and other seafood products initiated in 1994 by the Directorate of Fisheries in Norway and expected to continue beyond 2010. In marine fish fillets, the mean concentration of Hg was <0.1 mg/kg fresh weight in all species analysed. The highest Hg concentration found in the present study was in Greenland halibut with 0.09mg/kg fresh weight. Last year, the Norwegian National Institute of Nutrition and Seafood Research (NIFES), published a new investigation of analysis of mercury in seafood caught in the area around Fedje, Norway, where a German submarine was sunk in 1945. Mercury levels in fillets of tusks varied from 0.14 to 0.73 mg/kg wet weight. Twelve of the 75 tusk analysed showed a mercury concentration over the EU maximum limit of 0.5 mg/kg wet weight. Two out of 23 samples of brown meat from crab taken close to the wreck had a concentration of mercury over the EU maximum limit for crustaceans of 0.5 mg/kg wet weight.

Knutzen *et al.*, (2003) determined the levels of PCDD/Fs and PCBs in marine organisms from the Grenland fjords, in Norway. Composite samples of Atlantic cod, sea trout, flounder, eel, edible crab and blue mussel were analyzed. In edible fillets, or muscle of molluscs, TEQ for PCDD/Fs ranged between 0.85 (cod) and 28.0 ng/kg ww (flounder). The highest value was found in cod liver (587 ng TEQ/kg ww).

Poland. From 1996 to 2002 the Polish national food monitoring programme examined more than 900 samples of Baltic fish and fish products for Hg (Bykowski *et al.* 1997, Bykowski *et al.* 2002). These and studies from 1996 to 1998 of the content of MeHg in samples of selected Baltic species as well as the products made of Baltic fish (Barska, Skrzynski 2003), confirmed that the Hg content in Baltic fish and products does not pose any risk to the potential consumer. The lowest average content of MeHg was determined in sprat and herring, slightly higher in flounder and eelpout with the highest levels found in predators such cod and perch. Bykowski and Pawlak (2009) estimated that a Pole with an average fish diet (about 12,5kg fish fw/pers/y.) would ingest less than 1% of the PTWI.

Systematic investigations on the dioxins level in the Baltic fat fish started in 2002; the permissible and official EU limit of of PCDD/Fs and dl-PCBs (8 pg/g fw.) was exceeded mainly in salmon samples (80% of salmon samples studied). The elevated levels of dioxins were observed in only two of 72 herring samples and in ten of 62 sprat samples. The contribution of dl-PCBs to the total TEQ ranged between 50 and 70% dependently on the fish species, the highest being in salmon samples. In all samples the concentrations of PCDF were higher that of PCDD (Szlinder-Richert *et al.* 2009). In experiments it has been determined that there are possibilities of lowering dioxin concentrations during preliminary processing, for example by removing the lower part of salmon belly flaps (trimming of filet), deep skinning and removing brown muscle. Thus, it is possible to change dioxins level from 10 to 6 TEQ pg/g fw. (Bykowski 2002; Barska 2008). Similar results for herring were presented by Karl (2002). In the case of sprats canned in own juice Bykowski (2006) showed a lowering of dioxins level in drained product of about 20%.

From 2006 according to Commission Recommendations 2004/705/EC and 2006/794/EC Poland monitors dioxins in Baltic fat fish species from the Polish EEZ . During four years of investigation the elevated concentrations - over EU limits - were observed in only one of 37 of herring

samples (range: 1.15- 3.96) , in all 37 sprat samples dioxin content was lower than limit (range: 0.85- 6.1) but about 50% of salmon samples (38) had dioxin contents higher than the limit (range: 4.16- 12.22).

Russia. Muir *et al.*, (2003) assessed levels of dioxins in marine mammals, as well as in fish and invertebrates from the White Sea. The highest PCB concentrations were found in samples from seals (means of 4150 ng/g lipid weight). Among the fish species evaluated, Navaga (*Eleginus navaga*) had the highest concentrations of PCBs with mean of 41 ng/g wet weight, while lowest mean concentrations were present in cod muscle (16 ng/g ww). In the same study, temporal trends were also investigated by comparing concentrations of dioxins in seal pups collected in 1992 with pups of the same age collected in 1998. The decline over the 6 year period was approximately 60% for PCBs.

There is a very limited data on dioxin contents of fish from Russia. Shelepchikov *et al.* (2008) examined a few samples of herring and sprat from the Russian EEZ near Kaliningrad. PCDD/Fs ranged between 2.94- 3.39 TEQ, % dl-PCBs to total WHO-TEQ was 54.8 to 74.8, for sprat (one sample) PCDD/F was 2,09 and 45.3% PCB to total TEQ.

Slovakia. The maximum TEQ concentrations in fish specimens analysed were measured in imported smoked mackerel samples. Unexpectedly higher levels of PCDDs/PCDFs and PCBs were observed in river trout originating from a fish farm situated in a clean mountainous region of middle Slovakia.

Spain and Portugal. Cabañero *et al.*, (2005) measured the concentration of mercury in fish commonly consumed in Spain and Portugal. The following mercury levels were found: octopus (0.024 µg/g) < mackerel shad (0.033 µg/g) < sardine (0.048 µg/g) < tuna (0.31 µg/g) < swordfish (0.47 µg/g). The levels of total mercury were below the maximum level allowed by the European legislation. The results also showed that more than 93% of the total Hg occurring in fish samples was methylmercury. In a study by Sahuquillo *et al.*, (2007), the mercury content of 25 samples of fish and seafood products most frequently consumed in Spain was determined, with MeHg content ranging from >54 to 662 µg/kg. The highest levels were found in fresh tuna. Based on an average total fish consumption of 363 g/person/week, MeHg intake was estimated to be 46.2 µg/person/week, thus lower than the JECFA PTWI of 1.6 µg/kg body weight.

Gomara *et al.*, (2005) presented the results of a monitoring program on temporal trends in PCDDs, PCDFs, and dioxin-like PCB concentrations found in six fish and shellfish species (salmon, sardine, tuna, oyster, mussel, and clam) commercially available in Spanish markets from 1995 to 2003. A decline was observed in the samples studied through the years. The PCDDs/Fs and dioxin-like PCB concentrations declined statistically over the years (from 1995 to 2003) in almost all cases. The highest mean concentration of PCDDs/F was found in salmon (0.5 pg of TEQ/g of fresh weight (fw)), followed by oysters (0.46 pg of TEQ/g of fw), and sardines (0.44 pg of TEQ/g of fw). The lowest value was found in tuna with 0.23 pg of TEQ/g of fw, mussels (0.09 pg of TEQ/g of fw), and clams (0.05 pg of TEQ/g of fw). Concentrations of PCDDs, PCDFs and PCBs in samples from 14 fish and seafood species widely consumed by the population of Catalonia, Spain, were measured (Bocio *et al.*, 2007). The highest levels for both PCDD/Fs and PCBs were found in red mullet, followed by salmon and mackerel for PCDD/Fs, and by sardine and anchovy for PCBs. In contrast, the lowest PCDD/F and PCB concentrations were detected in cuttlefish and shrimp, respectively. The highest total TEQ values were for red mullet followed by anchovy and sardine, while the lowest values were found in cuttlefish, and shrimp and clam. On average, for a standard adult man (70 kg body weight) living in Catalonia, daily intake of PCDD/Fs and dioxin-like PCBs, through fish and seafood consumption, was estimated to be 6.02 pg TEQ for PCDD/Fs, 31.98 pg TEQ for dioxin-like PCBs, and 38.0 pg TEQ for the sum of both

PCDD/Fs and dioxin-like PCBs. Tuna, followed by hake and sardine, were the main contributors to total TEQ intake. The EU maximum permissible levels for human consumption are 4 and 8 ng/kg of wet weight (ww) of toxic equivalents, for PCDD/Fs and for PCDD/Fs plus dioxin-like compounds, respectively, in the muscle meat of fish and fishery products (EC, 2006). All fish and seafood species analyzed in the survey by Bocio *et al.*, (2007) showed PCDD/F + dioxin-like PCB concentrations under the EU maximum permissible level. Turbot aquaculture is a very important activity in Spain, producing fish of remarkable quality due to optimal conditions of sea water in the northwest of the country. In order to evaluate the safety of this aquaculture product and the relevance of the feedstuff in the final levels of contaminants found in fish, determinations of PCDD/Fs and dioxin-like PCBs in turbot and in feedstuff have been carried out in a recent study (Blanco *et al.*, 2007). Relatively low levels of PCDD/Fs and dioxin-like PCBs were found in the feed (0.52 pg TEQ/g for PCDD/Fs and 1.62 pg TEQ/g for PCBs), far below maximum levels set by the European Commission (2.25 pg/g TEQ for PCDD/Fs, and 4.75 pg/g for dioxin-like PCBs). Trout from French aquaculture showed very similar values for the same parameters, with mean values of 0.17 and 0.58 pg/g fresh weight for PCDD/Fs and dioxin-like PCBs respectively. Dietary intakes of PCDD/Fs and dioxin-like PCBs recently calculated in the Spanish population show that fish and seafood accounted for 11% of the intake, the sum of dioxin-like PCBs being an important component in the total TEQ.

Sweden. Björnberg *et al.*, (2005b) assessed exposure to MeHg in Swedish women of childbearing age with high consumption of various types of fish, using total mercury in hair and MeHg in blood as biomarkers. Fish consumption was assessed using a food frequency questionnaire. Average total fish consumption was approximately 4 times/week (range 1.6–19 times/week). Fish species potentially high in MeHg, included in the Swedish dietary advisories (pike, perch, pike-perch, burbot and eel), were consumed by 79% of the women. Other fish species potentially high in MeHg, not included in the Swedish dietary advisories (large tuna, halibut, swordfish and angler), were consumed by 54% of the women. Based on hair mercury levels exposure exceeded the EPA reference dose (RfD) of 0.1 ug MeHg/kg b.w. per day in 20% of the women.

In the Nordic countries the intake of fish is of major importance for the total intake of contaminants, and some Swedish and Finnish estimations show that 70–80% of the PCB intake originates from consumption of fish. Dietary intake estimations of organohalogen contaminants (including dioxin, and dioxin-like PCBs) based on Swedish market basket data, were recently assessed (Darnerud *et al.*, 2006). The authors estimated the total dioxin intake to be around 1.3 pg TEQ/kg bw/day. Relative contribution from the different food groups to the estimated total intakes of dioxins/dioxin-like PCBs were: fish 33%, fats and oils 22%, dairy products 20%, meat 15%, egg 6% and pastry 4%.

United Kingdom. The UK survey data on MeHg content of a wide range of domestic and imported fish and shellfish, found the highest levels of MeHg in shark (mean: 1.52 mg/kg), swordfish (1.36 mg/kg) and marlin (1.09 mg/kg) (SACN, 2004). Tuna (fresh, 0.40 mg/kg; canned, 0.19 mg/kg) contained higher levels of methylmercury than other commonly eaten fish. Consumption by adults of one weekly portion (140 g) of shark, swordfish or marlin would result in an intake in the range 2.2-3.0 ug/kg bw, without considering intake from the rest of the diet. This intake would exceed the revised JECFA PTWI by up to 90%. It was, therefore, considered that maternal consumption of one 140-g portion/week of these species of fish during pregnancy could present a risk to the foetus. Consumption of one portion per week of these species by children would result in a methylmercury intake of 3.0-5.2 ug/kg bw/week, while consumption of up to two 140-g portions/week of fresh tuna or four 140-g portions/week of canned tuna would not exceed the PTWI in women who were pregnant or likely to become pregnant in the next year.

North America

USA. Concentrations of MeHg in seafood from the United States are reported in the 2006 FDA database (<http://www.cfsan.fda.gov/~frf/sea-mehg.html>). For fish with detectable levels of MeHg (most of them), the lowest average MeHg concentrations were between 0.01 and 0.02 ppm. Those with the highest concentrations had averages that were just under 1.0 ppm, although the highest average concentration was 1.4 ppm for tilefish from the Gulf of Mexico. On a per-species basis, the average amount of methylmercury in the top 10 most consumed commercial species in the United States ranged from non detectable to 0.2 ppm, with the exception of albacore canned tuna, which averaged 0.35 ppm. The top 10 species comprise approximately 73% of commercial fish consumed in the United States. One of the most highly consumed commercial fish products, canned tuna in the aggregate contained on average 0.17 ppm. Albacore accounted for about one-third of canned tuna. Long-lived predatory fish tended to accumulate the most methylmercury. Shark and swordfish, which averaged around 1.0 ppm, were outside the top 20 in terms of U.S. consumption. Mercury concentrations in freshwater commercial species were low. In the FDA database the average mercury concentration for commercial freshwater species was 0.08 ppm on a per species basis, and the highest average for any species was 0.14 ppm.

In the U.S. population, major dietary sources of PCBs and dioxins are beef, chicken, and pork (34% of total TEQ), dairy products (30%), vegetables (22%), fish and shellfish (9%), and eggs (5%) (Schecter *et al.*, 2001). The concentrations of 14 organochlorine contaminants including PCDD/Fs and PCBs were determined in farmed salmon obtained from farms in eight major salmon farming regions of the world, samples of five species of wild Pacific salmon, and retail market samples of farmed salmon obtained in 16 cities in Europe and North America (Hites *et al.*, 2004). PCDD/F and PCB levels in salmon showed notable differences depending on the respective origin. Thus, farmed salmon had significantly higher contaminant burdens than wild salmon, whereas farmed salmon from Europe were significantly more contaminated than those from South and North America (Hites *et al.*, 2004).

Canada. Braune *et al.*, (1999) summarized data indicating that lake trout, walleye, and pike had higher mercury levels than whitefish and char; many trout, pike, and walleye populations had mean mercury levels that exceeded 0.5 ug/g. Kelly *et al.*, (2008) reported levels of mercury in commercial salmon feed, in farmed Atlantic, coho, and chinook salmon, and in wild coho, chinook, chum, sockeye, and pink salmon. Levels in farmed and wild salmon from British Columbia, were relatively low and below human health consumption guidelines. MeHg levels in all salmon samples (range, 0.03-0.1 ug/g wet wt) were below the 0.5 ug/g guideline set by Health Canada. Negligible differences in metal concentrations were observed between the various species of farmed and wild salmon.

Dewailly *et al.*, (2007) evaluated the concentrations of dioxin-like PCBs, and dioxins in fillets from farmed salmon and trout bought in various markets located in Quebec, as well as in fillets from wild salmonids obtained from fishermen and various Canadian agencies. The authors reported that PCDD/F concentrations appeared lower in farmed compared to wild salmonids, although statistically significant differences were not observed. In contrast, the mean total PCB concentrations in farmed Atlantic salmon fillets was approximately double that of their wild counterparts. Such difference was not observed between farmed and wild rainbow trout.

Central and South America

Argentina. A decreasing trend in mercury concentration, with values of 330 ± 200 ng/g (ww) in the 1988–2000 period, and down to 90 ± 10 ng/g (ww) in 2001–2004 was reported by De Marco *et al.* (2006).

Brazil. MeHg concentrations in three marine species, *Perna perna* (common mussel), *Mugil iza* (mullet), and *Micropogonias furnieri* (Atlantic croaker). MeHg in mussel ranged from 4.5 to 21.0 ug/kg wet wt., with similar levels found in mullet. The croaker, a carnivorous fish, had higher MeHg concentrations (194.7 ug/kg wet wt), particularly in liver (Kehrig *et al.*, 2009).

Chile. Cortes and Fortt, (2007) found the highest levels of mercury in swordfish (1.53mg/kg), which was significantly different from all other fish species. The mercury content of Chilean sea bass was 0.17mg/kg. Estimated exposure of the general population varied from 0.01 mg/kg bw/day for consumption of Chilean mussel, to 0.45 mg/kg/bw/day for swordfish. In the highest consumption group, exposure varied from 0.088 for Chilean mussel to 3.38 mg/kg/bw/day for swordfish. The latter fish is not usually consumed in Chile, and its main destination is the US market.

Colombia. Marrugo-Negrete *et al.*, (2008) evaluated total mercury and MeHg concentrations in the predominant fish species consumed in the municipalities of the Mojana region (northwest Colombia), to ascertain potential human exposure to mercury from fish consumption. The average concentration of mercury in fish muscle was 0.269 ug/g. The lowest level of mercury (0.043 ug/g) was observed in *Trichogaster* sp. (gurami), a non-carnivorous species, and the maximum concentration (0.512 ug/g) was in the carnivorous species *Ageneiosus caucanus* (doncella).

French Guiana. In French Guiana, clandestine gold mining using mercury is intensive on terrestrial sites or directly in the rivers. Mercury contamination of 35 freshwater fish species collected from the Courcibo and Leblond rivers were analyzed (Durrieu *et al.*, 2005).

Results showed a marked biomagnification along the food chain: the ratio between extreme mercury concentrations in the muscle from piscivorous species (14.3ug/g, dry weight (dw) for *Acestrorhynchus guianensis*) and from herbivorous species (0.02 ug/g, dw for *Myleus ternetzi*) was 715. The final predators in this food web are human beings, and consequently high mercury levels were observed in hair from some native Amerindian communities. This placed 57% of the Wayanas living in the upper reaches of the Maroni river above the WHO limit.

Nicaragua. Managua, the capital of Nicaragua, is situated on the shore of Lake Managua, which is used as the recipient of domestic and industrial wastewater from the city. Fish from this lake is an important part of the diet for the population living in poor communities surrounding the lake. Cuadra *et al.*, (2006) assessed PCB levels in serum collected from children working and living at the shore of Lake Managua. Fish consumption contributed to the levels of PCBs in children and young women, and the waste-disposal area was a source of local contamination for these chemicals.

Asia

Middle-East. Concentrations of total mercury and methylmercury were measured in 13 fish species from a coastal food web of the Gulf of Oman, an arm of the Arabian Sea between Oman and Iran (Al-Reasi *et al.*, 2007). Total mercury levels in fish species ranged from 3.0 ng/g (*Sardinella longiceps*) to 760 ng/g (*Rhizoprionodon acutus*) with a relatively lower content of MeHg (72%) than that found in other studies. Biomagnification of MeHg was lower in this

tropical ocean compared to arctic and temperate ecosystems and tropical African lakes. The calculated daily intake of methylmercury in the diet of local people through fish consumption was well below the established World Health Organization (WHO) tolerable daily intake threshold for most of the fish species.

China. The province of Guizhou in Southwestern China is currently one of the world's most important mercury production areas. Emissions of mercury from the province to the global atmosphere have been estimated to be approximately 12% of the world total anthropogenic emissions. A number of fish samples of different weight and size were taken from Lake Huaqiao, and the three most common fish species consumed by the local population were sampled (Horvat *et al.* 2003). Concentrations of mercury were as follows: 20-40 ng/g in common carp, 60 ng/g in grass carp, and between 60 and 70 ng/g in *Carassius auratus*.

Relatively high PCB concentrations were found in fish and other seafood, ranging from 0.20 (shrimp and mussel) to 2.5 (mackerel) ng/g ww. Levels of dioxins and dioxin-like PCBs were recently determined in various species of bivalves and gastropods, collected in eight sampling sites along Bohai Sea coastline (North East China) (Zhao *et al.*, 2005). For dioxin-like PCBs, TEQs ranged between 0.87 and 7.71 pg/g lipid weight (lw) for bivalves, and between 0.53 and 7.9 pg/g lw for gastropods, while for dioxin, TEQs oscillated between 0.016-27 and 0.05-44 pg/g lw, for bivalves and gastropods, respectively. The estimated daily intake of PCBs through fish and shellfish, considering a body weight of 60 kg and an average consumption of 30.5 g/person/day, was 1.83 ng/kg body weight. Jiang *et al.*, (2007) determined the concentrations of dioxins and dioxin-like PCBs in common seafood in two Chinese coastal cities (Guangzhou and Zhoushan), and assessed the health risk due to the daily consumption of contaminated seafood. Twenty-six pooled samples, belonging to five food categories (fish, bivalves, shrimp, crab, and cephalopods), were purchased from local markets in Guangzhou and Zhoushan in 2003 and 2004. The concentrations of total PCBs and coplanar PCBs in fish samples ranged from 1510 to 10 200 pg/g lipid weight. The total daily intake values of dioxin-like compounds were 1.05 and 0.86 pg TEQ/kg body weight in Guangzhou and Zhoushan, respectively.

India and Pakistan. Mishra *et al.*, (2007), analyzed mercury in different types of marine organisms (fish, bivalve, crab and prawn) collected from the Trans-Thane Creek area, Mumbai. The Thane Creek area is considered as the most polluted area in India due to industrial discharges. Potential risks associated with consumption of marine organisms collected from this particular area to human beings were also assessed in this study. Total concentrations of mercury in different types of fish species varied from 34 to 54 ng/g dry wt., while in crabs total mercury averaged 98.3 ng/g. MeHg was between 50–90% of total mercury.

Munshi *et al.*, (2004) found high levels of PCBs (78.35 ug/g of lipid) in different fish from the Karachi Coast. In dolphins, PCB concentrations ranged from 210 to 1220 ng/g (wet weight basis). The source of PCBs in dolphins collected from Indian waters was unclear, but was likely to be derived from ship breaking yards, as well as operational and defunct industrial equipment including transformers, capacitors and electrical appliances.

Indonesia. Concentrations of dioxins in fish from Indonesia were studied by Sudaryanto *et al.*, (2007). They found that mean concentrations of PCBs in fish samples were in the middle range, and generally comparable with those in other Southeast Asian Countries. The highest concentrations of dioxins and dioxin-like PCBs were observed in the waters in proximity to the anthropogenic sources from agriculture as well as highly industrialized and populated cities, like those surrounding the island of Java, whereas the levels in Sumatra were lower.

Japan. Endo *et al.*, (2005) surveyed mercury levels in small cetacean species sold for human consumption in markets throughout Japan from 2000 to 2003. Total mercury and MeHg concentrations in all products exceeded the provisional permitted levels for mercury (0.4 ug/g ww) and MeHg (0.3 ug/g ww) in fish and shellfish set by the Japanese government, respectively. The average MeHg level in the most contaminated species (false killer whale) was 11.5 ug/g ww, and that in the least contaminated species (Dall's porpoise) was about 1.0 ug/g ww, exceeding or equaling the Codex guideline of MeHg in predatory fishes (1.0 ug/g ww). The highest MeHg was about 26 ug/g ww in a sample from a striped dolphin, 87-times higher than the permitted level. The consumption of only 4 g of this product would exceed the provisional tolerable weekly intake of MeHg for someone of 60 kg body weight (1.6 ug/kg-bw/ week).

Concentrations and accumulation profiles of PCDD/Fs and dioxin-like PCBs in aquatic biota (e.g., plankton, shellfish, benthic invertebrate, and fish) and sediment from Tokyo Bay were examined by Naito *et al.*, (2003). Total PCDD/F concentration in Tokyo Bay biota ranged from 8.52 for akanishi (shellfish) to 259 pg/g wet weight for plankton. Total dioxin-like PCB concentration in Tokyo Bay biota ranged from 267 for akanishi to 29 900 pg/g ww for sea bass. Another evaluation of dioxin levels in fish indicated that mackerel had the highest TEQ levels (0.397-3.841 pg/g ww), followed by red sea-bream (0.013-0.272 pg/g ww), Japanese horse mackerel (0.128-1.916 pg/g ww), sardines (0.266-3.551 pg/g ww) and squid (0.013-0.272 pg/g ww). Among imports, the highest TEQ levels were found in flounder followed by salmon. Octopus, shrimp and yellow-fin tuna had very low TEQ levels. A study of the dietary intake of dioxins, through foods retailed in the metropolitan Tokyo area from 1999 to 2004 was carried out by Sasamoto *et al.*, (2006). The total daily intake (pg TEQ/day) was 109.2 in 1999, 93.3 in 2000, 64.2 in 2001, 80.1 in 2002, 80.0 in 2003, and 77.5 in 2004, corresponding to 2.18, 1.87, 1.28, 1.60, 1.60 and 1.55 pg TEQ/kg body weight/ day for an adult weighing 50 kg, respectively. These total intake values were below the TDI of 4 pg TEQ/kg/day set by the Environmental Agency and Ministry of Health and Welfare of Japan (1999) and were also below the TDI of 14 pg TEQ/kg/week evaluated by EC SCF (2001) except for 1999. They were also below the TDI of 70 pg TEQ/kg/month evaluated by JECFA (2001). The highest contribution to total intake was from fish and shellfish in each year and the contribution from this group accounted for over 80% in 2003 and 2004. A study by Tuksino *et al.*, (2006) found that Japanese women of reproductive age who consumed fish frequently tended to accumulate TEQ levels of PCDFs, cPCBs, PCBs in their body. The authors revealed that the frequency of fish consumption was the most significant contributor to serum total TEQ levels of PCDDs, PCDFs, dioxin-like PCBs among Japanese women of reproductive age, and these results were consistent with the results of the above studies estimating daily dietary intake for Japanese.

Korea. Moon and Ok (2006) measured dioxin levels in seafood and found levels ranging from 0.02 to 4.39 pg TEQ/g ww; for dioxin-like PCBs levels ranged between 0.008 and 0.6 pg TEQ/g ww. The highest pollutant concentrations were recorded in crustaceans, followed by fish, cephalopods, bivalves and gastropods. The contribution of dioxin-like PCBs to total intake from all organisms (0.68 pg TEQ/kg/bw/day) averaged 60%.

Philippines. Appleton *et al.*, (2006) found levels of mercury in tilapia from the Naboc River area, Mindanao of 0.277 ug/g, that did not exceed the maximum recommended limit commonly allowed for fish in most countries (0.5 mg Hg/kg wet weight; UNEP, 2002). Low concentrations of total mercury in freshwater fish and in tilapia have been reported also from the Tagum artisanal gold processing area, Mindanao.

Sri Lanka. In a study by Guruge and Tanabe (2004) six species of fish and one crab species were subjected to analysis for dioxin and PCB content. Concentrations of dioxins in samples ranged from 0.04 to 4.5, and 0.04 to 1.3 pg/g wet weight, respectively. The highest concentration of

dioxin was detected in mullet. The concentrations of dioxin-like PCBs were 1.3–140 pg/g wet weight. The highest dioxin-like PCB concentrations in fish were detected in mullet, followed by catfish.

Turkey. Coelhan *et al.*, (2006) evaluated the dioxin levels in samples of edible fish species from the Marmara Sea. Total PCB concentrations varied in the range of 63.30 and 508.71 ng/g at, with an average value of 253.08 ng/g fat. Compared with the results from 1998 (mean 403.40 ng/g fat) these levels were lower. In general, PCB contamination of red mullet from the Marmara Sea was lower or in the same order compared to different regions of the Mediterranean, where concentrations vary between 395 and 1119.80 ng/g fat .

Uzbekistan. An international team carried out analyses to quantify concentrations of dioxins and dioxin-like PCBs on different types of foods commonly produced and consumed in Uzbekistan (Muntean *et al.*, 2003). Fish and chicken samples had the highest levels of dioxin-like PCBs. The authors reported that dietary dioxin exposure for a typical Uzbekistan resident is estimated to be almost three times higher than the level that WHO considers safe.

Africa

Burundi. Concentrations of selected PCBs in seven fish species (cichlids) from the north end of the Lake Tanganyika, Burundi, were determined. Levels of PCBs were very low and provide evidence of a region with small or very recent industrial activities. Twelve PCB congeners were quantified in all fish samples except *Boulengerochromis microlepis*. The highest levels were found in *Oreochromis niloticus* (166.7 ng/g fat) and *Lates stappersii* (126.7 ng/g fat).

Egypt. Loufty *et al.* (2007) determined the concentrations of PCDD/Fs and dioxin-like PCBs in food samples randomly acquired in local markets from Ismailia, Egypt. For fish and seafood (mullet, boliti fish, bivalves and crab) samples, the upper bound levels for PCDD/Fs and dioxin-like PCBs ranged from 0.12 (crab) to 0.40 (mullet) pg TEQ/g ww, and from 0.14 (bivalves) to 0.76 (mullet) pg TEQ/g ww, respectively. The observed levels in seafood were lower than the average reported in the EU countries for PCDD/Fs (1.0 pg TEQ/g wet w) and for dioxin-like PCBs (1.0 pg TEQ/g wet w) The PCDD/F content in this group was much lower than the current EU limit of 4 pg TEQ/g wet w. In another study from the same research group, it was observed that in Egypt, fish and seafood played a less important role in total dioxin intake (Loufty *et al.*, 2006).

Ghana. Artisanal gold mining with metallic mercury has a long history in Ghana. The Pra River in south-western Ghana is a site of on going application of metallic mercury in prospecting gold. Mercury contamination occurs in the different environmental compartments in its watershed. Among fish, two bottom feeders (*Claria sp.* and *Synodontis sp.*) and the piscivorous fish *Hepsetus odoe* had average total mercury concentrations above the WHO's safe consumption guideline of 0.5 mg/kg. In contrast, the tilapia (*Sarotherodon melantheron*) had mercury concentrations below the above-mentioned guideline.

Morocco. Coastal populations with high seafood consumption in the Mediterranean have a significant exposure to dietary methylmercury, and areas where environmental mercury pollution is an issue due to industrial activities are of special concern. A study found a mercury concentration of 0.137 ug/g in pilchards (*Sardina pilchardus*), compared to levels of 0.08-0.12 ug/g for the same fish in a non-contaminated Mediterranean environment.

Tanzania. Total mercury and MeHg levels were determined in fish species representing various tropic levels in four major hydroelectric reservoirs (Mtera, Kidatu, Hale-Pangani, Nyumba ya Mungu) located in two distinct geographical areas in Tanzania. The tilapia (*Tilapia urolepis*) had the lowest mercury concentrations (6–11 ug/kg) and the tiger fish (*Hydrocynus vittatus*) had the

highest (37–143 ug/kg wet wt). The lowest mercury levels, in the range 1–10 ug/kg (mean 5 ug/kg), were found in fish from the Nyumba ya Mungu (NyM) Reservoir. Fish mercury levels in the Pangani and Hale mini-reservoirs, downstream of the NyM Reservoir, were in the order of 3–263 ug/kg, with an average level of 21 ug/kg. These mercury levels are among the lowest to be reported in freshwater fish from hydroelectric reservoirs. Approximately 56–100% of the total mercury in the fish was MeHg.

Oceania

Australia. Padule *et al.* (2008) found that the mean concentration of total mercury in wild Australian Southern Bluefin Tuna was 0.36 mg/kg (range 0.31-0.41), while that in farmed Southern Bluefin Tuna it was 0.31 mg/kg (range 0.18- 0.45). In another study, mercury levels were measured in fillets of muscle tissue of deep sea dog sharks (*Deania calcea*, *Centroscymnus crepidater*, and *Centroscymnus owstonii*), captured from the waters off western Victoria, Australia. The maximum permitted concentrations were exceeded in all species, and weekly consumption of 400 g of any of these sharks would result in an intake higher than the FAO's PTWI.

New Zealand. Love *et al.* (2003) presented information on the total mercury and MeHg content of New Zealand fish. These data should reflect the natural levels of mercury found in New Zealand marine fish, as the country is isolated, with the closest major land mass being Australia approximately 2000 km to the west. New Zealand has no significant man-made sources of mercury pollution, with the possible exception of historic pollution from a paper mill in the Waikato River Valley (Weissberg and Zobel 1973). In several fish species levels of total mercury ranged between 0.02 and 2.48 mg/kg, and mean levels of MeHg ranged from less than 0.04 to 1.97 mg/kg.

PCB levels were measured in long finned eels (*Anguilla dieffenbachii*) in 17 streams on the west coast of South Island, New Zealand. Eels have a worldwide distribution and are known to be highly contaminated by PCBs due to the high lipid content (up to 40%), and that makes them a good biomarker for levels of fish contamination. PCB concentrations were low in these eels compared to other studies on eels in different parts of the world, ranging from non detection to 54.6 ng/g. The levels of PCBs found in New Zealand eels were comparable to levels in arctic char (*Salvelinus alpinus*) in remote Arctic areas (0.1-100 ng/g).

VII. ABBREVIATIONS AND GLOSSARY

The terms, acronyms and abbreviations below may appear in this document.

< – less than;

> – greater than;

ug – microgram (10^{-6} gram);

ug/kg body weight per day – micrograms per kilogram body weight per day; units used for describing intakes (or doses) of mercury such as intakes that are considered safe for humans. In some cases the time unit weeks is also used.

ADI – Acceptable daily intake: Estimated maximum amount of an agent, expressed on a body mass basis, to which individuals in a (sub) population may be exposed daily over their lifetimes without appreciable health risk.

ADME – Absorption, Distribution, Metabolism and Excretion

AhR – Aryl hydrocarbon receptor

ATSDR – USA Agency for Toxic Substances and Disease Registry

BMD – Benchmark dose

bw – body weight

CDC – Centers for Disease Control and Prevention (in the USA)

DL-PCBs –Dioxin-like PCBs, dioxin-like compounds

ECACAN – Environmental Council of States and Clean Air Network

EPA –Environmental Protection Agency (in the USA)

FAO – Food and Agriculture Organization of the United Nations

FDA – Food and Drug Administration (in the USA)

Hg – mercury

Hg⁰ – elemental mercury

Hg(II) or Hg⁺² – divalent mercury - the dominating mercury form in organic and inorganic mercury compounds. In the atmosphere, mercury species with divalent mercury are more easily washed out of the air with precipitation and deposited than elemental mercury

IUPAC –International Union of Pure and Applied Chemistry

JECFA – Joint FAO/WHO Expert Committee on Food Additives and Contaminants

LD50 – Lethal concentration, causing 50% deaths

LOAEL – lowest observed adverse effect level

LOEL – Lowest observed effect level

MeHg – Methyl Mercury

mg – milligram (10^{-3} gram)

MRL – minimum risk level; term used in evaluation of risk of toxic effects from various chemicals (such as methylmercury) on humans; the MRL is defined by US ATSDR as an estimate of the level of human exposure to a chemical that does not entail appreciable risk of adverse non-cancer health effects

MTD – Maximum tolerated dose

ng – nanogram (10^{-9} gram)

NAS – National Academy of Sciences (in the USA)

NOEL – No observed effect level

NOEL/BMDL – No observed effect level/benchmark dose level

NRC – National Research Council (in the USA)

PCBs – Polychlorinated biphenyls

PCDD –Polychlorinated dibenzo-p-dioxins

PCDF –Polychlorinated dibenzo-p-furans

pH – An expression of both acidity and alkalinity on a scale of 0 to 14, with 7 representing neutrality; numbers less than 7 indicate increasing acidity and numbers greater than 7 indicate increasing alkalinity

POPs – Persistent organic pollutants

ppb – parts per billion

ppm – parts per million

ppt – parts per trillion

PTWI – Provisional Tolerable Weekly Intake The PTWI is an endpoint used for food contaminants such as heavy metals with cumulative properties. Its value represents permissible human weekly exposure to those contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious foods

RfC – reference concentration

RfD – reference dose; term used in evaluation of risk of toxic effects various chemicals (such as methylmercury) on humans; the RfD (or RfC) is defined by US EPA as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime

SACN – UK Scientific Advisory Committee on Nutrition

SCAN – Scientific Committee on Animal Nutrition of the European Commission

Se – selenium

TDI – Tolerable daily intake: analogous to the ADI and PTWI. The term ‘tolerable’ is used for agents that are not deliberately added, such as contaminants in food

TEFs – Toxic equivalency factors

TEQs – Toxic equivalents

T-Hg – Total Mercury

UN – United Nations;

UNEP – United Nations Environment Programme;

US – United States of America;

USDA – United States Department of Agriculture;

WHO – World Health Organization;

ww – wet weight.

VIII. REFERENCES

- Afghan, B.K. & Chau, A.S.Y.** 1989. Analysis of trace organics in the aquatic environment. Boca Raton, FL: CRC Press, Inc. 33-68.
- Ahluquist, M., Bengtsson, C., Lapidus, L., Bergdahl, I.A. & Schutz, A.** 1999. Serum mercury concentration in relation to survival, symptoms, and diseases: results from the prospective population study of women in Gothenburg, Sweden. *Acta Odontol Scand* 57: 168-174.
- Ali, S.F., LeBel, C.P. & Bondy, S.C.** 1992. Reactive oxygen species formation as a biomarker of methylmercury and trimethyltin neurotoxicity. *Neurotoxicology* 13, 637–648.
- Allen J.W., El-Oqayli, H., Aschner, M., Syversen, T. & Sonnewald, U.** 2001. Methylmercury has a selective effect on mitochondria in cultured astrocytes in the presence of [U-3C]glutamate. *Brain Res.* 908, 149–154.
- Al-Reasi, H.A., Ababneh, F.A. & Lean, D.R.** 2007. Evaluating mercury biomagnification in fish from a tropical marine environment using stable isotopes ($\delta^{13}\text{C}$ and $\delta^{15}\text{N}$). *Environ Toxicol Chem.* 26(8):1572-81.
- Al-Saleem, T.** 1976. Clinical Committee on Mercury Poisoning. Levels of mercury and pathologic changes in patients with organomercury poisoning. *Bull World Health Organ.* 53:99-104.
- Andersen, H.R. & Andersen, O.** 1993. Effects of dietary alpha-tocopherol and beta-carotene on lipid peroxidation induced by methylmercury chloride in mice. *Pharmacol Toxicol.* 73, 192-201.
- Ansoorge M.S., Hen, R. and Gingrich J. A.** 2007. Neurodevelopmental origins of depressive disorders. *Curr. Opin. Pharmacol.* 7:8–17.
- Appleton, J.D., Weeks, J.M., Calvez, J.P. & Beinhoff, C.** 2006. Impacts of mercury contaminated mining waste on soil quality, crops, bivalves, and fish in the Naboc River area, Mindanao, Philippines. *Sci Total Environ.* 354(2-3):198-211.
- Aschner M. & Aschner, J.L.** 1990. Mercury neurotoxicity: Mechanisms of blood-brain barrier transport. *Neurosci Biobehav Rev.* 14:169-176.
- Aschner, M. & Clarkson, T.W.** 1988. Distribution of mercury 203 in pregnant rats and their fetuses following systemic infusions with thiol-containing amino acids and glutathione during late gestation. *Teratology.* 38:145-155.
- Aschner, M. & Syversen, T.** 2005. Methylmercury: recent advances in the understanding of its neurotoxicity. *Ther. Drug Monit.* 27, 278–283.
- Aschner, M.** 2000. Astrocytic swelling, phospholipase A2, glutathione and glutamate: interactions in methylmercury induced neurotoxicity. *Cell. Mol. Biol.* 46, 843–854.
- Aschner, M.** 1996. Astrocytes as modulators of mercury-induced neurotoxicity. *Neurotoxicology* 17, 663–669.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological Profile for mercury. U.S. Dept. of Health and Human Services,

Ayotte, P., Muckle, G., Jacobson, J.L., Jacobson, S.W. & Dewailly, E. 2003 **Inuit Cohort Study.** Assessment of pre- and postnatal exposure to polychlorinated biphenyls: lessons from the Inuit Cohort Study. *Environ Health Perspect.* Jul;111(9):1253-8.

Baars, A.J., Bakker, M.I., Baumann, R.A., Boon, P.E., Freijer, J.I., Hoogenboom, L.A., Hoogerbrugge, R., van Klaveren, J.D., Liem, A.K., Traag, W.A. & de Vries, J. 2004. Dioxins, dioxin-like PCBs and non-dioxin-like PCBs in foodstuffs: occurrence and dietary intake in The Netherlands. *Toxicol Lett.* 1:51-61.

Baccarelli, A., Pesatori, A.C., Consonni, D., Mocarelli, P., Patterson, D.G. Jr., Caporaso, N.E., Bertazzi, P.A. & Landi, M.T. 2005. Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. *Br J Dermatol.* Mar;152(3):459-65.

Baeyens, W., Leermakers, M., Elskens, M., Van Larebeke, N., De Bont, R., Vanderperren, H., Fontaine, A., Degroot, J.M., Goeyens, L., Hanot, V. & Windal, I. 2007. PCBs and PCDD/FS in fish and fish products and their impact on the human body burden in Belgium. *Arch Environ Contam Toxicol.* May;52(4):563-71.

Bakir, F., Damluji, S.F., Amin-Zaki, L., Murtadha, M., Khalidi, A., al-Rawi, N.Y., Tikriti, S., Dahahir, H.I., Clarkson, T.W., Smith, J.C. & Doherty, R.A. 1973. Methylmercury poisoning in Iraq. *Science.* 181:230-241.

Banerji A, Bell A, Mills EL, McDonald J, Subbarao K, Stark G. Lower respiratory tract infections in Inuit infants on Baffin Island. *CMAJ.* 2001;164(13):1847–1850

Baraldi, M., Zanolli, P., Tascadda, F., Blom, J.M.C. & Brunello, N. 2002. Cognitive deficits and changes in gene expression of NMDA receptors after prenatal methylmercury exposure. *Environ Health Perspectives.* 110:855-858.

Barkay, T., Liebert, C. & Gillman, M. 1989. Environmental significance of the potential for mer(TN21)-mediated reduction of Hg²⁺ to Hg⁰ in natural waters. *Appl Environ Microbiol* 55(5):1196-1202.

Barska, I. 2008, About dioxins without emotion. (in Polish). *Wiad. Ryb .* 2008; 3-5,12- 13. 3-5,12-13.

Barska I. & Skrzynski, I. 2003. Contents of methylmercury and total mercury in Baltic Sea fish and fish products. *Bull.of SFI Gdynia.* 3 (160): 17-32

Beijer, K. & Jernelov, A. 1978. Ecological aspects of mercury-selenium interaction in the marine environment. *Environ Health Perspect* 25, 43–45.

Bemis, J.C. & Seegal, R.F. 1999. Polychlorinated biphenyls and methylmercury act synergistically to reduce rat brain dopamine content in vitro, *Environ. Health Perspect.* 107:879–885.

Bemis, J.C. & Seegal, R.F. 2000. Polychlorinated biphenyls and methylmercury alter intracellular calcium concentrations in rat cerebellar granule cells, *Neurotoxicology.* 21:1123–1134

- Björnberg, K.A., Vahter, M., Berglund, B., Niklasson, B., Blennow, M. & Sandborgh-Englund, G.** 2005. Transport of methylmercury and inorganic mercury to the foetus and breast-fed infant. *Environ. Health Perspect.* 113, 1381–1385.
- Björnberg, K.A., Vahter, M., Grawé, K.P. & Berglund, M.** 2005 b. Methyl mercury exposure in Swedish women with high fish consumption. *Sci Total Environ.*;341(1-3):45-52.
- Blanco, S.L., Sobrado, C., Quintela, C., Cabaleiro, S., Gonzalez, J.C. & Vieites, J.M.** 2007. Dietary uptake of dioxins (PCDD/PCDFs) and dioxin-like PCBs in Spanish aquacultured turbot (*Psetta maxima*). *Food Addit Contam. Apr*;24(4):421-8.
- Bloom, M.S., Weiner, J.M., Vena, J.E. & Beehler, G.P.** 2003. Exploring associations between serum levels of select organochlorines and thyroxine in a sample of New York state sportsmen: the New York State Angler Cohort Study. *Environmental Research* 93: 52–66.
- Bloom, N.S.** 1992. On the chemical form of mercury in edible fish and marine invertebrate tissue. *Can J Fish Aquat Sci.* 49:1010-1017.
- Bocio, A., Domingo, J.L., Falco, G. & Llobet, J.M.** 2007. Concentrations of PCDD/PCDFs and PCBs in fish and seafood from the Catalan (Spain) market: estimated human intake. *Environ Int.* Feb;33(2):170-5.
- Boffetta, P., Sallsten, G., Garcia-Gomez, M., Pompe-Kirn, V., Zaridze, D. & Bulbulyan, M.** 2001. Mortality from cardiovascular diseases and exposure to inorganic mercury. *Occup Environ Med* 58: 461-466.
- Braune, B.M., Outridge, P.M., Fisk, A.T., Muir, D.C.G., Helm, P.A. & Hobbs, K.** 2005. Persistent organic pollutants and mercury in marine biota of the Canadian Arctic: an overview of spatial and temporal trends. *Sci Total Environ.*351–352:4-56,
- Brunborg, L.A., Graff, I.E., Frøyland, L. & Julshamn, K.** 2006. Levels of non-essential elements in muscle from harp seal (*Phagophilus groenlandicus*) and hooded seal (*Cystophora cristata*) caught in the Greenland Sea area. *Sci.Total Environ.*
- Buck, G.M., Tee, G.P., Fitzgerald, E.F., Vena, J.E., Weiner, J.M., Swanson, M. & Msall, M.E.** 2003. Maternal fish consumption and infant birth size and gestation: New York State Angler Cohort Study. *Environ Health.* Jun 2;2(1):7.
- Bulger, R.E.** 1986. Renal damage caused by heavy metals. *Toxicol Pathol.* 14:58-65.
- Burel, C., Boujard, T., Escaffre, A.M., Kaushik, S.J., Boeuf, G., Mol, K.A., Van den Geyten, S. & Kühn, E.R.** 2000. Dietary low-glucosinolate rapeseed meal affects thyroid status and nutrient utilization in rainbow trout (*Oncorhynchus mykiss*). *Brit. J. Nutr.* 83: 653-664.
- Burger, J., Stern, A.H. & Gochfeld, M.** 2005. Mercury in commercial fish: optimizing individual choices to reduce risk. *Environ Health Perspect.* 113: 266-71.
- Bykowski, P.** Dioxins in fish products. 2002. *Mag.Przem.Ryb.* (in Polish),5: 9- 12.
- Bykowski, P., Pawlak, M.** 2009. Safety of Polish food products (in press). *Gdynia Marit. Univ. Works.*

Bykowski, P., Polak- Juszczak, I., Usyduś, Z., Barska, I., Malesa- Cieciewicz, M. & Ladkowska, M. 1997. Badania ryb morskich i przetworów rybnych, In : Michna W. (eds.) Raport z monitoringu jakości gleb, roślin, produktów rolniczych i spożywczych. Warsaw, 48-60.

Bykowski, P., Polak- Juszczak, L., Usyduś, Z., Guz, W., Skrzynski, I., Barska, I., Malesa- Cieciewicz, M. & Ladkowska M. 2002, Badania ryb morskich i przetworów rybnych, In: Michna W. (eds.) Raport z monitoringu jakości gleb, roślin, produktów rolniczych i spożywczych. Warsaw, 62-69.

Cabañero, A.I., Carvalho, C., Madrid, Y., Batoréu, C. & Cámara, C. 2005. Quantification and speciation of mercury and selenium in fish samples of high consumption in Spain and Portugal. *Biol Trace Elem Res.* 103(1):17-35.

Callahan, M.A., Slimak, M.W. & Gabel, N.W. 1979. Water related environmental fate of 129 priority pollutants, introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, D.C: U.S. Environmental Protection Agency, Office of Water Waste and Management. 440/4-79-029a., 14-1 -14-15.

Carratu, I. M.R., Borracci, P., Coluccia, A., Giustino, A., Renna, G., Tomasini, M.C., Raisi, E., Antonelli, T., Cuomo, V., Mazzoni, E. & Ferraro, L. 2006. Acute exposure to methylmercury at two developmental windows: focus on neurobehavioral and neurochemical effects in rat offspring. *Neuroscience.* 141:1619-29.

Caudle, W.M., Richardson, J.R., Delea, K.C., Guillot, T.S., Wang, M., Pennell, K.D. & Miller, G.W. 2006. Polychlorinated biphenyl-induced reduction of dopamine transporter expression as a precursor to Parkinson's disease-associated dopamine toxicity. *Toxicol Sci.* Aug;92(2):490-9.

Charnley, G. & Doull, J. 2005. Human exposure to dioxins from food, 1999-2002. *Food Chem. Toxicol.* 43: 671-679.

Chen, Y.W., Huang, C.F., Tsai, K.S., Yang, R.S., Yen, C.C., Yang, C.Y., Lin-Shiau, S.Y. & Liu, S.H. 2006. The role of phosphoinositide 3-kinase/akt signaling in low-dose mercury-induced mouse pancreatic {beta}-cell dysfunction in vitro and in vivo. *Diabetes* 55, 1614–1624.

Chiu, A., Beaubier, J., Chiu, J., Chan, L. & Gerstenberger, S. 2004. Epidemiologic studies of PCB congener profiles in North American fish consuming populations. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 22:13-36.

Choi, A.L., Levy, J.I., Dockery, D.W., Ryan, L.M., Tolbert, P.E., Altshul, L.M. & Korrick, S.A. 2006. Does living near a Superfund site contribute to higher polychlorinated biphenyl (PCB) exposure? *Environ Health Perspect.* Jul;114(7):1092-8.

Choi, B.H., Lapham, L.W., Amin-Zaki, L. & Saleem, T. 1978. Abnormal neuronal migration, deranged cerebral cortical organization and diffuse white matter astrocytosis of human fetal brain: A major effect of methylmercury poisoning in utero. *J Neuropathol Exp Neurol.* 37:719-732.

Choi, M.H. & Cech, J.J. 1998. Unexpectedly high mercury level in pelleted commercial fish feed. *Environ. Toxicol. Chem.* 17, 1979–1981.

Chuu, J.J., Hsu, C.J. & Lin-Shiau, S.Y. 2001a. Abnormal auditory brainstem responses for mice treated with mercurial compounds: involvement of excessive nitric oxide. *Toxicology* 162, 11–22.

- Chuu, J.J., Liu, S.H. & Lin-Shiau, S.Y.** 2001b. Effects of methyl mercury, mercuric sulfide and cinnabar on active avoidance responses, Na⁺/K⁺-ATPase activities and tissue mercury contents in rats. *Proc. Natl. Sci. Counc. Repub. China B* 25, 128–136.
- Clarkson, T.W. & Magos, L.** 2006. The toxicology of mercury and its chemical compounds. *Crit Rev Toxicol* 36:609–662.
- Clarkson, T.W.** 1995. Environmental contaminants in the food chain. *Am J Clin Nutr.* 61:682-686.
- Clarkson TW. Mercury. *J Am Coll Toxicol.* 8:1291-1296. 1989.
- Coccini, T., Roda, E., Castoldi, A.F., Goldoni, M., Poli, D., Bernocchi, G. & Manzo, L.** 2007. Perinatal co-exposure to methylmercury and PCB153 or PCB126 in rats alters the cerebral cholinergic muscarinic receptors at weaning and puberty. *Toxicology.* Aug 16;238(1):34-48.
- Coelhan, M. & Barlas, H.** 1998. Levels of some organochlorine contaminants in fishes from Turkey. *Fresenius Environ Bull* 7:388–95.
- Coelhan, M., Strohmeier, J. & Barlas, H.** 2006. Organochlorine levels in edible fish from the Marmara Sea, Turkey. *Environ Int.* Aug;32(6):775-80.
- Cope, W.G., Wiener, J.G. & Rada, R.G.** 1990. Mercury accumulation in yellow perch in Wisconsin Seepage Lakes: Relation to lake characteristics. *Environ Toxicol Chem.* 9:931-940.
- Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P. & Gosme-Seguret, S.** 2002. Neurodevelopmental investigation among methylmercury-exposed children in French Guiana. *Environ Res* 89:1–11.
- Cortes S. & Fortt, A.** 2007. Mercury content in Chilean fish and estimated intake levels. *Food Addit Contam.* 24(9):955-9.
- Costa, L.G., Aschner, M., Vitalone, A., Syversen, T. & Soldin, O.P.** 2004. Developmental neuropathology of environmental agents. *Annu Rev Pharmacol Toxicol.* 44:87-110.
- Costa, L.G., Aschner, M., Vitalone, A., Syversen, T. & Soldin, O.P.** 2004. Developmental neuropathology of environmental agents. *Annu Rev Pharmacol Toxicol.* 44:87-110
- Costa, L.G., Fattori, V., Giordano, G. & Vitalone, A.** 2007. An in vitro approach to assess the toxicity of certain food contaminants: methylmercury and polychlorinated biphenyls. *Toxicology.* Jul 31;237(1-3):65-76.
- Crump, K.S., Kjellstrom, T., Shipp, A.M., Silvers, A. & Stewart, A.** 1998. Influence of prenatal mercury exposure upon scholastic and psychological test performance: Benchmark analysis of a New Zealand cohort. *Risk Anal.* 18:701-13.
- Cuadra, S.N., Linderholm, L., Athanasiadou, M. & Jakobsson, K.** 2006. Persistent organochlorine pollutants in children working at a waste-disposal site and in young females with high fish consumption in Managua, Nicaragua. *Ambio.* May;35(3):109-16
- Curns, A.T., Holman, R.C., Shay, D.K., Cheek, J.E., Kaufman, S.F. & Singleton, R.J.** 2002. Outpatient and hospital visits associated with otitis media among American Indian and Alaska native children younger than 5 years. *Pediatrics.* 109(3):e41.

- Dallaire, F., Dewailly, E., Laliberte, C., Muckle, G. & Ayotte, P.** 2002. Temporal trends of organochlorine concentrations in umbilical cord blood of newborns from the lower north shore of the St. Lawrence river (Quebec, Canada). *Environ Health Perspect.* Aug;110(8):835-8.
- Dallaire, F., Dewailly, E., Muckle, G., Vézina, C., Jacobson, S.W. & Jacobson, J.** 2004. Acute infections and environmental exposure to organochlorines in Inuit infants from Nunavik. *Environ Health Perspect* 112:1359–1365.
- Dallaire, F., Dewailly, E., Vezina, C., Muckle, G., Weber, J.P., Bruneau, S. & Ayotte, P.** 2006. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. *Environ Health Perspect.* Aug;114(8):1301-5.
- Daré, E., Fetissoff, S., Hökfelt, T., Hall, H., Ögren, S.O. & Ceccatelli, S.** 2003. Effects of prenatal exposure to methylmercury on dopamine-mediated locomotor activity and dopamine D2 receptor binding. *Naunyn Schmiedebergs Arch Pharmacol.* 367:500-508.
- Darnerud, P.O., Atuma, S., Aune, M., Bjerselius, R., Glynn, A., Grawe, K.P. & Becker, W.** 2006. Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on Swedish market basket data. *Food Chem Toxicol.* Sep;44(9):1597-606.
- Davidson, P.W., Myers, G.J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M. & Clarkson, T.W.** 1998. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: Outcomes at 66 months of age in the seychelles child development study. *JAMA.*280:701-707.
- Davidson, P.W., Myers, G.J., Cox, C., Wilding, G.E., Shamlaye, C.F., Huang, L.S., Cernichiari, E., Sloane-Reeves, J., Palumbo, D. & Clarkson, T.W.** 2006. Methylmercury and neurodevelopment: longitudinal analysis of the Seychelles child development cohort. *Neurotoxicol. Teratol.* 28 (5), 529–535.
- Davidson, P.W., Palumbo, D., Myers, G.J., Cox, C., Shamlaye, C.F., Sloane-Reeves, J., Cernichiari, E., Wilding, G.E. & Clarkson, T.W.** 2000. Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet. *Environ. Res.* 84 (1), 1–11.
- De Marco, S.G., Botté, S.E. & Marcovecchio, J.E.** 2006. Mercury distribution in abiotic and biological compartments within several estuarine systems from Argentina: 1980-2005 period. *Chemosphere.* 65(2):213-23.
- Dean, J.G., Bosqui, F.L. & Lanoveite, K.H.** 1972. Removing heavy metals from waste water. *Environ Sci. Technol* 6:518-522.
- Debacker, N., Sasse, A., van Wouwe, N., Goeyens, L., Sartor, F. & van Oyen, H.** 2007. PCDD/F levels in plasma of a Belgian population before and after the 1999 Belgian PCB/DIOXIN incident. *Chemosphere.* Apr;67(9):S217-23.
- Debes, F., Budtz-Jørgensen, E., Weihe, P., White, R. & Grandjean, P.** 2006. Impact of prenatal methylmercury exposure on neurobehavioural function at age 14 years. *Neurotoxicol. Teratol.* 28, 363–375.
- Denison, M.S. & Nagy, S.R.** 2003. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu Rev Pharmacol Toxicol.* 43:309-34.

- Despres, C., Beuter, A., Richer, F. et al.** 2005. Neuromotor functions in Inuit preschool children exposed to Pb, PCBs and Hg. *Neurotoxicol. Teratol.* 27 (2): 245-257,
- Dewailly, E., Ayotte, P., Bruneau, S., Gingras, S., Belles-Isles, M. & Roy, R.** 2000. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environ Health Perspect* 108:205–211.
- Dewailly, E., Ayotte, P., Lucas, M. & Blanchet, C.** 2007. Risk and benefits from consuming salmon and trout: a Canadian perspective. *Food Chem Toxicol.* Aug;45(8):1343-8.
- Dolbec, J., Mergler, D., Larribe, F., Roulet, M., Lebel, J. & Lucotte, M.** 2001. Sequential analysis of hair mercury levels in relation to fish diet of an Amazonian population, Brazil. *Sci. Total Environ.* 271 (1–3), 87–97.
- Dolbec, J., Mergler, D., Sousa Passos, C.J., Sousa de Morais, S. & Lebel, J.** 2000. Methylmercury exposure affects motor performance of a riverine population of the Tapajos River, Brazilian Amazon. *Int. Arch. Occup. Environ. Health* 73 (3), 195–203.
- Donahue, D.A., Dougherty, E.J. & Meserve, L.A.** 2004. Influence of a combination of two tetrachlorobiphenyl congeners (PCB 47; PCB 77) on thyroid status, choline acetyltransferase (ChAT) activity, and short- and long-term memory in 30-day-old Sprague–Dawley rats. *Toxicology* 203: 99–107.
- Donkor, A.K., Bonzongo, J.C., Nartey, V.K. & Adotey, D.K.** 2006. Mercury in different environmental compartments of the Pra River Basin, Ghana. *Sci Total Environ.* 368 (1):164-76.
- Doré, F.Y., Goulet, S., Gallagher, A., Harvey, P.O., Cantin, J.F., D’Aigle, T. & Mirault, M.E.** 2001. Neurobehavioral changes in mice treated with methylmercury at two different stages of fetal development. *Neurotoxicol Teratol.* 23:463-472.
- Dunn, J.D. & Clarkson, T.W.** 1980. Does mercury exhalation signal demethylation of methylmercury? *Health Phys.* 38:411-414.
- Durrieu, G., Maury-Brachet, R. & Boudou, A.** 2005. Goldmining and mercury contamination of the piscivorous fish *Hoplias aimara* in French Guiana (Amazon basin). *Ecotoxicol Environ Saf.* 60:315–23.
- Easton, M.D.L., Luszniak, D. & Von der Geest, E.** 2002. Preliminary examination of contaminant loadings in farmed salmon, wild salmon and commercial salmon feed. *Chemosphere* 46, 1053–1074.
- EC (European Commission).** 2000. Opinion of the Scientific Committee on animal nutrition SCAN on the dioxin contamination of feedingstuffs and their contribution to the contamination of food of animal origin. Available at (<http://europa.eu.int/comm/food/fs/sc/scan/outcome.en.html>)
- EC (European Commission).** 2001. Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxins-like PCBs in food (update based on the new scientific information available since the adoption of the SCF opinion of 22 November 2000). Available at: http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html

EC Commission Regulation No. 199/2006 of 3 February 2006 amending Regulation (EC) No. 466/2001 setting maximum levels for certain contaminants in foodstuffs as regard to dioxins and dioxin-like PCBs. Official Journal of the European Union, L 32/34.

EFSA (European Food Safety Agency). 2005. Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the European Parliament related to the safety assessment of wild and farmed fish. EFSA-Q-2004-22.

Endo, T., Haraguchi, K., Cipriano, F., Simmonds, M.P., Hotta, Y. & Sakata, M. 2004. Contamination by mercury and cadmium in the cetacean products from Japanese market. *Chemosphere*, 54: 1653-1662.

Endo, T., Haraguchi, K., Hotta, Y., Hisamichi, Y., Lavery, S., Dalebout, M.L. & Baker, C.S. 2005. Total mercury, methyl mercury, and selenium levels in the red meat of small cetaceans sold for human consumption in Japan. *Environ Sci Technol.* 39(15):5703-8.

EPA. 2003. Exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Part III: Integrated summary and risk characterization for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. NAS Review Draft dated December 2003, National Center for Environmental Assessments, Research and Development, U.S. Environmental Protection Agency, Washington, D.C. U.S.A. Available at www.epa.gov/ncea/dioxin

EPA. 1984. Mercury health effects updates: Health issue assessment. Final report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Document no. EPA 600/8-84-019F..

EPA. 1971. Water quality criteria data book. Washington, DC: U. S. Environmental Protection Agency.

EPA. 2001. Water Quality Criterion for the Protection of Human Health: Methylmercury (EPA-823-R-01-001). U.S. EPA, Office of Science and Technology, Washington, DC. Available from: <http://www.epa.gov/waterscience/criteria/methylmercury/document.html>

Everett C.J., Frithsen, I.L., Diaz, V.A., Koopman, R.J., Simpson, W.M. Jr. & Mainous, A.G. 3rd. 2007. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. *Environ Res.* Mar;103(3):413-8.

Fairey, R., Taberski, K. & Lamerdin, S. 1997. Organochlorines and other environmental contaminants in muscle tissues of sportfish collected from San Francisco Bay. *Marine Pollution Bulletin.* 34:1058-1071.

Faroon, O.M., Jones, D. & de Rosa, C. 2001. Effects of polychlorinated biphenyls on the nervous system. *Toxicol. Ind. Health* 16:305-333.

Fattori, V. 2007. Evaluation of toxicity on the developing nervous system induced by some environmental contaminants: Methyl mercury and Polychlorinated Biphenyls (PCBs). PhD Thesis. University of Bari.

FDA. 1998. Mercury in fish: cause for concern? U.S. Food and Drug Administration. FDA Consumer.

FDA. 2006. Mercury Levels in Commercial Fish and Shellfish. Available at: <http://www.cfsan.fda.gov/~frf/sea-mehg.html>

Fitzgerald, E.F., Belanger, E.E., Gomez, M.I., Hwang, S.A., Jansing, R.L. & Hicks, H.E. 2007b. Environmental exposures to polychlorinated biphenyls (PCBs) among older residents of upper Hudson River communities. *Environ Res.*;104(3):352-60.

Fitzgerald, E.F., Hwang, S.A., Gomez, M., Bush, B., Yang, B.Z. & Tarbell, A. 2007. Environmental and occupational exposures and serum PCB concentrations and patterns among Mohawk men at Akwesasne. *J Expo Sci Environ Epidemiol.* May;17(3):269-78.

Fitzgerald, E.F., Hwang, S.A., Langguth, K., Cayo, M., Yang, B.Z., Bush, B., Worswick, P. & Lauzon, T. 2004. Fish consumption and other environmental exposures and their associations with serum PCB concentrations among Mohawk women at Akwesasne. *Environ Res.* Feb;94(2):160-70.

Food Safety Commission, Japan. 2005. Food Safety Risk Assessment Related to Methylmercury in Seafood. Available from: <http://www.fsc.go.jp/english/topics/methylmercury.html>.

Food Standards Agency. 2002. Mercury in imported fish and shellfish and UK farmed fish and their products. Food Surveillance Information Sheet 40/03. Available at: <http://www.food.gov.uk/science/surveillance/fsis-2003/fsis402003>

Foran, J.A., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. & Schwager, S.J. 2005b. Risk-based consumption advice for farmed Atlantic and wild Pacific salmon contaminated with dioxins and dioxin-like compounds. *Environm. Health Perspect.* 113: 552-556.

Foran, J.A., Good, D.H., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. & Schwager, S.J. 2005a. Quantitative analysis of the benefits and risks of consuming farmed and wild salmon. *J. Nutr.* 135: 2639-2643.

Foran, J.A., Hites, R.A., Carpenter, D.O., Hamilton, M.C., Mathews-Amos, A. & Schwager, S.J. 2004. A survey of metals in tissues of farmed atlantic and wild pacific salmon. *Environ. Toxicol. Chem.* 23, 2108–2110.

Gainetdinov, R.R. & Caron, M.G. 2003. Monoamine transporters: From genes to behavior. *Annu. Rev. Pharmacol. Toxicol.* 43:261–284.

Gao, H.M., Hong, J.S., Zhang, W. & Liu, B. 2003. Synergistic dopaminergic neurotoxicity of the pesticide rotenone and inflammogen lipopolysaccharide: relevance to the etiology of Parkinson's disease. *J Neurosci* 23:1228–36

Garcia, E. & Carignan, R. 2005. Mercury concentrations in fish from forest harvesting and fire-impacted Canadian boreal lakes compared using stable isotopes of nitrogen. *Environ. Toxicol. Chem.* 24: 685-693.

Gavis, J. & Ferguson, J.F. 1972. The cycling of mercury through the environment. *Water Res* 6:986-1008.

Gilmour, C.C. & Henry, E.A. 1991. Mercury methylation in aquatic systems affected by acid deposition. *Environmental Pollution* 71(2-4):131-169.

- Ginsberg, G., Slikker, W., Bruckner, J. & Sonawane, B.** 2004. Incorporating children's toxicokinetics into a risk framework. *Environ. Health Perspect.* 112, 272–283.
- Godfrey, K.M. & Barker, D.J.** 2001. Fetal programming and adult health. *Public Health Nutr.* 4:611–24
- Gomara, B., Bordajandi, L.R., Fernandez, M.A., Herrero, L., Abad, E., Abalos, M., Rivera, J. & Gonzalez, M.J.** 2005. Levels and trends of polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (PCBs) in Spanish commercial fish and shellfish products, 1995-2003. *J Agric Food Chem.* Oct 19;53(21):8406-13.
- Gotz, M.E., Koutsilieris, E., Riederer, P., Ceccatelli, S. & Dare, E.** 2002. Methylmercury induces neurite degeneration in primary culture of mouse dopaminergic mesencephalic cells. *J. Neural Transm.* 109, 597–605.
- Goulet, S., Doré, F.Y. & Mirault, M.E.** 2003. Neurobehavioral changes in mice chronically exposed to methylmercury during fetal and early postnatal development. *Neurotoxicol Teratol.* 25:335–347.
- Grandjean, P. & Landrigan, P.J.** 2006. Developmental neurotoxicity of industrial chemicals. *Lancet.* Dec 16;368(9553):2167-78.
- Grandjean, P., Weihe, P., Burse, V.W., Needham *et al.*** 2001. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol. Teratol.* 23 (4): 305-317,
- Grandjean, P., Weihe, P., Jørgensen, P.J., Clarkson, T., Cernichiari, E. & Viderø, T.** 1992. Impact of Maternal Seafood Diet on Fetal Exposure to Mercury, Selenium, and lead. *Archives of Environmental Health.* 47(3), 185-195.
- Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R. & Jorgensen, P.J.** 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol.* 19:417-428.
- Grandjean, P., Weihe, P., White, R.F. & Debes, F.** 1998. Cognitive performance of children prenatally exposed to “safe” levels of methylmercury. *Environ Res.* 77:165-172.
- Grandjean, P., Weihe, P. & White, R.F.** 1995. Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicology* 16, 27–33.
- Grieb, T.M., Driscoll, C.T. & Gloss, S.P.** 1990. Factors affecting mercury accumulation in fish in the upper Michigan peninsula. *Environ Toxicol Chem.* 9:919-930.
- Guallar, E., Sanz-Gallardo, M.I., van't Veer, P., Bode, A, Gomez-Aracena, J. & Kark, J,D.I.** 2002. Mercury, fish oils, and the risk of myocardial infarction. *N Engl J Med.* 347:1747N–54N.
- Guruge, K.S. & Tanabe, S.** 2004. Polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxin-like biphenyls in biota from Sri Lankan coast. *Marine Pollution Bulletin.* 48:986–1008.
- Gutenmann, W.H., Ebel, J.G. Jr, Kuntz, H.T., Yourstone, K.S. & Lisk, D.J.** 1992. Residues of p,p'-DDE and mercury in lake trout as a function of age. *Arch Environ Contam Toxicol.* 22:452-455.

- Hagele, T.J., Mazerik, J.N., Gregory, A., Kaufman, B., Magalang, U. & Kuppusamy, M.L.** 2007. Mercury activates vascular endothelial cell phospholipase D through thiols and oxidative stress. *Int J Toxicol* 26: 57-69.
- Haggqvist, B., Havarinasab, S., Bjorn, E. & Hultman, P.** 2005. The immunosuppressive effect of methylmercury does not preclude development of autoimmunity in genetically susceptible mice. *Toxicology* 208, 149–164.
- Hagmar, L., Bjork, J., Sjodin, A., Bergman, A. & Erfurth, E.M.** 2001b. Plasma levels of persistent organohalogenes and hormone levels in adult male humans. *Archives of Environmental Health* 56: 138–143.
- Hagmar, L., Rylander, L., Dyremark, E., Klasson-Wehler, E. & Erfurth, E.M.** 2001. Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. *International Archives of Occupational and Environmental Health* 74: 184–188.
- Hallgren, C.G., Hallmans, G., Jansson, J.-H., Marklund, S.L., Huhtasaari, F. & Schutz, A.** 2001. Markers of high fish intake are associated with decreased risk of a first myocardial infarction. *Brit J Nutrition* 86: 397-404.
- Hallgren, S. & Darnerud, P.O.** 2002. Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats – testing interactions and mechanisms for thyroid hormone effects. *Toxicology* 177: 227–243.
- Hallgren, S., Sinjari, T., Hakansson, H. & Darnerud, P.O.** 2001. Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. *Archives of Toxicology* 75: 200–208.
- Hammerschmidt, C.R. & Fitzgerald, W.F.** 2006. Bioaccumulation and trophic transfer of methylmercury in Long Island Sound. *Arch Environ Contam Toxicol.* 51(3):416-24.
- Hammerschmidt, C.R. & Fitzgerald, W.F.** 2004. Geochemical controls on the production and distribution of methylmercury in nearshore marine sediments. *Environ Sci Technol* 38:1487–1495.
- He, Y., Imam, S.Z., Dong, Z., Jankovic, J., Ali, S.F. & Appel, S.H.** 2003. Role of nitric oxide in rotenone-induced nigro-striatal injury. *J Neurochem* 86:1338–45.
- Hellou, J., Fancey, L.L. & Payne, J.F.** 1992. Concentrations of twenty-four elements in bluefin tuna, *Thunnus thynnus*, from the Northwest Atlantic. *Chemosphere.* 24:211-218.
- Hennig B., Reiterer, G., Majkova, Z., Oesterling, E., Meerarani, P. & Toborek, M.** 2005. Modification of environmental toxicity by nutrients: implications in atherosclerosis. *Cardiovasc Toxicol.* 5:153-60.
- Hites, R.A., Foran, J.A., Carpenter, D.O., Hamilton, M.C., Knuth, B.A. & Schwager, S.J.** 2004. Global Assessment of Organic Contaminants in Farmed Salmon Science. 303: 226-229.
- Holman, R.C., Curns, A.T., Kaufman, S.F., Cheek, J.E., Pinner, R.W. & Schonberger, L.B.** 2001. Trends in infectious disease hospitalizations among American Indians and Alaska natives. *Am J Public Health* 91(3):425–431.

- Horvat, M., Nolde, N., Fajon, V., Jereb, V., Logar, M., Lojen, S., Jacimovic, R. & Falnoga, I.** 2003. Total mercury methylmercury and selenium in mercury polluted areas in the province Guizhou, China. *Sci. Total Environ.* 304, 231–256.
- Houserová, P., Kubán, V., Krácmár, S. & Sitko, J.** 2007. Total mercury and mercury species in birds and fish in an aquatic ecosystem in the Czech Republic. *Environ Pollut.* 145(1):185-94.
- Hueter, R.E., Fong, W.G. & Henderson, G.** 1995. Methylmercury concentration in shark muscle by species, size and distribution of sharks in Florida coastal waters. In: Porcella DB, Wheatley B, eds. *Mercury as a global pollutant. Proceedings of the Third International Conference Whistler, British Columbia, July 10-14, 1994.* Boston, MA: Kluwer Academic Publishers. 893-899.
- Isosaari, P., Hallikainen, A., Kiviranta, H., Vuorinen, P.J., Parmanne, R., Koistinen, J, et al.** 2006. Polychlorinated dibenzo-p-dioxins, dibenzofurans, biphenyls, naphthalenes and polybrominated diphenyl ethers in the edible fish caught from the Baltic Sea and lakes in Finland. *Environ Pollut* 141:213–25.
- Itai, Y., Fujino, T., Ueno, K. & Motomatsu, Y.** 2004. An epidemiological study of the incidence of abnormal pregnancy in areas heavily contaminated with methylmercury. *Environ. Sci.* 11, 83–97.
- Jackson, T.A.** 1991. Biological and environmental control of mercury accumulation by fish in lakes and reservoirs of northern Manitoba, Canada. *Can J Fish Aquat Sci.* 48:2449-2470.
- Jacobson, J.L. & Jacobson, S.W.** 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. *J Pediatr.* Dec;143(6):780-8.
- JECFA (Joint FAO/WHO Expert Committee on Food Additives).** 2003. Sixty-first Meeting, Summary and Conclusions. Rome, 10–19 June Available from: <ftp://ftp.fao.org/es/esn/jecfa/jefcs61sc.pdf>
- Jiang, Q., Hanari, N., Miyake, Y., Okazawa, T., Lau, R.K., Chen, K., Wyrzykowska, B., So, M.K., Yamashita, N. & Lam, P.K.** 2007. Health risk assessment for polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins and dibenzofurans, and polychlorinated naphthalenes in seafood from Guangzhou and Zhoushan, China. *Environ Pollut.* Jul;148(1):31-9.
- Johansson, C., Castoldi, A.F., Onishchenko, N., Manzo, L., Vahter, M. & Ceccatelli, S.** 2007. Neurobehavioural and molecular changes induced by methylmercury exposure during development. *Neurotox Res.* 11(3-4):241-60.
- Johansson, C., Tofighi, R., Tamm, C., Goldoni, M. et al.** 2006. Cell death mechanisms in AtT20 pituitary cells exposed to polychlorinated biphenyls (PCB126 and PCB153) and methylmercury. *Toxicol. Lett.* 167 (3): 183-190,
- Johnsson, C., Sallsten, G., Schutz, A., Sjors, A. & Barregard, L.** 2004. Hair mercury levels versus freshwater fish consumption in household members of Swedish angling societies. *Environ. Res.* 96, 257–263.
- Julshamn, K., Grøsvik, B.E., Nedreaas, K. & Maage, A.** 2006. Mercury concentration in fillets of Greenland halibut (*Reinhardtius hippoglossoides*) caught in the Barents Sea in January 2006. *Sci Total Environ.* 372(1):345-9.
- Kanai, Y. & Endou, H.** 2003. Functional properties of multispecific amino acid transporters and their implications to transporter-mediated toxicity, *J. Toxicol. Sci.*, 28 (1): 1-17.

- Karl, H., Ruoff, U. & Blüthgen, A.** 2002. Levels of dioxins in fish and fishery products on the German market. *Chemosphere* 49:765–73.
- Karl, H. & Ruoff, U.** 2007. Dioxins, dioxin-like PCBs and chloroorganic contaminants in herring, *Clupea harengus*, from different fishing grounds of the Baltic Sea. *Chemosphere*. Apr;67(9):S90-5.
- Karmaus, W. & Zhu, X.** 2004. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study. *Environ Health*. Jan 28;3(1):1.
- Kehrig Hdo, A., Seixas, T.G., Palermo, E.A., Baêta, A.P., Castelo-Branco, C.W., Malm, O. & Moreira, I.** 2009. The relationships between mercury and selenium in plankton and fish from a tropical food web. *Environ Sci Pollut Res Int*. 16(1):10-24,
- Kelly, B.C., Ikonomou, M.G., Higgs, D.A., Oakes, J. & Dubetz, C.** 2008. Mercury and other trace elements in farmed and wild salmon from British Columbia, Canada. *Environ Toxicol Chem*. 27(6):1361-70.
- Kilic, N., Sandal, S., Colakoglu, N., Kutlu, S., Seyran, A. & Yilmaz, B.** 2005. Endocrine disruptive effects of polychlorinated biphenyls on the thyroid gland in female rats. *Tohoku Journal of Experimental Medicine* 206: 327–332.
- Kimbrough, R.D., Doemland, M.L. & Mandel, J.S.** 2003. A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. *J Occup Environ Med* 45:271 – 82.
- Kimura-Kuroda, J., Nagata, I. & Kuroda, Y.** 2007. Disrupting effects of hydroxy-polychlorinated biphenyl (PCB) congeners on neuronal development of cerebellar Purkinje cells: a possible causal factor for developmental brain disorders? *Chemosphere*. Apr;67(9):S412-20.
- Kitamura, S., Jinno, N., Suzuki, T., Sugihara, K., Ohta, S., Kuroki, H. & Fujimoto, N.** 2005. Thyroid hormone-like and estrogenic activity of hydroxylated PCBs in cell culture. *Toxicology* 208: 377–387.
- Kiviranta, H., Vartiainen, T., Parmanne, R., Hailikainen, A. & Koistinen, J.** 2003. PCDD/Fs i PCBs in Baltic herring during the 1990s. *Chemosphere*. 50: 1201- 1216
- Kiviranta, H., Ovaskainen, M.L. & Vartiainen, T.** 2004. Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. *Environ. Int.* 30: 923–932.
- Kjellstrom, T., Kennedy, P., Wallis, S. & Mantell, C.** 1986. Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 1. Preliminary Tests at Age 4, Report 3080. National Swedish Environmental Protection Board, Solna, Sweden.
- Kjellstrom, T., Kennedy, P., Wallis, S., Stewart, A., Friberg, L., Lind, B., Witherspoon, P. & Mantell, C.** 1989. Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish. Stage 2. Interviews and Psychological Tests at Age 6, Report 3642. National Swedish Environmental Protection Board, Solna, Sweden.
- Knutzen, J., Bjerkgeng, B., Næs, K. & Schlabach, M.** 2003. Polychlorinated dibenzofurans/dibenzo-p-dioxins (PCDF/PCDDS) and other dioxin-like substances in marine organisms from the Grenland fjords, S. Norway, 1975-2001: present contamination levels, trends and species specific accumulation of PCDF/PCDD congeners. *Chemosphere* 52:745–60.

Koch, A., Sorensen, P., Homoe, P., Molbak, K., Pedersen, F.K. & Mortensen, T. 2002. Population-based study of acute respiratory infections in children, Greenland. *Emerg Infect Dis* 8(6):586–593.

Koibuchi, N., Jingu, H., Iwasaki, T. & Chin, W.W. 2003. Current perspectives on the role of thyroid hormone in growth and development of cerebellum, *Cerebellum* 2: 279–289.

Kraepiel, A.M.L., Keller, K., Chin, H.B., Malcolm, E.G. & Morel, F.M.M. 2003. Sources and variations of mercury in tuna. *Environ Sci Technol* 37:5551–5558.

Kumar, M. & Aalbersberg, B. 2008. Mercury Levels in Fish from Solomon Islands and Kiribati and Public Health Implications. Report for: World Health Organization (WHO).

Kutsuna, M. 1968. Minamata disease: Study group of Minamata disease. Japan: Kumamoto University.1-4.

Landrigan, P.J., Kimmel, C.A., Correa, A. & Eskenazi, B. 2004. Children's health and the environment: public health issues and challenges for risk assessment. *Environ. Health Perspect.* 112, 257–265.

Langer, P., Kocan, A., Tajtakova, M., Petrik, J., Chovancova, J., Drobna, B., Jursa, S., Pavuk, M., Koska, J., Trnovec, T., Sebkova, E. & Klimes, I. 2003. Possible effects of polychlorinated biphenyls and organochlorinated pesticides on the thyroid after long-term exposure to heavy environmental pollution. *Journal of Occupational and Environmental Medicine* 45: 526–532.

Larsen, J.C. 2006 Risk assessments of polychlorinated dibenzo- p-dioxins, polychlorinated dibenzofurans, and dioxin-like polychlorinated biphenyls in food. *Mol Nutr Food Res.* Oct;50(10):885-96.

Lee, D.H., Lee, I.K., Song, K., Steffes, M., Toscano, W., Baker, B.A., Jacobs, D.R. Jr. 2006. A strong dose–response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care.* 29: 1638–1644.

Lee, D.W. & Opanashuk, L.A. 2004. Polychlorinated biphenyl mixture aroclor 1254-induced oxidative stress plays a role in dopaminergic cell injury. *Neurotoxicology* 25: 925–939.

Lim, C. & Klesius, P.H. 2004. Use of Alternative Protein Sources in Diets of Warmwater Fish. *Proc. 11th ISNFF, Phuket, Thailand:* 30.

Lim S, Chung HU, Paek D. Low dose mercury and heart rate variability among community residents nearby to an industrial complex in Korea. *Neurotoxicology* 2009 (in press).

Limke, T.L. & Atchison, W.D. 2002. Acute exposure to methylmercury opens the mitochondrial permeability transition pore in rat cerebellar granule cells. *Toxicol. Appl. Pharmacol.* 178, 52–61.

Lindberg, A., Bjornberg, K.A., Vahter, M. Berglund, M. 2004. Exposure to methylmercury in non-fish-eating people in Sweden. *Environ. Res.* 96, 28–33.

Link, B., Gabrio, T., Zollner, I., Piechotowski, I. & Kouros, B. 2007. Sentinel health department project in Baden-Wuerttemberg (Germany)--a useful tool for monitoring children's health and environment. *Int J Hyg Environ Health.* May;210(3-4):351-5.

Lockhart, W.L., Stern, G.A., Wagemann, R., Hunt, R.V., Metner, D.A., DeLaronde, J., Dunn, B., Stewart, R.E., Hyatt, C.K., Harwood, L. & Mount, K. 2005. Concentrations of mercury in tissues of beluga whales (*Delphinapterus leucas*) from several communities in the Canadian Arctic from 1981 to 2002. *Sci.Total Environ.* 351-352: 391-412.

Longnecker, M.P. 2006. Pharmacokinetic variability and the miracle of modern analytical chemistry. *Epidemiology.* 17: 350–351.

Loufty, N., Fuerhacker, M., Tundo, P., Raccanelli, S. & Tawfic Ahmed, M. 2007. Monitoring of polychlorinated dibenzo-p-dioxins and dibenzofurans, dioxin-like PCBs and polycyclic aromatic hydrocarbons in food and feed samples from Ismailia city, Egypt. *Chemosphere* 66:1962–70.

Love, J.L., Rush, G.M. & McGrath, H. 2003. Total mercury and methylmercury levels in some New Zealand commercial marine fish species. *Food Addit Contam.* 20(1):37-43.

Mallin, K., McCann, K. & D'Aloisio, A., et al. 2004. Cohort mortality study of capacitor manufacturing workers, 1944-2000. *J Occup Environ Med* 46:565 – 76.

Mambrini, M., Roem, A.J., Cravèdi, J.P., Lallès, J.P. & Kaushik, S.J. 1999. Effects of Replacing Fish Meal with Soy Protein Concentrate and of DL-Methionine Supplementation in High- Energy, Extruded Diets on the Growth and Nutrient Utilization of Rainbow Trout, *Oncorhynchus mykiss*. *J. Anim. Sci.* 77: 2990-2999.

Marrugo-Negrete J, Verbel JO, Ceballos EL, Benitez LN. Total mercury and methylmercury concentrations in fish from the Mojana region of Colombia. *Environ Geochem Health.* 30(1):21-30. 2008.

Matsumoto, H., Koya, G. & Takeuchi, T. 1965. Fetal Minamata disease--a neuropathological study of two cases of intrauterine intoxication by a methylmercury compound. *J Neuropathol Exp Neurol.* 24:563-574.

Mazerik JN, Hagele T, Sherwani S, Ciapala V, Butler S, Kuppusamy ML, Hunter M, Kuppusamy P, Marsh CB, Parinandi NL. Phospholipase A2 activation regulates cytotoxicity of methylmercury in vascular endothelial cells. *Int J Toxicol.* 26: 553-569. 2007.

McElroy, J.A., Kanarek, M.S., Trentham-Dietz, A., Robert, S.A., Hampton, J.M., Newcomb, P.A., Anderson, H.A. & Remington, P.L. 2004. Potential exposure to PCBs, DDT, and PBDEs from sport-caught fish consumption in relation to breast cancer risk in Wisconsin. *Environ Health Perspect.* Feb;112(2):156-62.

Meerts, I.A., Assink, Y., Cenijn, P.H., Van Den Berg, J.H., Weijers, B.M., Bergman, A., Koeman, J.H. & Brouwer, A. 2002. Placental transfer of a hydroxylated polychlorinated biphenyl and effects on fetal and maternal thyroid hormone homeostasis in the rat. *Toxicological Sciences* 68: 361–371.

Meerts, I.A., Lilienthal, H., Hoving, S., Van Den Berg, J.H., Weijers, B.M., Bergman, A., Koeman, J.H. & Brouwer, A. 2004. Developmental exposure to 4-hydroxy-2,3,30,40,5-pentachlorobiphenyl (4-OH-CB107): long-term effects on brain development, behavior, and brain stem auditory evoked potentials in rats. *Toxicological Sciences* 82: 207–218.

Meili, M. 1991. The coupling of mercury and organic matter in the biogeochemical cycle - towards a mechanistic model for the boreal forest zone. *Water Air Soil Pollut* 56:333-347.

- Miller, K.P., Borgeest, C., Greenfeld, C., Tomic, D. & Flaws, J.A.** 2004. In utero effects of chemicals on reproductive tissues in females. *Toxicol Appl Pharmacol.* 198:111-31
- Miniero, R., Ceretti, G., Cherin, E., Dellatte, E., De Luca, S., Ferri, F., Fulgenzi, A.R., Grim, F., Iacovella, N., Iamiceli, A.L., Ingelido, A.M., Vio, P. & di Domenico, A.** 2005. PCDD and PCDF intake through consumption of locally produced seafood by Venice lagoon residents: elements for risk management. *Mar Pollut Bull.* 50:1727-32.
- Mishra, S., Bhalke, S., Saradhi, I.V., Suseela, B., Tripathi, R.M., Pandit, G.G. & Puranik, V.D.** 2007. Trace metals and organometals in selected marine species and preliminary risk assessment to human beings in Thane Creek area, Mumbai. *Chemosphere.* 69(6):972-8.
- Miyakawa, T., Murayama, E., Sumiyoshi, S., Deshimaru, M. & Fujimoto, T.** 1976. Late changes in human sural nerves in Minamata disease and in nerves of rats with experimental organic mercury poisoning. *Acta Neuropath.* 35:131-138.
- Moon, H.B. & Ok, G.** 2006. Dietary intake of PCDDs, PCDFs and dioxin-like PCBs, due to the consumption of various marine organisms from Korea. *Chemosphere* 62:1142–52.
- Morreale de Escobar, G., Obregon, M.J. & Escobar del Rey, F.** 2004. Role of thyroid hormone during early brain development. *European Journal of Endocrinology* 151: 25-37.
- Morrisette, J., Takser, L., St-Amour, G., Smargiassi, A., Lafond, J. & Mergler, D.** 2004. Temporal variation of blood and hair mercury levels in pregnancy in relation to fish consumption history in a population living along the St. Lawrence River. *Environ. Res.* 95, 363–374.
- Muckle G, Ayotte P, Dewailly E, Jacobson SW, Jacobson JL. Determinants of polychlorinated biphenyls and methylmercury exposure in Inuit women of childbearing age. *Environ. Health Perspect.* 109, 957–963. 2001.
- Muir, D., Savinova, T., Savinov, V., Alexeeva, L., Potelov, V. Svetochev, V.** 2003. Bioaccumulation of PCBs and chlorinated pesticides in seals, fishes and invertebrates from the White Sea, Russia. *Sci Total Environ.* May 1;306(1-3):111-31.
- Mundy, W.R. & Freudenrich, T.M.** 2000. Sensitivity of immature neurons in culture to metal-induced changes in reactive oxygen species and intracellular free calcium. *Neurotoxicology.* 21, 1135–1144.
- Munshi, A.B., Detlef, S.B., Schneider, R. & Zuberi, R.** 2004. *Mar Pollut Bull.* Organochlorine concentrations in various fish from different locations at Karachi Coast. Oct;49(7-8):597-601.
- Muntean, N., Jermini, M., Small, I., Falzon, D., Furst, P., Migliorati, G., Scortichini, G., Forti, A.F., Anklam, E., von Holst, C., Niyazmatov, B., Bahkridinov, S., Aertgeerts, R., Bertollini, R., Tirado, C. & Kolb, A.** 2003. Assessment of dietary exposure to some persistent organic pollutants in the Republic of Karakalpakstan of Uzbekistan. *Environ Health Perspect.* Aug;111(10):1306-11.
- Murata, K., Weihe, P., Budtz-Jørgensen, E., Jørgensen, P.J. & Grandjean, P.** 2004. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J. Pediatr.* 144, 177–183.
- Muscat, J.E., Britton, J.A., Djordjevic, M.V., Citron, M.L., Kemeny, M., Busch-Devereaux, E., Pittman, B. & Stellman, S.D.** 2003. Adipose concentrations of organochlorine compounds and

breast cancer recurrence in Long Island, New York. *Cancer Epidemiol Biomarkers Prev.* Dec;12(12):1474-8.

Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Tanner, M.A., Choisy, O., Sloane-Reeves, J., Marsh, D., Cernichiari, E. & Choi, A. 1995a. Neurodevelopment outcomes of Seychellois children sixty-six months after in utero exposure to methylmercury from maternal fish diet: pilot study. *Neurotoxicology* 16, 639–652..

Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Tanner, M.A., Marsh, D.O., Cernichiari, E., Lapham, L.W., Berlin, M. & Clarkson, T.W. 1995b. Summary of the Seychelles child development study on the relationship of fetal methylmercury exposure to neurodevelopment. *Neurotoxicology* 16, 711–716.

Myers, G.J., Davidson, P.W., Cox, C., Shamlaye, C.F., Palumbo, D., Cernichiari, E, et al. 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet.* 361:1686-1692.

Myers, G.J., Marsh, D.O., Cox, C., Davidson, P.W., Shamlaye, C.F., Tanner, M.A., Choi, A., Cernichiari, E., Choisy, O. & Clarkson, T.W. 1995c. A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish diet. *Neurotoxicology* 16, 629–638.

Myhre, O. & Fonnum, F. 2001. The effect of aliphatic, naphthenic, and aromatic hydrocarbons on production of reactive oxygen species and reactive nitrogen species in rat brain synaptosome fraction: the involvement of calcium, nitric oxide synthase, mitochondria, and phospholipase A. *Biochem. Pharmacol.* 62, 119–128.

Nagayama, J., Kohno, H., Kunisue, T., Kataoka, K., Shimomura, H., Tanabe, S. & Konishi, S. 2007. Concentrations of organochlorine pollutants in mothers who gave birth to neonates with congenital hypothyroidism. *Chemosphere.* Jun;68(5):972-6.

Naito, W., Jin, J., Kang, Y.S., Yamamuro, M., Masunaga, S. & Nakanishi, J. 2003. Dynamics of PCDDs/DFs and coplanar-PCBs in an aquatic food chain of Tokyo Bay. *Chemosphere.* Oct;53(4):347-62.

Nakagawa, R., Yumita, Y. & Hiromoto, M. 1997. Total mercury intake from fish and shellfish by Japanese people. *Chemosphere* 35: 2909-2913.

Norseth, T. & Clarkson, T.W. 1970. Studies on the biotransformation of Hg-203-labeled methylmercury chloride. *Arch Environ Health.* 21:717-727.

NRC (National Research Council). 2000. *Toxicological Effects of Methylmercury.* National Academy Press, Washington, DC.

Oken, E., Radesky, J.S., Wright, R.O., Bellinger, D.C., Amarasiriwardena, C.J. & Kleinman, K.P. 2008. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. *Amer J Epidemiol* 167: 1171-1181.

Oken, E., Wright, R.O., Kleinman, K.P., Bellinger, D., Amarasiriwardena, C.J. & Hu, H. 2005. Maternal fish consumption, hair mercury and infant cognition in a U.S. Cohort. *Environ Health Perspect* 113: 1376-1380.

Oskarsson, A., Schultz, A., Skerfving, S., Hallen, I.P., Ohlin, B. & Lagerkvist, B.J. 1996. Total and inorganic mercury in breast milk in relation to fish consumption and amalgam in lactating women. *Arch. Environ. Health* 51, 234–241.

Padula, D.J., Daughtry, B.J. & Nowak, B.F. 2008. Dioxins, PCBs, metals, metalloids, pesticides and antimicrobial residues in wild and farmed Australian southern bluefin tuna (*Thunnus maccoyii*). *Chemosphere*. 72(1):34-44.

Pandelova, M., Henkelmann, B., Roots, O., Simm, J., Jarv, L., Bebfenati, E. & Schram, K.W. 2008. Level of PCDD/F and dioxin-like PCB's in Baltic fish of different age and gender. *Chemosphere*. 71:369-378,

Pavuk, M., Cerhan, J.R., Lynch, C.F., Schecter, A., Petrik, J., Chovancova, J. & Kocan, A. 2004. Environmental exposure to PCBs and cancer incidence in eastern Slovakia. *Chemosphere*. Mar;54(10):1509-20.

Pereg, D., Robertson, L.W. & Gupta, R.C. 2002. DNA adduction by polychlorinated biphenyls: adducts derived from hepatic microsomal activation and from synthetic metabolites. *Chem Biol Interact* 139:129 – 44.

Persky, V., Turyk, M., Anderson, H.A., Hanrahan, L.P., Falk, C., Steenport, D.N., Chatterton, R. Jr & Freels, S. 2001. The effects of PCB exposure and fish consumption on endogenous hormones. *Environmental Health Perspectives* 109: 1275–1283.

Ponce, R.A. & Bloom, N.S. 1991. Effect of pH on the bioaccumulation of low level, dissolved methylmercury by rainbow trout (*Oncorhynchus mykiss*). *Water Air Soil Pollut.* 56:631-640.

Prince, M.M., Hein, M.J., Ruder, A.M., Waters, M.A., Laber, P.A. & Whelan, E.A. 2006. Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940-1998. *Environ Health*. May 22;5:13.

Prince, M.M., Ruder, A.M., Hein, M.J., Waters, M.A., Whelan, E.A., Nilsen, N., Ward, E.M., Schnorr, T.M., Laber, P.A. & Davis-King, K.E. 2006b. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environ Health Perspect.* 114(10):1508-14.

Purkey, H.E., Palaninathan, S.K., Kent, K.C., Smith, C., Safe, S.H., Sacchettini, J.C. & Kelly, J.W. 2004. Hydroxylated polychlorinated biphenyls selectively bind transthyretin in blood and inhibit amyloidogenesis: rationalizing rodent PCB toxicity. *Chemistry and Biology* 11: 1719–1728.

Raaschou-Nielsen, O., Pavuk, M., Leblanc, A., Dumas, P., Philippe Weber, J., Olsen, A., Tjonneland, A., Overvad, K. & Olsen, J.H. 2005. Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. *Cancer Epidemiol Biomarkers Prev.* Jan;14(1):67-74.

Regnell, O. & Tunlid, A. 1991. Laboratory study of chemical speciation of mercury in lake sediment and water under aerobic and anaerobic conditions. *Appl Environ Microbiol* 57(3):789-795.

Reuhl, K.R. 1991. Delayed expression of neurotoxicity: the problem of silent damage. *Neurotoxicology.* 12:341–346.

Richardson, J.R. & Miller, G.W. 2004. Acute exposure to aroclor 1016 or 1260 differentially affects dopamine transporter and vesicular monoamine transporter 2 levels. *Toxicol. Lett.* 148:29–40.

Riisgard, H.U. & Hansen, S. 1990. Biomagnification of mercury in a marine grazing food-chain: Algal cells *phaeodactylum tricornutum*, mussels *Mytilus edulis* and flounders *platichthys flesus* studied by means of a stepwise-reduction-CVAA method. *Mar Ecol Prog Ser.*62:259-270.

Rissanen, T., Voutilainen, S., Nyssonen, K., Lakka, T.A. & Salonen, J.T. 2000. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events. The Kuopio Ischaemic Heart Disease Risk Factor Study. *Circulation* 102: 2677-2679.

Rodier, P.M. 1980. Chronology of neuron development: animal studies and their clinical implications, *Dev. Med. Child Neurol.* 22: 525–545.

Rodrigo, R., Bachler, J.P., Araya, J., Prat, H. & Passalacqua, W. 2007. Relationship between (Na + K)-ATPase activity, lipid peroxidation and fatty acid profile in erythrocytes of hypertensive and normotensive subjects. *Mol. Cell. Biochem.* 303, 73–81.

Roegge, C.S., Morris, J.R., Villareal, S., Wang, V.C., Powers, B.E., Klintsova, A.Y., Greenough, W.T., Pessah, I.N. & Schantz, S.L. 2006. Purkinje cell and cerebellar effects following developmental exposure to PCBs and/or MeHg. *Neurotoxicol Teratol.* 28:74-85.

Ruder, A.M., Hein, M.J., Nilsen, N. et al. 2006. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. *Environ Health Perspect* 114:18 – 23.

Rusiecki, J.A., Holford, T.R., Zahm, S.H. & Zheng, T. 2004. Polychlorinated biphenyls and breast cancer risk by combined estrogen and progesterone receptor status. *Eur J Epidemiol.* 19(8):793-801.

Sager, P.R., Doherty, R.A. & Olmsted, J.B. 1983. Interaction of methylmercury with microtubules in cultured cells and in vitro. *Exp Cell Res.* 146:127-137.

Sahaphong, S. & Trump, B.F. 1971. Studies of cellular injury in isolated kidney tubules of the flounder. *Am J Pathol.* 63:277-290.

Sahuquillo, I., Lagarda, M.J., Silvestre, M.D. & Farré, R. 2007. Methylmercury determination in fish and seafood products and estimated daily intake for the Spanish population. *Food Addit Contam.* 24(8):869-76.

Sakamoto, M., Kubota, M., Liu, X.J., Murata, K., Nakai, K. & Satoh, H. 2004. Maternal and foetal mercury and n-3 polyunsaturated fatty acids as a risk and benefit of fish consumption to foetus. *Environ Sci Technol* 38:3860-3863.

Sakamoto, M., Nakano, A. & Akagi, H. 2001. Declining Minamata male birth ratio associated with increased male fetal death due to heavy methylmercury pollution. *Environ. Res.* 87, 92–98.

Salonen, J.T., Seppanen, K., Lakka, T.A., Salonen, R. & Kaplan, G.A. 2000. Mercury accumulation and accelerated progression of carotid atherosclerosis: a population-based prospective 4-year follow-up study in men in eastern Finland. *Atherosclerosis.* 148:265–73.

- Salonen, J.T., Seppanen, K., Nyyssonen, K., Korpela, H., Kauhanen, J., Kantola, M. et al.** 1995. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation*. 91:645–55.
- Sasamoto, T., Ushio, F., Kikutani, N., Saitoh, Y., Yamaki, Y., Hashimoto, T., Horii, S., Nakagawa, J. & Ibe, A.** 2006. Estimation of 1999–2004 dietary daily intake of PCDDs, PCDFs and dioxin-like PCBs by a total diet study in metropolitan Tokyo, Japan. *Chemosphere*. Jul;64(4):634–41.
- Schantz, S., Gasior, D., Polverejan, E., McCaffrey, R., Sweeney, A. & Humphrey, H.** 2001. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of great lakes fish. *Environ. Health Perspect.* 109: 605–611.
- Schantz, S.L., Gardiner, J.C., Gasior, D.M., Sweeney, A.M., Humphrey, H.E.B. & McCaffrey, R.J.** 1999. Motor function in aging Great Lakes fisheaters. *Environ. Res.* 80: 46–56.
- Schechter, A., Cramer, P. & Boggess, K.** 2001. Intake of dioxins and related compounds from food in the U.S. population. *J Toxicol Environ Health A.* 63: 1–18.
- Schwarz, M. & Appel, K.E.** 2005. Carcinogenic risks of dioxins: mechanistic considerations. *Regul. Pharmacol. Toxicol.* 43 (1): 19–34,
- Schweinsberg, F.** 2003. Mercury in fish and its effect on health: German methods of assessment. *Int. J. Hyg. Environ. Health* 206 (3): 241–243,
- Scientific Advisory Committee on Nutrition and Committee on Toxicology (SACN).** 2004. Advice on fish consumption: benefits & risks. United Kingdom Food Standards Agency and Department of Health. Her Majesty's Stationary Office. London. Available at: <http://www.sacn.gov.uk>
- Seegal, R.F.** 2003;PCBs and dopamine function. *Ann. N.Y. Acad. Sci.* 991:322–325.
- Shanker, G., Allen, J.W., Mutkus, L.A. & Aschner, M.** 2001. Methylmercury inhibits cysteine uptake in cultured primary astrocytes, but not in neurons. *Brain Res.* 914, 159–165.
- Shanker, G. & Aschner, M.** 2001. Identification and characterization of uptake systems for cystine and cysteine in cultured astrocytes and neurons: evidence for methylmercury-targeted disruption of astrocyte transport. *J. Neurosci. Res.* 66, 998–1002.
- Shanker, G. & Aschner, M.** 2003. Methylmercury-induced reactive oxygen species formation in neonatal cerebral astrocytic cultures is attenuated by antioxidants. *Brain Res. Mol. Brain. Res.* 110, 85–91,
- Shanker, G., Syversen, T. & Aschner, M.** 2003. Astrocyte-mediated methylmercury neurotoxicity. *Biol. Trace Elem. Res.* 95, 1–10.
- Sharlin, D.S., Bansal, R. & Zoeller, R.T.** 2006. Polychlorinated biphenyls exert selective effects on cellular composition of white matter in a manner inconsistent with thyroid hormone insufficiency. *Endocrinology* 14: 846–858.
- Shenker, B.J., Guo, T.L. & Shapiro, I.M.** 1998. Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction. *Environ. Res.* 77, 149–159.

- Sherer, T.B., Betarbet, R., Kim, J.H. & Greenamyre, J.T.** 2003. Selective microglial activation in the rat rotenone model of Parkinson's disease. *Neurosci Lett* 341:87–90.
- Shields, P.G.** 2006. Understanding population and individual risk assessment: the case of polychlorinated biphenyls. *Cancer Epidemiol Biomarkers Prev.* May;15(5):830-9.
- Silbergeld, E.K., Silva, I.A. & Nyland, J.F.** 2005. Mercury and autoimmunity: implications for occupational and environmental health. *Toxicol. Appl. Pharmacol.* 207, 282–292.
- Sirof, V., Guérin, T., Mauras, Y., Garraud, H., Volatier, J.L. & Leblanc, J.C.** 2008. Methylmercury exposure assessment using dietary and biomarker data among frequent seafood consumers in France CALIPSO study. *Environ Res.* 107(1):30-8.
- Szlinder-Richert, J., Barska, I., Usydus, Z., Ruczynska, W. & Grabic, R.** 2009. Investigation of PCDD/Fs and dl -PCBs in fish from the southern Baltic Sea during the 2002- 2006 period. *Chemosphere.* 74: 1509- 1515.
- Soechitram, S.D., Athanasiadou, M., Hovander, L., Bergman, A. & Sauer, P.J.** 2004. Fetal exposure to PCBs and their hydroxylated metabolites in a Dutch cohort. *Environ Health Perspect.* 112(11):1208-12.
- Steenland, K., Hein, M.J., Cassinelli, R.T., Prince, M.M., Nilsen, M.B., Whelan, E.A., Waters, M.A., Ruder, A.M. & Schorr, T.M.** 2006. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. *Epidemiology* 17, 8–13.
- Stern, A.H. & Smith, A.E.** 2003. An assessment of the cord blood:maternal blood methylmercury ratio: implications for risk assessment. *Environ. Health Perspect.* 111, 1465-1470,
- Stern, A.H.** 2005. A review of the studies of the cardiovascular health effects of methylmercury with consideration of their suitability for risk assessment. *Environmental Res* 98: 133-42.
- Steuerwald, U., Weihe, P., Jørgensen, P.J., Bjerve, K., Brock, J., Heinzow, B., Budtz-Jørgensen, E. & Grandjean, P.** 2000. Maternal seafood diet, methylmercury exposure and neonatal neurologic function. *J. Pediatr.* 136, 599–605.
- Stewart, P.W., Reihman, J., Lonky, E.I., Darvill, T.J. & Pagano, J.** 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol. Teratol.* 25 (1): 11-22,
- Storelli, M.M., Giacomini-Stuffler, R., Storelli, A., D'Addabbo, R., Palermo, C. & Marcotrigiano, G.O.** 2003. Survey of total and methylmercury levels in edible fish from the Adriatic sea. *Food Addit. Contam.* 20: 1114-1119.
- Storelli, M.M., Stuffler, R.G. & Marcotrigiano, G.O.** 2002. Total and methylmercury residues in tuna-fish from the Mediterranean sea. *Food Addit Contam.* 19: 715-20.
- Sudaryanto, A., Kunisue, T., Tanabe, S., Niida, M. & Hashim, H.** 2005. Persistent organochlorine compounds in human breast milk from mothers living in Penang and Kedah, Malaysia. *Arch Environ Contam Toxicol.* Oct;49(3):429-37.
- Sundberg, J. & Oskarsson, A.** 1992. Placental and lactational transfer of mercury from rats exposed to methylmercury in their diet: Speciation of mercury in the offspring. *J Trace Elem Exp Med.* 5:47-56.

- Sunderland, E.M., Gobas, F.A.P.C, Branfireun, B.A. & Heyes, A.** 2006. Environmental controls on the speciation and distribution of mercury in coastal sediments. *Mar Chem* 102:111–123.
- Tard, A., Gallotim S., Leblanc, J.C. & Volatier, J.L.** 2007. Dioxins, furans and dioxin-like PCBs: Occurrence in food and dietary intake in France. *Food Addit Contam.* 24:1007-17.
- Todaka, T., Hirakawa, H., Kajiwara, J., Hori, T., Tobiishi, K., Onozuka, D., Iida, T., Yoshimura, T. & Furue, M.** 2007. Dioxin concentration in the blood of patients collected during medical check-up for Yusho in 2004-2005. *Fukuoka Igaku Zasshi.* May;98(5):222-31.
- Tsai, P.C., Ko, Y.C., Huang, W., Liu, H.S. & Guo, Y.L.** 2007. Increased liver and lupus mortalities in 24-year follow-up of the Taiwanese people highly exposed to polychlorinated biphenyls and dibenzofurans. *Sci Total Environ.* Mar 15;374(2-3):216-22.
- Tsubaki, T. & Takahashi, H.** 1986. Recent advances in Minamata disease studies. Tokyo, Japan: Kodansha, Ltd.
- Tsukino, H., Hanaoka, T., Sasaki, H., Motoyama, H., Hiroshima, M., Tanaka, T., Kabuto, M., Turner, W., Patterson, D.G. Jr, Needham, L. & Tsugane, S.** 2006. Fish intake and serum levels of organochlorines among Japanese women. *Sci Total Environ.* Apr 15;359(1-3):90-100.
- Turner, M.D., Smith, J.C. & Kilpper, R.W.** 1975. Absorption of natural methylmercury (MeHg) from fish. *Clin Res.* 23:2.
- Ulbrich, B. & Stahlmann, R.** 2004. Developmental toxicity of polychlorinated biphenyls (PCBs): a systematic review of experimental data. *Archives of Toxicology* 78: 252–268.
- United Nations Environment Programme (UNEP).** 2002. Global Mercury Assessment. UNEP Chemicals Mercury Programme. Available at: <http://www.chem.unep.ch/mercury/Report/Final%20Assessment%20report.htm>.
- Urban, P., Pelclova, D., Lukas, E., Kupka, K., Preiss, J., Fenclova, Z. & Smerhovsky, Z.** 2007. Neurological and neurophysiological examinations on workers with chronic poisoning by 2,3,7,8-TCDD: follow-up 35 years after exposure. *Eur J Neurol.* Feb;14(2):213-8.
- US Environmental Protection Agency,** 2003. Available at: www.epa.gov/opptintr/pcb/effects.html.
- Valera, B., Dewailly, E. & Poirier, P.** 2009. Environmental mercury exposure and blood pressure among Nunavik Inuit adults. *Hypertension* 54: 981-986,
- Van der Plas, S.A., Lutkeschipholt, I., Spenkelink, B. & Brouwer, A.** 2001. Effects of subchronic exposure to complex mixtures of dioxinlike and non-dioxin-like polyhalogenated aromatic compounds on thyroid hormone and vitamin A levels in female Sprague–Dawley rats. *Toxicological Sciences* 59:92–100.
- Van Oostdam, J., Donaldson, S.G., Feeley, M., Arnold, D., Ayotte, P., Bondy, G., Chan, L. & Dewailly, E.** 2005. Human health implications of environmental contaminants in Arctic Canada: a review. *Sci. Total. Environ.* 351–352 165–246.
- Van Oostdam, J., Donaldson, S.G., Feeley, M., Arnold, D., Ayotte, P., Bondy, G., Chan, L., Dewailly, E., Furgal, C.M., Kuhnlein, H., Loring, E., Muckle, G., Myles, E., Receveur, O., Tracy, B.,**

Gill, U. & Kalhok, S. 2005. Human health implications of environmental contaminants in Arctic Canada: A review. *Sci Total Environ.* 351-352:165-246.

Vasiliu, O., Cameron, L., Gardiner, J., DeGuire, P. & Karmaus, W. 2006. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. *Epidemiology.* 17: 352–359.

Verkasalo, P.K., Kokki, E., Pukkala, E., Vartiainen, T., Kiviranta, H., Penttinen, A. & Pekkanen, J. 2004. Cancer risk near a polluted river in Finland. *Environ Health Perspect.* Jun;112(9):1026-31.

Virtanen, J.K., Voutilainen, S., Rissanen, T.H., Mursu, J., Tuomainen, T.P. & Korhonen, M.J. 2005. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and allcause mortality in men in eastern Finland. *Arterioscler Thromb Vasc Biol.* 25:228– 33.

Voigt, H.R. 2001. High summer concentrations of mercury in big perch (*Perca fluviatilis* L) from the Tvärminne archipelago (SW Finland) and Natö (Aland Islands) Baltic sea. *Nahrung.* 45(2):109-13.

Vreugdenhil, H.J., Slijper, F.M., Mulder, P.G. & Weisglas-Kuperus, N. 2002. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. *Environ Health Perspect.* Oct;110(10):A593-8.

Wagemann, R. & Kozłowska, H. 2005. Mercury distribution in the skin of beluga (*Delphinapterus leucas*) and narwhal (*Monodon monoceros*) from the Canadian Arctic and mercury burdens and excretion by moulting. *Sci.Total Environ.* 351-352: 333-343.

Wakita, Y. 1987. Hypertension caused by methyl mercury in rats. *Toxicol Appl Pharmacol* 89: 144-147.

Watras, C.J. & Bloom, N.S. 1992. Mercury and methylmercury in individual zooplankton: Implications for bioaccumulation. *Limnol Oceanogr.* 37:1313-1318.

Watras, J.J. et al. 1998. Bioaccumulation of mercury in pelagic food webs. *Sci. Total Environ.* 219: 183-208.

Weisglas-Kuperus N, Vreugdenhil HJ, Mulder PG. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. *Toxicol Lett.* 2004 Apr 1;149(1-3):281-5.

Weisskopf, M.G., Andersonm H.A., Hanrahanm, L.P., Kanarek, M.S., Falk, C.M., Steenport, D.M. & Draheim, L.A; 2005. Great Lakes Consortium. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. *Environ Res.* Feb;97(2):149-62.

WHO. Joint FAO/WHO Expert Committee on Food Additives (JECFA). 2001. Safety Evaluation of Certain Food Additives and Contaminants. Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls. Food Additives Series: 48. World Health Organization, Geneva, Switzerland.
<http://www.inchem.org/documents/jecfa/jecmono/v48je20.htm>

WHO. 1990. Methyl mercury. Vol. 101. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety.

- Wiener, J.G., Fitzgerald, W.F. & Watras, C.J.** 1990. Partitioning and bioavailability of mercury in an experimentally acidified Wisconsin Lake. In: Symposium on Metal Chemistry and Bioavailability in Acid Waters Ninth Annual Meeting of the Society of Environmental Toxicology and Chemistry, Arlington, VA, November 16, 1988. *Environ Toxicol Chem* 9(7):909-918.
- Wren, C.** 1992. Relationship of mercury levels in sportfish with lake sediment and water quality variables. Toronto: Ontario Environmental Research Program. Govt Reports Announcements and Index (GRA&I). 8.
- Xie, Z. & Cai, T.** 2003. Na⁺-K⁺-ATPase-mediated signal transduction: from protein interaction to cellular function. *Mol. Interv.* 3, 157–168.
- Yang, C.Y., Yu, M.L., Guo, H.R., Lai, T.J., Hsu, C.C., Lambert, G. & Guo, Y.L.** 2005. The endocrine and reproductive function of the female Yucheng adolescents prenatally exposed to PCBs/PCDFs. *Chemosphere*. Oct;61(3):355-60.
- Yannai, S., Berdicevsky, I. & Duek, L.** 1991. Transformations of inorganic mercury by candida-albicans and saccharomyces-cerevisiae. *Appl Environ Microbiology* 57(1):245-247.
- Yin Z, Milatovic D, Aschner JL, Syversen T, Rocha JB, Souza DO, Sidoryk M, Albrecht J, Aschner M. Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. *Brain Res.* 1131:1-10. 2007
- Yoshida, M., Satoh, H. & Kishimoto, T.** 1992. Exposure to mercury via breast milk in suckling offspring of maternal guinea pigs exposed to mercury vapor after parturition. *J Toxicol Environ Health.* 35:135-139.
- Yoshizawa, K., Rimm, E.B., Morris, J.S., Spate, V.L. & Hsieh, C-C.** 2002. Spiegelman D. Mercury and the risk of coronary heart disease in men. *N Eng J Med* 347: 1755-1760.
- Ysart, G., Miller, P., Croasdale, M., Crews, H., Robb, P., Baxter, M., de L'Argy, C. & Harrison, N.** 2000. 1997 UK Total Diet Study—dietary exposures to aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin, and zinc. *Food Addit. Contam.* 17, 775–786.
- Yu, M.L., Guo, Y.L., Hsu, C.C. & Rogan, W.J.** 1997. Increased mortality from chronic liver disease and cirrhosis 13 years after the Taiwan “Yucheng” (“oil disease”) incident. *Am J Ind Med* 31:172–5
- Yu, S.P.** 2003. Na⁽⁺⁾, K⁽⁺⁾-ATPase: the newface of an old player in pathogenesis and apoptotic/hybrid cell death. *Biochem. Pharmacol.* 66, 1601–1609.
- Zambon, P., Ricci, P., Bovo, E., Casula, A., Gattolin, M., Fiore, A.R., Chiosi, F. & Guzzinati, S.** 2007. Sarcoma risk and dioxin emissions from incinerators and industrial plants: a population-based case-control study (Italy). *Environ Health.* Jul 16;6:19.
- Zhao, X., Zheng, M., Liang, L., Zhang, Q., Wang, Y. & Jiang, G.** 2005. Assessment of PCBs and PCDD/Fs along the Chinese Bohai Sea coastline using mollusks as bioindicators. *Arch Environ Contam Toxicol* 49:178–85.
- Zoeller, R.T., Dowling, A.L., Herzig, C.T., Iannacone, E.A., Gauger, K.J. & Bansal, R.** 2002. Thyroid hormone, brain development, and the environment, *Environ. Health Perspect.* 110:355–361.

Zoeller, R.T., Dowling, A.L.S. & Vas, A.A. 2000. Developmental exposure to polychlorinated biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic protein messenger ribonucleic acids in the developing rat brain. *Endocrinology*, 141:181-189.

APPENDIX 1

Dioxins levels in seafood from different areas of the world

Area	Fish species	Dioxins levels	Total daily intake	Food groups contribution	Ref.
Baltic Sea	Herring and salmon	herring (11.5 ng TEQ/kg ww) salmon (16.5 ng TEQ/kg ww)			1
Belgium	shark, ray, whiting, shrimps and turbot	shark (0.53 pg TEQ/g wet weight (ww)), ray (0.71 pgTEQ/g ww), sole (0.72 pgTEQ/ g ww), whiting (0.73 pgTEQ/ g ww), shrimps (1.96 pg TEQ/ g ww) turbot (2.36 pgTEQ/g ww)	71 pg TEQ/day (only fish considered)		2
Belgium	Total Diet Study		151 pg TEQ/day	seafood 47%; meat and meat products 33%; milk and diary products 20%	3, 4
Finland	Total Diet Study		1.5 pg TEQ/kg bw/day	fish 71%, cereal products 7%, meat and eggs 6%, beverages, and sweets 6%	5
France	fish captured along the Drome river	from 7.8 to 56.9 μ g/kg ww			6
France	Total Diet Study	wild and farmed fish (between 2.7 and 2.9 pg TEQ/g fresh weight) Farmed trout (0.75 pg TEQ/g fresh weight) shellfish (range between 0.73 and 1.34 pg TEQ/g fresh weight)	1.8 pg TEQ/kg/bw/day	fish 48%, dairy products 30%, meat products 8%, vegetables 5–6%, fats 4–5% and eggs 2–3%.	7
Germany	fish and fishery products (canned fish)	herring (from 0.317 to 3.163 ng TEQ/kg ww), halibut (0.645 ngTEQ/kg ww) sardine (0.603 ng TEQ/kg ww) cat fish (0.576 ngTEQ/kg ww)			8
Greece	Fish samples from the Greek Market	PCDD/Fs; sums ranging between 0.12 (wild fish) and 0.47 (aquaculture fish) pg TEQ/g fat Non-			9

		ortho PCBs; average sums: from 0.33 to 1.19 pg TEQ/fat for wild and aquaculture fish, respectively			
Italy	Anchovy, squid, mussel, lobster, mackerel, red mullet, clam	PCDD/Fs and PCBs: 0.23–1.07 pg TEQ/g ww for mackerel, red mullet and anchovy; 0.07–0.25 pgTEQ/g ww for the remaining species			10
Italy	fishes, cephalopods, bivalves and crustacean	PCBs (17 congeners); mean values: 4.54, 0.33, 4.31 and 4.69 ng/g ww, respectively for the indicated groups			11
Italy	Edible clams (pools)	PCBs; mean value: 4.8 (1.6–15.4) ng/g ww			12
Italy	Mussel, lobster, red mullet, cuttlefish, squid, anchovy, sardine, mackerel	PCBs (7 congeners); highest value: 20.8 ng/g ww (mackerel); lowest value: 0.73 ng/g ww (cuttlefish)			13
Italy	several fish species	PCBs (20 congeners); range between 407 (octopus) and 22287 (bass) ng/g lw			14
Italy	Eel, herring, mullet, mackerel, bass, trout	PCDD/Fs; highest and lowest mean values: 1.11 and 0.18 pgTEQ/g for eel and trout, respectively			15
Italy (Northern part)	Total Diet Study		2.3 pg TEQ/kg/bw/day	cereals 89.8%, vegetables 9.9%, and dairy 0.3%	16, 17
Netherlands	Total Diet Study		1.1 pg TEQ/kg/bw/day	dairy 27%, meat products 23%, fats 17%, fish 16%, vegetable 13, eggs 4%	18

Norway	Atlantic cod, sea trout, flounder, eel, edible crab and blue mussel	cod (0.85 ng/kg ww) flounder (28 ng/kg ww)			19
Spain	salmon, tuna, sardines, oysters, mussels, clams	salmon (3.63 pg TEQ/g fw), tuna (3.24 pg TEQ/g fw), sardines (2.35 pgTEQ/g fw), oysters (0.79 pg TEQ/g fw), mussels (0.46 pgTEQ/g fw), clams (0.17 pg of TEQ/g of fw)			20
Spain			38.0 pg TEQ/day (only fish considered)	meat products 35%, dairy 29%, vegetable 19%, fish 11%, eggs 4%	21, 22
Sweden	Total Diet Study		1.3 pg TEQ/kg bw/day	fish 33%, fats and oils 22%, dairy products 20%, meat 15%, egg 6% and pastry 4%	23
Canada	Fish products available on the Canadian retail market	PCBs: salmon (12,900 pg/g whole weight), trout (11,300 pg/g whole weight), crab (6090 pg/g whole weight), char (5450 pg/g whole weight), oysters (804 pg/g whole weight), mussels (787 pg/g whole weight), tilapia (665 pg/g whole weight) and shrimp (182 pg/g whole weight)	0.64 pg TEQ/kg/bw/day		24, 25
USA	Total Diet Study		2.2 pg TEQ/kg/bw/day	meat 34%, dairy 30%, egetables 22%, fish 9%, eggs 5%	26
USA	aquacultured salmon, wild salmon,stripp	stripped bass (1.9 ng/kg ww), salmon (0.73 ng/kg ww) and crab (1.05			27

	ed bass, Pollack, scallops, lobster, crab, crawfish	ng/kg ww)		
USA	bluefish, “rockfish”, wild caught Alaska King, Sockeye and Coho salmon, and farm- raised salmon	wild bluefish fillet (800 ng/g ww) wild Coho salmon fillet (0.35 ng/g ww), rockfish (0.07 pg TEQ/g ww) bluefish (27 pg TEQ/g ww)		28
Brazil	blue shark and swordfish	blue shark (3.15 ng/g ww) and swordfish (6.50 ng/g ww)		29
Brazil	meat and meat products	mean (10.30 ng/g), maximum levels (257.54 ng/g) mixed>pork>bovine		30
China	shrimp, mussel and mackerel	shrimp and mussel (0.20 ng/g ww), mackerel (2.5 ng/g ww)		31
China	fish and shellfish collected from local supermarkets	flathead flounder (8.04 ng/g ww), white sardine (5.60 ng/g ww), cuttlefish (0.83 ng/g ww), white sardine (1.11 ng/g ww)	1.83 ng/kg body weight	32
Japan	plankton, shellfish, benthic invertebrate, and fish	shellfish (8.52 pg/g ww), plankton (259 pg/g ww)		33
Japan	fish and shellfish	mackerel (0.397-3.841 pgTEQ /g ww), red sea- bream (0.013-0.272 pgTEQ/g ww), horse mackerel (0.128-1.916 pgTEQ/g ww), sardines (0.266-3.551 pgTEQ/g ww) and squid (0.013- 0.272 pgTEQ/g ww)		34
Japan	Total Diet Study		1.55 pg TEQ/kg/bw/day	fish and shellfish 80% 35

Japan	Total Diet Study		2.25 pg TEQ/kg/bw/day	fish and shellfish 76.9%, meat and eggs 15.5%	36
Korea	fish, crustaceans, cephalopods, bivalves and gastropods	from 0.02 to 4.39 pg TEQ/g ww	0.68 pg TEQ/kg/bw/day (only seafood considered)		37
Korea	sport and market fish	sport fish (23.0 ng/g ww), market fish (8.91 ng/g ww)			38
Pakistan	several fish species	mean 78.35 μ g/g lipid weight			39
Russia	fish and marine mammals	seals (4150 ng/g lipid weight), cod muscle (16 ng/g ww)			40
Sri Lanka	six species of fish and one crab species	from 0.04 pg/g ww, to 4.5 pg/g ww			41
Taiwan	Total Diet Study		9.93 pg TEQ/kg/bw/week; 42.1 pg TEQ/kg/bw/month	fish and fishery products 46%, meat products 20%	42
Turkey	12 edible fish species taken from the Central Fish Market of Istanbul	PCBs; average value: 253.08 ng/g fat (range: 63.30–508.71 ng/g fat)			43
Burundi	fish species (cichlids)	Oreochromis niloticus (166.7 ng/g fat) and Lates stappersii (126.7 ng/g fat)			44
Egypt	mullet fish, bolti fish, bivalves and crab, and total diet study	crab (0.12 pg TEQ/g ww), mullet (0.40 pg TEQ/g ww), bivalves (0.14 pg TEQ/g ww), mullet (0.76 pg TEQ/g ww)	3.69–4.0 pg TEQ/kg bw/day for PCDD/Fs	dairy 89%, fish/seafood 5.4%, and meat 5.6%	45, 46

APPENDIX 2

Mercury levels in seafood from different areas of the world

Area	Fish species	Mercury levels	MeHg	Total daily intake	Ref.
Czech Republic	carp	0.13 mg/kg dry	65.1-87.9%		47
Finland	sea perch	0.22 mg/kg (coastal waters); 0.18 mg/kg (outer waters)			48
France	swordfish, tuna, eel, anchovy, salmon, octopus, crab	0.94, 0.33, 0.31, 0.02, 0.04, 0.22, 0.17 ug/g, respectively (MeHg)		1.33 ug/kg bw (adult males); 1.56 ug/kg bw (adult females) 1.33 ug/kg bw (women of childbearing age)	49
Germany	Tuna, halibut, eel; rainbow trout, carp	mg/kg raw sample; 0.02 mg/kg raw sample			50
Italy	ghost shark, electric eel, eagle ray	3.14, 2.42, 0.83 mg/kg wet wt, respectively	72-83%		51
Italy	several species from the Adriatic Sea	0.06-0.76 ug/g wet wt	70-100%		52
Italy	conger eel, starry ray, forkbeard, frostfish, striped mullet, red gurnard, yellow gurnard	0.80, 0.75, 0.67, 0.59, 0.55, 0.33, 0.22 ug/g, respectively			53
Norway	Greenland halibut, sprat, prawn	0.09, 0.02, 0.02 mg/kg fresh wt, respectively. Levels <0.1 mg/kg fresh wt in 17 species			54
Norway	tusk	0.14-0.75 mg/kg (12/75 exceeded 0.5 mg/kg EU limit)			55
Portugal	octopus,	0.024, 0.033, 0.048,	>93%		56

	mackerel, shad, sardine, tuna, swordfish	0.31, 0.47 ug/g fresg wt, respectively		
Spain	several species	<54-662 ug/kg (MeHg)	46.2 ug/person/ week	57
Spain	zebra mussel	0.22-0.60 ug/g wet wt (MeHg)		58
Spain	swordfish, bluefin tuna	0.33 ug/g; 0.71 ug/g		59
Sweden	several species	N.A.	EPA's Rfd (0.1 ug/kg bw/day exceeded in 20% of women)	60
United Kingdom	shark, swordfish, marlin, fresh tuna, canned tuna	1.52, 1.36, 1.09, 0.40, 0.19 mg/kg, respectively (MeHg)	2.2-3.0 ug/kg bw (adult) and 3.0-5.2 ug/kg bw (children) (one portion/wk of high MeHg species (exceeds JECFA PTWI of 1.6). Consumption of up to 2 portions/wk o tuna does not exceed PTWI	61
Canada	Lake trout	0.2 ug/g		62
Canada	Artctic cod	0.19 ug/g dw		63
Canada	Salmon	0.03-0.1 ug/g wet wt		64
U.S.A.	Mackerel, tilefish, canned tuna, canned albacore tuna	0.17, 1.45, 0.17, 0.35 ppm, respectively (MeHg)		65
U.S.A.	Pacific salmon, Pacific halibut	<0.1 mg/kg; <0.3 mg/kg		66
Argentina	Gatuzo shark	890 ng/g ww		67
Brazil	Mussel, carnivorous fish	4.5-21.0 and 194.7 ug/kg ww, respectively (MeHg)		68
Chile	Swordfish, Chilean bass,	1.53, 0.17, 0.01 mg/kg, respectively	0.088-3.38 mg/kg bw/day	69

Chilean mussel				
Colombia	Carnivorous and non carnivorous species	0.37 and 0.15 ug/g, respectively	80-98 %	70
Franch Guiana	Piscivorous and herbivorous species	14.3 and 0.02 ug/g dry wt, respectively		71
China	Common carp, grass carp	20-40 ng/g; 60 ng/g		72
China	Silver carp, common carp, crucian carp, snakehead	195.1, 39.3, 184.8, 371.1 ug/g ww, respectively (MeHg)		73
India	Various fish species, crabs	34-54 ng/g dry wt; 90-103 ng/g dry wt	71-95%	74
Japan	Small cetaceans	1.0-11.5 ug/g wet wt		75
Japan	Bullshark, sandbar shark, tiger shark	3.65, 1.66, 0.78 ug/g wet wt		76
Philippines	Tilapia	0.27 ug/g		77
Philippines	Various species	1.29-931.6 ng/g (MeHg)		78
Ghana	Tuna	0.108 (0.04-0.20) ug/g	97%	79
Morocco	Pilchard, mullet	0.137 and 0.096 ug/g, respectively		80
Tanzania	Tilapia, catfish, tiger fish	6-11, 30-62, and 37-143 ug/kg, respectively	56-100%	81
Australia	Wild and farmed Bluefin tuna	0.36 and 0.31 mg/kg, respectively		82
New Zealand	Various species	0.04-1.97 mg/kg (MeHg)		83

REFERENCES (APPENDIXES 1 AND 2)

1. **Gallani B., Boix A., Verstraete F., von Holst C. & Anklam E.** 2004, Dioxins and PCBs in Food and Feed: data available to the European Commission, EUR 21093 EN
2. **Baeyens, W., Leermakers, M., Elskens, M., Van Larebeke, N., De Bont, R., Vanderperren, H., Fontaine, A., Degrootd, J.M., Goeyens, L., Hanot. V. & Windal, I.** 2007, PCBs and PCDD/FS in fish and fish products and their impact on the human body burden in Belgium. *Arch Environ Contam Toxicol.* May; 52(4):563-71.
3. **De Bont R., Elskens, M., Baeyens, W., Hens, L. & Van Larebeke, N.** 2004, A survey of three PCB and dioxin contamination episodes: From contamination of food items to body burdens. In: Preedy VR, Watson RR. *Annual reviews in food and nutrition: Toxic and pathological aspects.* CRC Press, Boca Raton, FL, pp 301– 342
4. **Focant, J.F., Eppe, G., Pirard, C., Massart, A.C., Andr, J.E. & De Pauw, E.** 2002, Levels and congener distributions of PCDDs, PCDFs and non-ortho PCBs in Belgian foodstuffs. Assessment of dietary intake. *Chemosphere*; 48:167–179.
5. **Kiviranta, H., Ovaskainen, M.L. & Vartiainen, T.** 2004, Market basket study on dietary intake of PCDD/Fs, PCBs, and PBDEs in Finland. *Environ. Int.* 30: 923–932
6. **Mazet, A., Keck, G. & Berny P.** 2005, Concentrations of PCBs, organochlorine pesticides and heavy metals (lead, cadmium, and copper) in fish from the Drome river: potential effects on otters (*Lutra lutra*). *Chemosphere.* Nov;61(6):810-6.
7. **Tard, A., Gallotti, S., Leblanc, J.C. & Volatier, J.L.** 2007, Dioxins, furans and dioxin-like PCBs: occurrence in food and dietary intake in France. *Food Addit Contam. Sep*;24(9):1007-17.
8. **Karl, H., Ruoff, U. & Blüthgen, A.** 2002, Levels of dioxins in fish and fishery products on the German market. *Chemosphere*; 49:765–73.
9. **Papadopoulos, A., Vassiliadou, I., Costopoulou, D., Papanicolaou, C. & Leondiadis, L.** 2004, Levels of dioxins and dioxin-like PCBs in food samples on the Greek market. *Chemosphere.* Nov;57(5):413-9.
10. **Bayarri, S., Baldassarri, L.T., Iacovella, N., Ferrara, F. & Di Domenico, A.** 2001, PCDDs, PCDFs, PCBs and DDE in edible marine species from the Adriatic Sea. *Chemosphere*; 43:601–10.
11. **Marcotrigiano, G.O. & Storelli, M.M.** 2003, Heavy metal, polychlorinated biphenyl and organochlorine pesticide residues in marine organisms: risk evaluation for consumers. *Vet Res Commun*;27(suppl 1):183–95.
12. **Binelli, A. & Provini, A.** 2003, POPs in edible clams from different Italian and European markets and possible human health risk. *Mar Pollut Bull*; 46:879–86.
13. **Perugini, M., Cavaliere. M., Giammarino. A., Mazzone. P., Olivieri. V. & Amorena, M.** 2004, Levels of polychlorinated biphenyls and organochlorine pesticides in some edible marine organisms from the Central Adriatic Sea. *Chemosphere*; 57:391–400
14. **Naso, B., Perrone, D., Ferrante, M.C., Bilancione, M. & Lucisano, A.** 2005, Persistent organic pollutants in edible marine species from the Gulf of Naples, Southern Italy. *Sci Total Environ*; 343:83–95

15. **Taioli, E., Marabelli, R., Scortichini, G., Migliorati, G., Pedotti, P., Cigliano A, et al.** 2005, Human exposure to dioxins through diet in Italy. *Chemosphere*;61:1672–6
16. **Turci R, Turconi G, Comizzoli S, Roggi C, Minoia C.** 2006, Assessment of dietary intake of polychlorinated biphenyls from a total diet study conducted in Pavia, Northern Italy. *Food Addit Contam.* 23(9):919-38
17. **Fattore, E., Fanelli, R., Turrini, A. & di Domenico, A.** 2006, Current dietary exposure to polychlorodibenzo-p-dioxins, polychlorodibenzofurans, and dioxin-like polychlorobiphenyls in Italy. *Mol Nutr Food Res.* 50(10):915-21
18. **Baars, A.J., Bakker, M.I., Baumann, R.A., Boon, P.E., Freijer, J.I., Hoogenboom, L.A., van Klaveren, J.D., Liem, A.K., Traag, W.A. & de Vries, J.** 2004, Dioxins, dioxin-like PCBs and non-dioxin-like PCBs in foodstuffs: occurrence and dietary intake in The Netherlands. *Toxicol Lett.* 1:51-61.
19. **Knutzen, J., Bjerkeng, B., Næs, K. & Schlabach, M.** 2003, Polychlorinated dibenzofurans/dibenzo-p-dioxins (PCDF/PCDDS) and other dioxin-like substances in marine organisms from the Grenland fjords, S. Norway, 1975-2001: present contamination levels, trends and species specific accumulation of PCDF/PCDD congeners. *Chemosphere*; 52:745–60.
20. **Gomara, B., Bordajandi, L.R., Fernandez, M.A., Herrero, L., Abad, E., Abalos, M., Rivera, J. & Gonzalez, M.J.** 2005, Levels and trends of polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (PCBs) in Spanish commercial fish and shellfish products, 1995-2003. *J Agric Food Chem.* Oct 19;53(21):8406-13.
21. **Bocio, A., Domingo, J.L., Falco, G. & Llobet, J.M.** 2007. Concentrations of PCDD/PCDFs and PCBs in fish and seafood from the Catalan (Spain) market: estimated human intake. *Environ Int.* Feb;33(2):170-5.
22. **Fernandez, M.A., Gomara, B., Bordajandi, L.R., Herrero, L., Abad, E., Abalos, M., Rivera, J. & Gonzalez, M.J.** 2004. Dietary intakes of polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxinlike polychlorinated biphenyls in Spain. *Food Additives and Contaminants* 21:983–991.
23. **Darnerud, P.O., Atuma, S., Aune, M., Bjerselius, R., Glynn, A., Grawe, K.P. & Becker, W.** 2006. Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on Swedish market basket data. *Food Chem Toxicol.* Sep;44(9):1597-606.
24. **Dewailly, E., Ayotte, P., Lucas, M. & Blanchet, C.** 2007. Risk and benefits from consuming salmon and trout: a Canadian perspective. *Food Chem Toxicol.* Aug;45(8):1343-8
25. **Rawn, D.F., Forsyth, D.S., Ryan, J.J., Breakell, K., Verigin, V., Nicolidakis, H., Hayward, S., Laffey, P. & Conacher, H.B.** 2006. PCB, PCDD and PCDF residues in fin and non-fin fish products from the Canadian retail market 2002. *Sci Total Environ.* Apr 15;359(1-3):101-10
26. **Schechter, A., Cramer, P. & Boggess, K.** 2001 Intake of dioxins and related compounds from food in the U.S. population. *J Toxicol Environ Health A*; 63: 1-18
27. **Hayward, D.G., Holcomb, J., Glidden, R., Wilson, P., Harris, M. & Spencer, W.** 2001. Quadrupole ion storage tandem mass spectrometry and high-resolution mass spectrometry:

complementary application in the measurement of 2,3,7,8-chlorine substituted dibenzo-p-dioxins and dibenzofurans in US foods. *Chemosphere*:407–15.

28. **Hayward, D., Wong, J. & Krynitsky, A.J.** 2007. Polybrominated diphenyl ethers and polychlorinated biphenyls in commercially wild caught and farm-raised fish fillets in the United States. *Environ Res.* 103:46-54.
29. **de Azevedo e Silva, C.E., Azeredo, A., Lailson-Brito, J., Torres, J.P. & Malm, O.** 2007. Polychlorinated biphenyls and DDT in swordfish (*Xiphias gladius*) and blue shark (*Prionace glauca*) from the Brazilian coast. *Chemosphere.* 67: S48-53
30. **Costabeber, I., Dos Santos, J.S., Xavier, A.A., Weber, J., Leaes, F.L., Junior, S.B. & Emanuelli, T.** 2006. Levels of polychlorinated biphenyls (PCBs) in meat and meat products from the state of Rio Grande do Sul, Brazil. *Food Chem Toxicol.* Jan;44(1):1-7
31. **Nakata, H., Kawazoe, M., Arizono, K., Abe, S., Kitano, T., Shimada, H., Li, W. & Ding, X.** 2002. Organochlorine pesticides and polychlorinated biphenyl residues in foodstuffs and human tissues from China: status of contamination, historical trend, and human dietary exposure. *Archives of Environmental Contamination and Toxicology*; 43: 473-480
32. **Yang, N., Matsuda, M., Kawano, M. & Wakimoto, T.** 2006 PCBs and organochlorine pesticides (OCPs) in edible fish and shellfish from China. *Chemosphere*;63:1342–52
33. **Naito, W., Jin, J., Kang, Y.S., Yamamuro, M., Masunaga, S. & Nakanishi, J.** 2003. Dynamics of PCDDs/DFs and coplanar-PCBs in an aquatic food chain of Tokyo Bay. *Chemosphere.* Oct;53(4):347-62
34. **Nakatani, T., Ogaki, S., Itano, K., Fujita, T., Mori, Y. & Endo, G.** 2006 Toxic equivalent (TEQ) levels and characteristics of PCDD/DF and CoPCB concentrations in marine foods in Japan. *Bull Environ Contam Toxicol.* Aug;77(2):237-44
35. **Sasamoto, T., Ushio, F., Kikutani, N., Saitoh, Y., Yamaki, Y., Hashimoto, T., Horii, S., Nakagawa, J. & Ibe, A.** 2006. Estimation of 1999-2004 dietary daily intake of PCDDs, PCDFs and dioxin-like PCBs by a total diet study in metropolitan Tokyo, Japan. *Chemosphere.* Jul;64(4):634-41
36. **Tsutsumi, T., Yanagi, T., Nakamura, M., Kono, Y., Uchibe, H., Iida, T., Hori, T., Nakagawa, R., Tobiishi, K., Matsuda, R., Sasaki, K. & Toyoda, M.** 2001. Update of daily intake of PCDDs, PCDFs, and dioxin-like PCBs from food in Japan. [Chemosphere](#). 45: 1129-1137.
37. **Moon, H.B. & Ok, G.** 2006 Dietary intake of PCDDs, PCDFs and dioxin-like PCBs, due to the consumption of various marine organisms from Korea. *Chemosphere*;62:1142–52
38. **Yim, U.H., Hong, S.H., Shim, W.J. & Oh, J.R.** 2005 Levels of persistent organochlorine contaminants in fish from Korea and their potential health risk. *Arch Environ Contam Toxicol.* 48:358–66
39. **Munshi, A.B., Detlef, S.B., Schneider, R. & Zuberi, R.** 2004 *Mar Pollut Bull.* Organochlorine concentrations in various fish from different locations at Karachi Coast. Oct;49(7-8):597-601.

40. **Muir, D., Savinova, T., Savinov, V., Alexeeva, L., Potelov, V. & Svetochev, V.** 2003. Bioaccumulation of PCBs and chlorinated pesticides in seals, fishes and invertebrates from the White Sea, Russia. *Sci Total Environ.* May 1;306(1-3):111-31
41. **Guruge, K.S. & Tanabe, S.** 2004 Polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxin-like biphenyls in biota from Sri Lankan coast. *Marine Pollution Bulletin*; 48:986–1008
42. **Hsu, M.S., Hsu, K.Y., Wang, S.M., Chou, U., Chen, S.Y., Huang, N.C., Liao, C.Y., Yu, T.P. & Ling, Y.C.** 2007 A total diet study to estimate PCDD/Fs and dioxin-like PCBs intake from food in Taiwan. *Chemosphere*; 67(9):S65-70
43. **Coelhan, M. & Barlas, H.** 1998 Levels of some organochlorine contaminants in fishes from Turkey. *Fresenius Environ Bull.* 7:388–95
44. **Manirakiza, P., Covaci, A., Nizigiyimana, L., Ntakimazi, G. & Schepens, P.** 2002 Persistent chlorinated pesticides and polychlorinated biphenyls in selected fish species from Lake Tanganyika, Burundi, Africa. *Environ Pollut.*117(3):447-55
45. **Loufty, N., Fuerhacker, M., Tundo, P., Raccanelli, S., El Dien, A.G. & Tawfic Ahmed, M.** 2006. Dietary intake of dioxins and dioxin-like PCBs, due to the consumption of dairy products, fish/seafood and meat from Ismailia city, Egypt. *Sci Total Environ*;370:1–8.
46. **Loufty, N., Fuerhacker, M., Tundo, P., Raccanelli, S. & Tawfic Ahmed, M.** 2007. Monitoring of polychlorinated dibenzo-p-dioxins and dibenzofurans, dioxin-like PCBs and polycyclic aromatic hydrocarbons in food and feed samples from Ismailia city, Egypt. *Chemosphere*; 66:1962–70
47. **Houserová, P., Kubán, V., Krácmár, S. & Sitko, J.** 2007. Total mercury and mercury species in birds and fish in an aquatic ecosystem in the Czech Republic. *Environ Pollut.* 145(1):185-94.
48. **Voigt, H.R.** 2001. High summer concentrations of mercury in big perch (*Perca fluviatilis* L) from the Tvärminne archipelago (SW Finland) and Natö (Åland Islands) Baltic sea. *Nahrung.* 45(2):109-13.
49. **Sirof, V., Guérin, T., Mauras, Y., Garraud, H., Volatier, J.L. & Leblanc, J.C.** 2008. Methylmercury exposure assessment using dietary and biomarker data among frequent seafood consumers in France CALIPSO study. *Environ Res.* 107(1):30-8.
50. **Schweinsberg, F.** 2003. Mercury in fish and its effects on health: German method of assessment. *Int. J. Hyg. Environ. Health* 206 (3): 241-243,
51. **Storelli, M.M., Giacomini-Stuffler, R. & Marcotrigiano, G.O.** 2002b *Mar Pollut Bull.* Total and methylmercury residues in cartilaginous fish from Mediterranean Sea.;44(12):1354-8.
52. **Storelli, M.M., Giacomini-Stuffler, R., Storelli, A., D'Addabbo, R., Palermo, C. & Marcotrigiano, G.O.** 2003. Survey of total and methylmercury levels in edible fish from the Adriatic sea. *Food Addit. Contam.* 20: 1114-1119.
53. **Storelli, M.M., Barone, G., Piscitelli, G. & Marcotrigiano, G.O.** 2007. Mercury in fish: concentration vs. fish size and estimates of mercury intake. *Food Addit Contam.* 24(12):1353-7.

54. **Julshamn, K., Grøsvik, B.E., Nedreaas, K. & Maage, A.** 2006. Mercury concentration in fillets of Greenland halibut (*Reinhardtius hippoglossoides*) caught in the Barents Sea in January 2006. *Sci Total Environ.* 372(1):345-9.
55. **National Institute of Nutrition and Seafood Research.** Status 2008 – Mercury analyses of seafood from the area around U864 at Fedje. Available at: http://www.nifes.no/index.php?page_id=150&article_id=2823&lang_id=2
56. **Cabañero, A.I., Carvalho, C., Madrid, Y., Batoréu, C. & Cámara, C.** 2005. Quantification and speciation of mercury and selenium in fish samples of high consumption in Spain and Portugal. *Biol Trace Elem Res.* 103(1):17-35.
57. **Sahuquillo, I., Lagarda, M.J., Silvestre, M.D. & Farre, R.** 2007. Methylmercury determination in fish and seafood products and estimated daily intake for the Spanish population. *Food Addit. Contam.* 24 (8): 869-876,
58. **Carrasco, L., Díez, S., Soto, D.X., Catalan, J. & Bayona, J.M.** 2008. Assessment of mercury and methylmercury pollution with zebra mussel (*Dreissena polymorpha*) in the Ebro River (NE Spain) impacted by industrial hazardous dumps. *Sci Total Environ.* 407(1):178-84.
59. **Ortega-García, J.A., Rodríguez, K., Calatayud, M., Martín, M., Vélez, D., Devesa, V., Sánchez-Alarcon, M.C., Torres Cantero, A.M., Galindo-Cascales, C., Gil-Vázquez, J.M., Sánchez-Sauco, M.F., Sánchez-Solís, M., Alfonso-Marsilla, B., Romero-Braquehais, F.** 2009. Estimated intake levels of methylmercury in children, childbearing age and pregnant women in a Mediterranean region, Murcia, Spain. *Eur J Pediatr.* 168 (9): 1075-1080,
60. **Björnberg, K.A., Vahter, M., Grawé, K.P. & Berglund, M.** 2005 b Methyl mercury exposure in Swedish women with high fish consumption. *Sci Total Environ.*;341(1-3):45-52.
61. **Scientific Advisory Committee on Nutrition and Committee on Toxicology (SACN).** 2004. Advice on fish consumption: benefits & risks. United Kingdom Food Standards Agency and Department of Health. Her Majesty's Stationary Office. London. Available at: <http://www.sacn.gov.uk>
62. **Lockhart, W.L., Stern, G.A., Wagemann, R., Hunt, R.V., Metner, D.A., DeLaronde, J., Dunn, B., Stewart, R.E., Hyatt, C.K., Harwood, L. & Mount, K.** 2005. Concentrations of mercury in tissues of beluga whales (*Delphinapterus leucas*) from several communities in the Canadian Arctic from 1981 to 2002. *Sci.Total Environ.* 351-352: 391-412.
63. **Campbell, L.M., Norstrom, R.J., Hobson, K.A., Muir, D.C., Backus, S. & Fisk, A.T.** 2005. Mercury and other trace elements in a pelagic Arctic marine food web (Northwater Polynya, Baffin Bay). *Sci Total Environ.* 351-352:247-63.
64. **Kelly, B.C., Ikonomou, M.G., Higgs, D.A., Oakes, J. & Dubetz, C.** 2008 Mercury and other trace elements in farmed and wild salmon from British Columbia, Canada. *Environ Toxicol Chem.* 27(6):1361-70.
65. **FDA.** Mercury Levels in Commercial Fish and Shellfish. 2006. Available at: <http://www.cfsan.fda.gov/~frf/sea-mehg.html>
66. **Jewett, S.C. & Duffy, L.K.** 2007. Mercury in fishes of Alaska, with emphasis on subsistence species. *Sci Total Environ.* 387(1-3):3-27.

67. **Marcovecchio, J.E., Obenat, S.M., Perez, A. & Moreno, V.J.** 1986. Total mercury and lead contents in the biota at Mar Chiquita coastal lagoon, Province of Buenos Aires, Argentine Republic. *J. Shoreline Manage.* 2, 207–222.
68. **Kehrig, H.A., Costa, M., Moreira, I. & Malm, O.** 2002. Total and methylmercury in a Brazilian estuary, Rio de Janeiro. *Mar Pollut Bull.* 44(10):1018-23.
69. **Cortes, S. & Fortt, A.** 2007. Mercury content in Chilean fish and estimated intake levels. *Food Addit Contam.* 24(9):955-9.
70. **Marrugo-Negrete, J., Verbel, J.O., Ceballos, E.L. & Benitez, L.N.** 2008. Total mercury and methylmercury concentrations in fish from the Mojana region of Colombia. *Environ Geochem Health.* 30(1):21-30.
71. **Durrieu, G., Maury-Brachet, R. & Boudou, A.** 2005. Goldmining and mercury contamination of the piscivorous fish *Hoplias aimara* in French Guiana (Amazon basin). *Ecotoxicol Environ Saf.* 60:315–23.
72. **Horvat, M., Nolde, N., Fajon, V., Jereb, V., Logar, M., Lojen, S., Jacimovic, R. & Falnoga, I.** 2003. Total mercury methylmercury and selenium in mercury polluted areas in the province Guizhou, China. *Sci. Total Environ.* 304, 231–256.
73. **Jin, L., Liang, L., Jiang, G. & Xu, Y.** 2006. Methylmercury, total mercury and total selenium in four common freshwater fish species from Ya-Er Lake, China. *Environ Geochem Health.* 28(5):401-7.
74. **Mishra, S., Bhalke, S., Saradhi, I.V., Suseela, B., Tripathi, R.M., Pandit, G.G. & Puranik, V.D.** 2007. Trace metals and organometals in selected marine species and preliminary risk assessment to human beings in Thane Creek area, Mumbai. *Chemosphere.* 69(6):972-8.
75. **Endo, T., Haraguchi, K., Hotta, Y., Hisamichi, Y., Lavery, S., Dalebout, M.L. & Baker, C.S.** 2005. Total mercury, methyl mercury, and selenium levels in the red meat of small cetaceans sold for human consumption in Japan. *Environ Sci Technol.* 39(15):5703-8.
76. **Endo, T., Hisamichi, Y., Haraguchi, K., Kato, Y., Ohta, C. & Koga, N.** 2008. Hg, Zn and Cu levels in the muscle and liver of tiger sharks (*Galeocerdo cuvier*) from the coast of Ishigaki Island, Japan: relationship between metal concentrations and body length. *Mar Pollut Bull.* 56(10):1774-80.
77. **Appleton, J.D., Weeks, J.M., Calvez, J.P. & Beinhoff, C.** 2006. Impacts of mercury contaminated mining waste on soil quality, crops, bivalves, and fish in the Naboc River area, Mindanao, Philippines. *Sci Total Environ.* 354(2-3):198-211.
78. **Maramba, N.P.C., Reyes, J.P., Francisco-Rivera, A.T., Panganiban, L.C., Dioquino, C., Dando, N., Timbang, R., Akagi, H., Castillo, M.T., Quitariano, C., Afuang, M., Matsuyama, A., Eguchi, T. & Fuchigami, Y.** 2006. Environmental and human exposure assessment monitoring of communities near an abandoned mercury mine in the Philippines: a toxic legacy. *J. Environ. Manage.* 81(2):135-45.
79. **Voegborlo, R.B., Adimado, A.A. & Ephraim, J.H.** 2007. Total mercury distribution in different tissues of frigate tuna (*Auxis thazard thazard*) from the Atlantic Coastal Waters of Ghana, Gulf of Guinea. *Environ Monit Assess.* 132(1-3):503-8.

80. **Elhamri, H., Idrissi, L., Coquery, M., Azemard, S., El Abidi, A., Benlemlih, M., Saghi, M. & Cubadda, F.** 2007. Hair mercury levels in relation to fish consumption in a community of the Moroccan Mediterranean coast. *Food Addit Contam.* 24(11):1236-46.
81. **Ikingura, J.R. & Akagi, H.** 2003. Total mercury and methylmercury levels in fish from hydroelectric reservoirs in Tanzania. *Sci Total Environ.* 304(1-3):355-68.
82. **Padula, D.J., Daughtry, B.J. & Nowak, B.F.** 2008. Dioxins, PCBs, metals, metalloids, pesticides and antimicrobial residues in wild and farmed Australian southern bluefin tuna (*Thunnus maccoyii*). *Chemosphere.* 72(1):34-44.
83. **Love, J.L., Rush, G.M. & McGrath, H.** 2003, Total mercury and methylmercury levels in some New Zealand commercial marine fish species. *Food Addit. Contam.* 20(1):37-43.