PERGAMON

Food and Chemical Toxicology 40 (2002) 767–779

Food and Chemical Toxicology

www.elsevier.com/locate/foodchemtox

Organochlorine chemicals in seafood: occurrence and health concerns

A.G. Smith*, S.D. Gangolli

MRC Toxicology Unit, Hodgkin Building, University of Leicester, Lancaster Road, Leicester LE1 9HN, UK

Summary

The cheap availability of chlorine gas, together with the development of industrial chlorinating procedures in the 20th century, led to the production of a wide range of organochlorine compounds many with a variety of commercial applications, including usage as insecticides and defoliants and polychlorinated biphenyls (PCBs) used as coolants in electricity supply transformers. However, it was soon found that many of these technologically valuable chemicals suffered from a major disadvantage in that they resisted biodegradation and that the continued use of these compounds would lead to their persistence and accumulation in the environment and thus enter the human food chain. Despite regulatory bans or strict limits on usage being imposed on organochlorine pesticides in most countries, these compounds continue to be detected in measurable amounts in the eco-system including marine life. In general, organochlorine levels in fish intended for human consumption are low and probably below levels likely to adversely affect human health. Populations at higher risk than most people are those subsisting largely on fish and other marine life. Additionally, fish oils obtained from contaminated fish, if consumed in substantial quantities by infants and young children, might present potential health problems if levels are not continually regulated. Behavioral and neurological effects have been reported in children and ascribed to the consumption of PCB contaminated diet including fish. Another current major human health concern, yet to be resolved, about organochlorine contaminants in the human diet relates to the potential ability of many of these chemicals at low doses to act as "endocrine disruptors". © 2002 Published by Elsevier Science Ltd.

Keywords: Organochlorine chemicals; Dioxins; Polychlorinated biphenyls; Fish; Seafood; Risks

1. Background

The last century witnessed a massive expansion of the chemical industry, with the development of a wide range of new chemical entities of great technological importance and benefit to mankind. These chemicals include compounds used as therapeutic agents in human and veterinary medicine, chemicals used for the protection of public health and agrochemicals used for pest control or for increasing crop yield. The Second World War period provided a further impetus for research leading to the discovery and synthesis of new chemical entities with antibiotic or pesticidal properties (West and Campbell, 1946; Hayes, 1991). The discovery of DDT and the benefits resulting from its use against insects led to the recognition of its potential as an insecticide for the protection of both civilians and the armed forces from the ravages of malaria and other vector-borne diseases such as typhus. Organochlorine chemicals in general made a significant contribution in the development of new pesticides, and these compounds together with DDT were widely and extensively used worldwide with little or no regulatory control. The benefits in terms of the control of pandemic infectious diseases such as malaria, and the increased food production to meet the needs of the growing world population, were immediate and obvious (Hayes, 1991). Appreciation by regulatory authorities and the general public of the gravity and seriousness of problems related to the development of pesticide resistance and the persistence of these compounds in the environment with consequent damage to the ecosystem and to man, was slow to come. Regulatory authorities were increasingly aware of the accumulating body of scientific evidence showing the

Abbreviations: Ah, aryl hydrocarbon; BHC, benzene hexachlorides; ECEH, European Centre for Environment and Health; HCB, hexachlorobenzene; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzodioxins; PCDFs, polychlorinated dibenzofurans; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEF, Toxic Equivalency Factor; TEQs, Toxic Equivalents; WHO, World Health Organization.

* Corresponding author.Tel.: +44-116-252-5617; fax: +44-116-252-5616.

E-mail address: ags5@leicester.ac.uk (A.G. Smith).

0278-6915/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0278-6915(02)00046-7

damaging consequences resulting from the indiscriminate use of organochlorine pesticides and the urgent need for control on their use. This review will limit attention to the contamination of seafood, intended for human consumption, with organochlorine compounds and the possibility that they may present a health hazard to man. Particular use has been made of Food Surveillance documents from the UK Ministry of Agriculture, Fisheries and Food and the Food Standards Agency.

2. Organochlorine chemicals in the environment: sources and distribution

The three main categories of organochlorine compounds present as contaminants in the environment (Table 1) are insecticides and agrochemicals, as exemplified by the hydrocarbon insecticide DDT (Smith, 1991), electricity supply transformer liquid coolants, for example the polychlorinated biphenyls (PCBs) and the contaminants polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) (IPCS, 1989, 1993). PCDDs and PCDFs are complex mixtures present as adventitious contaminants formed in poorly controlled manufacturing conditions in the production of various chlorinated compounds and also in combustion and incineration processes (IPCS, 1989). 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), first detected in commercial formulations of the defoliant 2,4,5-trichlorophenoxyacetic acid, is the model "bench-mark" compound used for relating other PCDDs, PCDFs and PCBs.

The main reasons for the increasing presence of these compounds in the environment are, first, the cheap and ready availability of chlorine gas on an industrial scale led to the production of a plethora of chlorinated compounds of technological importance. Secondly, many of these polychlorinated organic compounds, cyclic in structure, and highly thermostable in character, were resistant to biodegradation; and thirdly, the uncontrolled use and discharge of these chemicals resulted in their accumulation and persistence in the environment. The development of sensitive and specific analytical methods for their detection led to the growing awareness of their increasing presence in the ecosystem.

Chronologically, the first category of organochlorine compounds of technological importance, were the PCBs, synthesized in the late 19th century. The PCBs are a group of 209 related compounds (known as congeners), which differ only in the number of chlorine atoms attached to the parent biphenyl molecule. These compounds, found to have high dielectric constants and heat absorbing properties, readily found application as heat-exchange coolants in transformers used for electricity power supply, leading to their manufacture in bulk. Other applications of PCBs included use in the manufacture of hydraulic fluids, lubricating oils and carbonless copy paper. The total world production of PCBs in 1980 was estimated to be in excess of 1 million tonnes (IPCS, 1993).

DDT, synthesized in 1874 and first shown in Switzerland to be a useful agricultural pesticide in 1939, was extensively used as an insecticide with amazing success during the Second World War for the control of vector-borne diseases such as malaria and typhus, infections which had produced more casualties than enemy action during the 1914–1918 World War I. In the 1950s, and onwards, DDT was being manufactured and used on a massive scale in agriculture and in public health. Additionally, research developments gave rise to the commercial production of a spate of new organochlorine pesticides such as benzene hexachlorides (BHC), containing the active isomer lindane. Other insecticides were dieldrin, chlordane, heptachlor, toxaphenes, mirex and chlordecone (Hayes, 1991; Smith, 1991).

The initial enthusiasm for the application of organochlorine pesticides gradually began to wane with the growing recognition of their declining efficacy with continued use. Insect pests were developing resistance to the compounds. Furthermore, the relative chemical stability of these compounds and their resistance to complete biodegradation under conditions of use, which in part accounted for their efficacy (Smith, 1991), resulted in their persistence and accumulation in the environment. Thus, for example, DDE, a major metabolite of DDT refractory to further degradation, can often be

Table 1
Organochlorine compounds present as contaminants in the environment and in the human food chain

Insecticides and agrochemicals	Transformer coolants, etc.	Dioxins and furans
DDT and DDE; methoxychlor; chlordane; dicofol; dieldrin; endosulfan; lindane; heptachlor; hexachlorobenzene	Polychlorinated biphenyls (PCBs) (commercial products–mixtures of 209 congeners) e.g.	Polychlorinated dibenzodioxins (PCDDs): e.g. 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin (2,3,7,8-TCDD)
2,4-Dichloro- and 2,4,5-trichloro-phenoxyacetic acids	Aroclor 1254; Aroclor 1260; Kanechlor 500	polychlorinated dibenzofurans (PCDFs): e.g. 2,3,7,8-tetra-chlorodibenzofuran (2,3,7,8-TCDF)

detected either together with DDT or alone, in crops and soils sprayed earlier with DDT.

The consumption by birds and other wildlife of organochlorine pesticide treated food grains and the gradual leaching away by rainfall and underground streams of pesticide residues in soil led to the widespread dissemination of organochlorine compounds in the ecosystem (Cooper, 1991) and eventually in the human food chain. Traces of DDT, DDE and other organochlorine residues have been detected in penguins and seals in places as remote as Antarctica (Sladen et al., 1966). As regards marine life, the highest levels were detected in species of fish in coastal waters adjacent to highly industrialized areas, for example, off the Pacific rim countries, and in the Baltic and Mediterranean Seas (Jensen et al., 1969; Burnett, 1971; Young et al., 1976; Stout, 1980; Yamagishi et al., 1981; Albaigés et al., 1987; Kannan et al., 1994). The mounting evidence of the environmental persistence and accumulation of organochlorine pesticide residues and the observed carcinogenicity of many of these compounds in experimental animals (Smith, 1991) raised public alarm of the likely possibility that similar effects might be produced in humans. This was reinforced by the apocalyptic scenario presented by Rachel Carson in her book "*Silent Spring*" (1962). Governments of most countries in the world were thus compelled to take immediate regulatory action to ban, or severely restrict, the use of organochlorine pesticides.

Thus far the problem of the bioaccumulation of organochlorine residues was thought to be restricted to pesticides. Advances in analytical methodologies showed that this was not the case; PCBs, which had been in industrial use for a much longer time than the organochlorine pesticides, were found to be the major source of organochlorine residues in some environments. Jensen et al. (1969) showed that marine life in Swedish coastal waters contained measurable amounts of DDT and also PCBs. Many similar findings were made, for example, by Albaigés et al. (1987) in tissues of fish in the western Mediterranean. Subsequent to these findings, the distribution of PCBs in the ecosystem has been intensively investigated (IPCS, 1993; IARC, 1997; see also Risebrough et al. 1968, 1976a). Studies on commercial samples of PCBs have shown that in addition to containing PCB congeners of variable composition, some of which are relatively innocuous, these products contain highly toxic chlorinated naphthalenes and PCDFs. The latter compounds are also formed by the partial decomposition of PCBs at low temperature. Traces of these contaminants have been detected in marine life (Oehm et al., 1989). In recent years, polybrominated biphenyls and polybrominated diphenyl ethers, used as flame retardants, have been detected in marine mammals (De Boer et al., 1998).

Other sources of organochlorine compounds in the environment include the herbicides 2,4-dichloro- and 2,4,5-trichlorophenoxyacetic acids, the highly toxic and non-biodegradable PCDDs, formed inadvertently in the manufacture of pentachlorophenols, and the chlorophenoxyacetic acids, and the fungicide hexachlorobenzene (HCB).The chlorophenoxyacetic acids and HCB are no longer permitted for use but continue to be detected in marine life (IPCS, 1997).

3. Accumulation in marine environment and uptake by aquatic life

The pollution of lakes, inland waterways, rivers and eventually the seas by chlorinated pesticides, PCBs and related chemicals follows the dissolving of these substances present in the atmosphere from burning waste, in soils and landfills by rainfall, and by the uncontrolled discharge of contaminated industrial and sewage effluents. Low-level distillation from the land to the atmosphere with eventual disposition in the oceans can also occur. Although these compounds have low water solubility, particularly in seawater, they are lipophilic with high octanol/water partition coefficients (log P o/w), thereby enabling fish and invertebrates to absorb, retain and concentrate them particularly in fatty tissues (Cooper, 1991). Organochlorine chemicals adsorbed on particulates and on underwater sediments (Young et al., 1976; Ernst, 1986; Lohse, 1991; Elijarrat et al., 2001) provide a ready source for the intake of these compounds by crustaceans and bottom feeders (Tanabe and Tasukawa, 1987; Porte and Albaigés, 1993). Disturbance of sediments can release more pollutants. The uptake and concentration factor of up to 690,000 has been reported for DDT in mussels (Risebrough et al., 1976b). The distribution and uptake of organochlorine compounds from aquatic environments by marine life is dynamic, complex and subject to seasonal variations and local conditions (McDowell Cupuzzo et al.,1989; Vassilopoulou and Georgakopoulos-Gregoriades,1993). Fig. 1 depicts the interplay of some of the relevant factors in the transfer and concentration of these compounds in marine life. Of particular concern has been the discharge of industrial effluents into relatively enclosed waters such as the Norwegian fjords (Oehm et al., 1989), the North Sea (Lohse, 1991; De Boer et al., 1993) and the Mediterranean Sea (Porte and Albaigés, 1993). Thus, fish caught from coastal regions and estuaries close to regions of industrialization, for instance California, the north-western Atlantic, Japan and the Baltic and Mediterranean Seas, can be particularly at risk of contamination especially those that are non-migratory (Strandberg et al., 1998). However, deepwater fish can also have significant levels of contamination that can be highly variable (Atuma et al., 1996; Ali et al., 1997).

There is a substantial body of literature on the variation in the levels of various organochlorine compounds found in fish and aquatic life from freshwater lakes and rivers and in the seas (IPCS, 1993). As an example, Table 2 shows the variation in levels of HCB found in fish and shellfish obtained from various locations, some geographically close to each other, and marked differences between species.

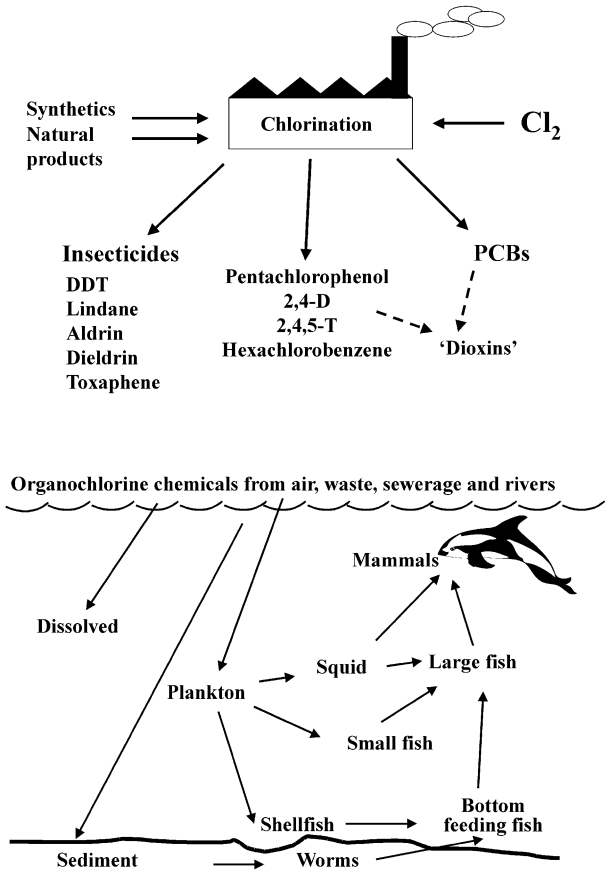

Fig. 1. Production and distribution of persistent organochlorine chemicals in the environment and their accumulation in the marine food chain to edible shellfish, fish and mammals.

In view of the complexities in the chemical compositions, particularly of PCBs, PCDDs and PCDFs mixtures in the environment and in the food chain, and since the ultimate aim of the analytical data is to facilitate the assessment of the health risks posed by these compounds to man, the concept of Toxic Equivalency Factor (TEF) was developed by the World Health Organization (WHO) jointly with the European Centre for Environment and Health (ECEH). The term TEF indicates approximately one-half to one of *order of magnitude* estimate of the toxic potency of a compound relative to TCDD.

The WHO–ECEH TEF values of compounds, derived after careful consideration of all available relevant scientific data, are based on the following four criteria:

- The compound must show structural relationship to PCDDs and PCDFs;
- The compound must bind to the Ah receptor;
- The compound must elicit Ah receptor-mediated biochemical and toxic responses;
- The compound must be persistent and accumulate in the food chain.

The TEF values for some congeners of PCDDs, PCDFs and PCBs are shown in Table 3.

On the general assumption that the metabolic disposition, tissue distribution, body burden and toxicity of congeners of PCBBs, PCDFs and PCBs operate on an additive basis, the quantitative levels of these dioxin-like congeners can be expressed as Toxic Equivalents (TEQs). The TEQ of a congener is obtained as a product of the concentration of the congener × the TEF value, and the total TEQ value of a dioxin-like mixture present in a food matrix is obtained by the summation

Table 2
Some levels of hexachlorobenzene (HCB) in fish and shellfish from different locations

Location	Fish/shellfish	Average HCB content (μ/kg)	Reference
Clyde, Scotland	Herring muscle	<1	Kelly and Campbell (1999)
	Cod liver	<5	
Firth of Forth, Scotland	Herring muscle	2	Ernst (1986)
North Sea, Germany	Cod liver	42	
	Plaice liver	3	MAFF/HSE (1994)
Greenland	Cod liver	30	
Coastal waters, England/Wales	Cod liver	2–29	
Baltic coastal waters	Herring muscle	1–39	Hansen (1985)
Friesfjord, Norway	Cod liver	16,800	Bjerk and Brevik (1980)
Sogndalfjord, Norway	Cod liver	18	
Baltic	Mussels	200–800[a]	Ostfeldt et al. (1994)
Kattegat	Mussels	11–20[a]	
Ebro Delta, Spain	Sea bass	0.6	Pastor et al. (1996)
	Sea mullet	8.7	

[a] By lipid weight.

Table 3
Toxic equivalency factors (TEFs) for the risk assessment of PCDDs, PCDFs and PCBs based on WHO recommendations (Van Den Berg et al., 2000)

Congener	TEF value
Dibenzo-p-dioxins	
2,3,7,8-TCDD	1
1,2,3,7,8-PnCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,23,7,8.9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0001
Dibenzofurans	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PnCDF	0.05
2,3,4,7,8-PnCDF	0.5
1,2,3,4,7,8	
1,2,3,6,7,8-HxCDF	0.1
1,2,3,6,7,8,9	
2,3,4,6,7,8	
1,2,3,4,6,7,8	
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.0001
Non-ortho-PCBs	
PCB 77	0.0001
PCB 81	0.0001
PCB 126	0.1
PCB 169	0.01
Mono-ortho PCBs	
PCBs: 114, 156, 157	0.0005
PCBs: 105, 118, 123, 189	0.0001
PCB 167	0.00001

Toxic equivalency factor (TEF) of a compound, (i.e. toxicity expressed as one-half to one *order of magnitude* relative to TCDD = 1), based on the following criteria: Exibits a structural relationship to PCDDs and PCDFs; Binds to the Ah receptor; Elicits an Ah receptor-mediated biochemical response and toxic effect; Persists and accumulates in the food chain.

of each of the individual TEQ values of the congeners present. The Department of Health in the UK has endorsed the recommendation of the International Committee for the Exploration of the Sea that the following PCB congeners should be quantified in marine fish: PCBs 28, 52, 101, 118, 138, 153 and 180. The choice of these congeners was based on those that had been found to be relatively abundant in fish and before the application of TEFs was applied to PCBs. The TEQ values of dioxins and PCBs in edible tissues of UK-landed and imported marine fish and fish products are given in Table 4. It should be noted, however, that many of the PCB congeners present in the environment and which have been measured in fish are not considered to be 'dioxin'-like in their action (the so-called non-coplanar PCBs), but may be implicated in toxicity to humans associated with low-level exposure. Further comparisons are required to relate exposure to these PCBs with risk assessment.

Table 4
Dioxins and PCBs in marine fish for human consumption and fish products in UK

Fish type	Concentration (ng WHO-TEQ/kg fat)[a]					
	Dioxins		PCBs		Total	
	Mean	Range	Mean	Range	Mean	Range
UK landed						
Cod	9.0	2.1–24	17	3.3–76	26	7.2–98
Haddock	6.9	1.1–14	7.4	2.2–22	14	5.5–24
Plaice	25	3.6–43	42	9.5–55	67	13–90
Whiting	8.3	2.0–20	23	2.4–91	32	4.4–110
Herring	24	13–38	59	12–110	83	26–140
Mackerel	3.8	1.0–9.0	14	2.5–31	17	3.4–40
Salmon	6.5	4.6–11	19	12–30	25	16–38
Trout	5.7	2.4–14	18	8.7–50	24	12–61
Eels[(2)]						11–95
Imported						
Cod	6.1	1.4–18	9.7	2.0–30	16	6.3–50
Haddock	4.6	1.9–8.5	5.4	1.9–12	10	4.2–19
Plaice	20	16–27	33	21–57	54	37–84
Salmon	3.4	3.4	12	12	16	16
Red fish	14	12; 16	43	42; 44	57	57; 57
Fish products						
Fish fingers	0.7	0.3–2.4	1.6	0.3–6.2	2.3	0.9–6.6

[a] Results are given to 2 significant figures. The exact dioxins and PCBs measured in this survey can be found in MAFF (1997a, 1999). They include dioxins to which WHO-TEFs have been assigned (Table 3) and the *ortho* and *non-orth o* PCBs in Table 3 (except for PCB 81). In addition, PCBs 18,28,31,47,49,51,52,99,101,128,153 and 180 were measured but do not contribute to WHO-TEFs.

4. Estimates of human intake of organochlorine compounds from seafood

Surveys carried out in a number of countries on the daily exposure to PCDDs, PCDFs and PCBs in humans have shown that over 90% occurs through the diet, with foods of animal origin usually being the predominant source (see Table 5).

There is conclusive evidence showing that, in general, fish in the human diet contributes a significant proportion of the total intake of PCBs and related organochlorine compounds, particularly fish with higher fat levels, the so-called oily fish such as mackerel (Fujiwara, 1975; Westoo and Noren, 1978; Mussalo-Rauhamaa et al., 1984; Mes et al., 1991; Svensson et al., 1991; Duarte-Davidson and Jones, 1994; Kannan et al., 1994; Becher et al., 1995; Anderson et al., 1998; Tsutsumi et al., 2001). Furthermore, it has been found that levels of organochlorine compounds in plasma or mother's milk provide a reliable marker of human exposure to these compounds (Kuwabara et al., 1979; Gosset et al., 1989; Asplund et al., 1994; Grandjean et al., 1995; Johansen et al., 1996; Grimvall et al., 1997). In elderly Germans, plasma levels of PCBs, dieldrin and α-hexachlorocyclohexane (from usage of impure lindane) correlated

Table 5
Estimated daily exposure of people to PCDDs and PCDFs, expressed as toxic equivalents (TEQs), in various countries

Exposure source	Canada[a] (pg/day)	Germany[b]	Netherlands[c]	USA[d]
Ambient sources	5.1	4.5	3.2	3.0
Total diet	140	130	115	116
Other sources	0.30	5.0	9.1	
Total from all sources	145	140	127	120
Dietary sources				
Meat and meat products	61	39	22	66
Milk and dairy products	31.1	41.7	43	42
Fish and fish oil	17	33.9	31.2	7.8
Vegetables + fruit	24.3	6.3	15.8–21	
Cereals, etc.	6.3	10.3		

(TEQ = sum total of individual congener exposure, pg/day×TEF value)

[a] Birmingham et al. (1989).
[b] Beck et al. (1992).
[c] Theelen (1991).
[d] Schaum et al. (1994).

positively with the consumption of salt-water fish (Devoto et al., 1998). Women who ate more than 100 g of fish per week had higher levels of PCBs and β-hexachlorocyclohexane in their breast milk than those who consumed less fish (Schade and Heinzow, 1998). Similarly, in parts of the world where fish, crustaceans and other marine source of food such as whale, walrus and seal meat constitute a major part of the human diet, levels of organochlorine compounds in women's blood and breast milk were consistently higher than in control populations (Anon., 1998). Breast-milk samples obtained from 109 Inuit women in Arctic Quebec had 3.5-times higher levels of PCBs, PCDDs and PCDFs than a control group consisting of 96 Caucasians (Dewailly et al., 1989). Plasma levels of co-planar PCBs in fishermen living off the Gulf of St Lawrence were markedly elevated compared with controls (Dewailly et al., 1994). In a comparison between indigenous Arctic women in Canada, up to 50% of those Inuit on Baffin Island who consumed appreciable quantities of meat and blubber from ringed seal, walrus and narwhal exceeded the acceptable or tolerable daily intakes of chlordane-related compounds, toxaphene, PCBs and dieldrin (Kuhnlein et al., 1995). Far fewer women exceeded these guidelines in indigenous communities whose major food sources were caribou, white fish and duck. In the Faroe Islands, where the normal seafood diet includes whale meat and blubber, a number of studies have shown that PCB levels in breast milk were consistently higher than samples obtained from other parts of Europe (Grandjean et al., 1995; Weihe et al., 1996). Similarly, elevated levels of DDT and DDE were found in breast-milk samples obtained from women eating bottom-feeding fish from the lower Yakima River in Washington, USA compared with controls

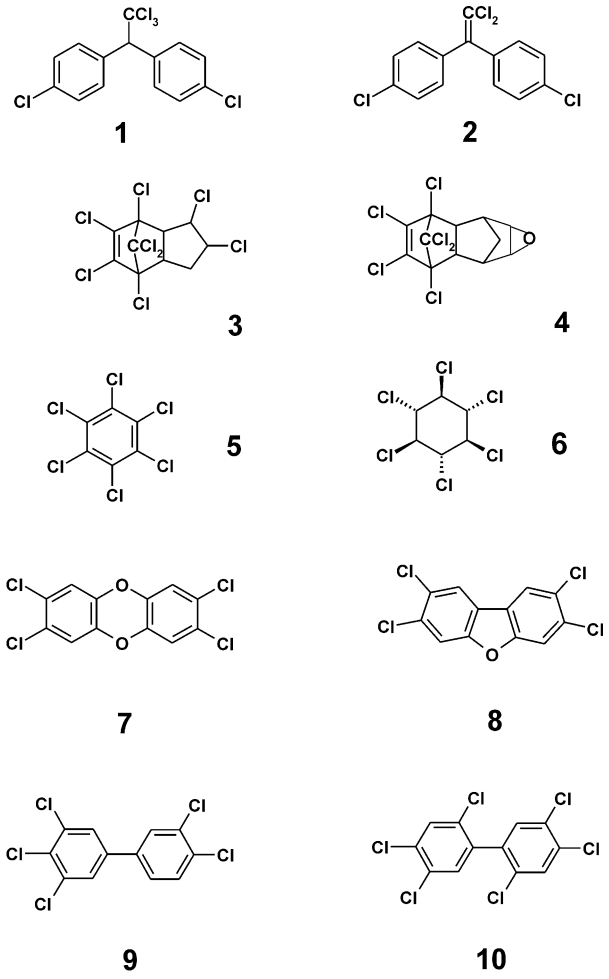

Fig. 2. Examples of some persistent organochlorine chemicals that accumulate in humans and possibly seafood. (1) DDT; (2) DDE (dechlorination product of DDT and highly persistent); (3) chlordane; (4) dieldrin; (5) hexachlorobenzene; (6) β-hexachlorocyclohexane; (7) 2,3,7,8 - tetrachlorodibenzo - *p* - dioxin; (8) 2,3,7,8 - tetrachlorodibenzofuran; (9) 3,4,5,3′,4′-pentachlorobiphenyl (PCB126); (10) 2,4,5,2′,4′,5′-hexachlorobiphenyl (PCB153).

(Marien and Laflamme, 1995). How seafood is cooked can influence the amount of contaminants ingested by consumers (Trotter and Corneliussen, 1989; Zabik et al., 1992, 1996; Salama et al., 1998). This can arise by removal of parts likely to contain contaminants before cooking (e.g. the hepatopancreas of crabs or skin of fish), by loss into water when simmering (even of PCBs), and by loss of oils and juice from fish when grilling. Some chlorinated chemicals that have been detected in humans and are pertinent to consumption of seafood are shown in Fig. 2.

In the process of the production of fish oils, organochlorine compounds, together with other lipid soluble substances present in the fish used, are unavoidably extracted and concentrated in the final products. Some samples of cod liver oil obtained from fish in the Baltic Sea and in north Atlantic waters off the shores of northern Europe have been found to be contaminated

Table 6
Dioxins and PCBs in fish oil dietary and medicinal products

Cod liver oil products (concentration ng TEQ/kg oil)				
	Bottled		Capsules	
	Mean	Range	Mean	Range
Dioxins	7.5	6.2–9.2	3.6	1.5–6.2
Non-*ortho*-PCBs	20	17–22	16	11–26
Ortho-PCBs	7.9	6.8–8.5	6.9	3.7–12
Total (TEQs)	36	3138	27	1841
Halibut liver oil capsules (concentration ng TEQ/kg oil)				
Dioxins	3.9		1.7–6.1	
Non-*ortho*-PCBs	5.4		3.5–7.3	
Ortho-PCBs	1.8		1.5–2.2	
Total (TEQs)	11		7.4–15	

MAFF (1997b).

with PCBs and related organochlorine compounds (Falandysz, 1994). Fish oil dietary supplements and medicinal products containing fish oils intended for administration to infants and young children have been found to contain significant amounts of PCBs and related organochlorine residues (Jimenez et al., 1996; Stringer et al., 1996; MAFF, 1997b; see Table 6). In certain instances this could have resulted in some high-level consumers exceeding the recommended maximum daily intake for PCBs unless efforts were made to reduce exposure levels.

Estimates of the daily dietary intake of dioxins and PCBs from seafood in average and high-level consumers in adults and in children of various ages are shown in Tables 7 and 8, respectively.

Table 7
Estimated *upper bound* daily dietary consumption of dioxins + PCBs from types of marine fish by adults in the UK (Total Diet Study conducted in 1992)

Fish type	Estimated dietary exposure (pg WHO-TEQ/kg body weight/day)	
	Average consumer	High-level consumer
White fish		
Cod	0.05	0.13
Haddock	0.02	0.04
Plaice	0.29	0.52
Whiting	0.04	0.09
Fish/fingers/cakes	0.04	0.12
All white fish	0.09	0.39
Oily fish		
Herring	3.0	6.1
Mackerel	1.0	2.4
Salmon	0.68	4.8
All oily fish	0.82	2.3
All fish	0.47	3.4
Total diet	2.6	5.6

MAFF (1999).

Table 8
Estimated *upper bound* daily dietary consumption of dioxins/furans and PCBs from marine fish and the rest of the diet by age group in the UK (based on Total Diet Study 1992)

Age group	PCDDs/PCDFs and PCBs estimated *upper bound* dietary exposure (pg WHO-TEQ/kg body weight/day)	
	Average consumers	High-level consumers
Toddlers	6.5	10
Age: 1.5–2.5 yr	6.0	8.9
2.5–3.5 yr	5.9	8.3
3.5–4.5 yr (boys)	5.5	8.3
3.5–4.5 yr (girls)		
School children	2.8	4.7
Age: 10–15 yr		
Adults	2.6	5.6

MAFF (1999).

5. Toxicity characteristics of polychlorinated compounds

Although there is a measure of similarity in the metabolic disposition of organochlorine compounds in mammalian species, ascribable to the high lipophilicity of the compounds, there are distinct differences in their toxicities in animals and in humans (Guzelian, 1982; Smith, 1991; Pohjanvirta and Tuomisto, 1994).

5.1. Chlorinated insecticides

At high doses, including dietary administration, DDT, chlordecone, dieldrin, lindane and toxaphenes are neurotoxic (Smith, 1991). In addition, many of the compounds appear to be non-genotoxic liver carcinogens following prolonged administration at high doses to rodents. However, the relevance of these effects in terms of human exposure levels is questionable (Smith, 1991). There is evidence that some of these insecticides can adversely affect the reproductive system of experimental animals and humans at occupational exposure levels (Guzelian, 1982), but again there is little evidence that this can occur at levels relevant to environmental exposure (Key and Reeves, 1994; Smith, 2000). Metabolism of these compounds mediated by the mixed-function oxidase system, centered on cytochrome P450, is slow, accounting for their persistence and storage in the adipose tissues of the body.

5.2. PCBs, PCDDs, PCDFs and HCB

A large proportion of the diverse toxic effects produced by these compounds in experimental animals and

in man are initiated by a common mechanism. Many non-*ortho*-coplanar PCBs and the PCDDs, PCDFs and HCB act as ligands with the aryl hydrocarbon (Ah) receptor and thereby trigger the expression of an array of genes that are responsible for the manifestation of a variety of adverse effects, including chloracne, thymic atrophy, liver damage, birth defects, immunotoxicity and cancers (IPCS, 1989, 1993; IARC, 1997).

As stated above, not all effects of PCBs are attributable to their activity as ligands for the Ah receptor. There is increasing evidence that some aspects of the toxicity are mediated by the non-coplanar PCBs by mechanisms that have not yet been amply detailed. In recent years, concern has been directed to the potential ability of PCBs and related polychlorinated compounds to act as endocrine modulators. Thyroid hormone homeostasis and development of goitre has been found to be affected by these compounds in experimental animals (Smith et al., 1987; IPCS, 1993). The mechanism is thought to involve the binding of PCB metabolites to transthyretin, thereby inhibiting the formation of the protein complex carrying both retinol and thyroxin (Brouwer and Van Den Berg, 1986). There is also an accumulating body of experimental evidence that organochlorine compounds can adversely affect the male and female reproductive systems by exhibiting oestrogenic or anti-androgenic activities (Kelce et al., 1995; Daston et al., 1997; Golden et al., 1998). Immunotoxic effects of dioxin-like chemicals have been described to occur at exposures of experimental animals to low levels (Birnbaum, 1995; Voss et al., 1997/1998; Tryphonas, 1998). Whether these endocrine or immunological effects can occur at low enough levels relevant to human environmental exposure is not yet clear.

6. Evidence for toxicity to humans from consumption of organochlorine chemicals in seafood

Despite the concerns that exposure to organochlorine chemicals from contaminated fish diets may be a health hazard, the direct evidence for this is poor. Of considerable debate have been the studies of Jacobson and Jacobson (1996). Infants born to women who had eaten fish from Lake Michigan contaminated by PCBs were followed over more than a decade and appeared to have reduced IQ scores and reading comprehension at 11 years of age. In utero exposure was calculated from umbilical cord serum and post-partum exposure from mothers' milk. However, exposures were estimated at only slightly higher than controls. Earlier studies of this cohort had suggested defects in fetal and postnatal growth and short-term memory (Fein et al., 1984).

A cohort of fishermen and their wives from the Baltic coast of Sweden has been compared with a cohort living near the less-polluted North Sea. Weak associations were observed between PCB levels in fish, fish consumption and incidence of some cancers and low infant birth weight (Svensson et al., 1991, 1995; Ryland and Hagmar, 1995; Rylander et al., 1996). However, causal relationships were not established. Although high occupational exposure to the insecticide chlorodecone has been associated with sperm malfunction (Guzelian, 1982), no studies on the influence of organochlorines on endocrine function associated with fish consumption have been reported. More general proposals that PCBs and DDT levels from dietary exposure are associated with breast cancer are controversial (Key and Reeves, 1994; Smith, 2000). In a series of studies from the Netherlands, environmental exposure to dioxins and PCBs has been linked to influence on cognitive development and to greater susceptibility to infectious diseases or decreased incidence of allergic disease (Patandin et al., 1999; Weisglas-Kuperus et al., 2000). So far though, proof of a causal relationship still requires more evidence and studies of possible confounding factors (CoT, 2001). Hence the proposal that elevated intake of organochlorine chemicals through fish consumption might be associated with health risks is not yet proven. With these chemicals, risk assessment has therefore been based on experimental animal data rather than on evidence of human toxicity (Smith, 2000).

7. Risk assessment and regulatory advice

Although DDT, DDE and other chlorinated pesticides continue to be detectable in human plasma or breast milk, in the last few years concern has mainly focused on the risks from exposure to the dioxins and PCBs. Most countries, excepting the USA and Canada, have accepted the concept of the TDI for assessing the health risks from dioxin-like compounds and for setting permitted limits for these substances in foods intended for human consumption. The TDI for a contaminant, in a manner analogous to the ADI for a food additive, is derived on the assumption that there is an experimental threshold dose level below which no toxic effect is produced by the compound in an animal model, and the application of an appropriate uncertainty factor for extrapolating animal data to man. The TDI for TCDD, and the TEQs for dioxin-like compounds, PCDDs, PCDFs and PCBs, have been derived based on this premise. The WHO Expert Committee recommended a TDI for TCDD at 10 pg/kg body weight/day and the use of TEFs for evaluating dioxin-related compounds and limiting their dietary intake to 10 pg TEQ/kg body weight/day (WHO/EURO, 1991). At a further meeting the WHO European Centre for Environment and Health (ECEH) and the International Programme on Chemical Safety (IPCS) reassessed the health risks of

dioxin in the light of the new data (Van Leeuwen and Younes, 2000). The WHO Committee, in expressing an opinion on the recommended TDI value for dioxin-like compounds, stated that, since the TDI represented the average intake over long periods, occasional short-term excursions above the TDI probably did not present a serious health hazard provided the averaged intake was not exceeded. However, note must be taken of possible subtle health effects occurring following prolonged exposure in some sections of the general population. The at-risk groups thus might include developing fetuses and breast-fed infants of mothers having high intake of contaminated seafoods. The Committee recommended a TDI of 1–4 pg WHO TEQ/kg body weight/day. Subsequent assessments by the Scientific Committee on Food for the European Union (SCF, 2001) and the joint FAO/WHO Expert Committee on Food Additives (JECFA, 2001) have proposed a Tolerable Weekly Intake of 14 pg WHO TEQ/kg body weight and a provisional Tolerable Monthly Intake of 70 pg WHO-TEQ/ kg body weight, respectively. Most recently, using much of the same toxicity data, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment have recommended a TDI of 2 pg WHO-TEQ/kg body weight/day (CoT, 2001). All of these assessments are based on studies showing that the developing fetus is likely to be at most risk as suggested from experimental data.

In the USA, the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have been using probabilistic models to derive a Risk Specific Dose (RsD) of a compound. This is the lowest dose that could result in a specific risk to man, for example the dose with a lifetime cancer risk of one in one million. The final results are not yet available.

Whereas on average the UK daily intake of PCBs, PCDDs and PCDFs from seafood by adults is still estimated to be below the recommended TDI value for "dioxin-like" compounds, concern on the health hazard posed by seafood centers on two groups in the population. The first group consists of young children and toddlers, particularly those that are on a high dietary intake of seafood, and possibly additionally receiving fish oil medicinal preparations (cod liver oil/halibut liver oil capsules). The estimated *upper bound* daily dietary consumption of dioxin-like compounds from seafood in toddlers, aged 1.5–4.5 years and school children (aged 10–15 years) in average consumers are 6.3–5.5 pg TEQ/kg body weight/day and 2.8 pg TEQ/kg body weight/day, respectively; in high-level consumers it is 10–8.3 pg TEQ/kg body weight/day and 4.7 pg TEQ/kg body weight/day, respectively. The second group in the population likely to ingest higher levels of dioxin-like compounds consists of individuals, who by complying with recommendations (COMA, 1994) for the consumption of fish twice a week of which one should be 'oily', may be exceeding the TDI value for dioxin-like compounds (see Table 7). Oily fish (particularly herring, mackerel and salmon) have higher levels than other fish of dioxin-like compounds. Additionally, in certain parts of the world there are defined population groups whose diets consist wholly or mainly of seafood. In the case of the Inuit Eskimo Indians, whale and seal meat and blubber constitutes a substantial part of their diet. These marine mammals are known to be sometimes relatively rich in dioxin-like compounds. It is not easy to regulate intake of organochlorine chemicals and thus their risk, by recommending alternative lifestyles or diets.

The fact that in many countries the two major sources of organochlorine chemicals contributing to body burdens of these contaminants in humans are mothers' breast milk and oily fish could be viewed as problematic. It is difficult to compare long-term cardiovascular advantages in adults from increased consumption of some polyunsaturated fatty acids (COMA, 1994), with elevation of the body burden of dioxins. Similarly, even though young children being breast fed might be considered to be at greater risk from increased intake of PCBs and dioxins, this must be set against the obvious increased immunological advantages and bonding between an infant and mother. Thus it usually accepted that the advantages of consumption of polyunsaturated fatty acids from oily fish by the average consumer and the benefits of breast feeding outweigh the potential risks from intake of contaminants by these routes (MAFF, 1999; CoT, 2001).

In Japan, Yoshida et al. (2000) have used a probabilistic approach to determine the risk to Japanese subpopulations from dioxin/PCBs toxicity. It was calculated that one-half of the daily intake of dioxins by the general population came from eating fish. For the toxicity endpoints considered, the highest risk from exposure to dioxins was for heavy fish consumers and their infants and fetuses especially for neurobehavioural effects. However, since in the immediate future it was considered to be very difficult to sufficiently lower exposure to dioxin and PCBs from a fish diet, the benefits of breast feeding and of eating fish were anticipated to outweigh the risk from the contaminants, but that this must be examined in more detail.

8. Summary and conclusions

In conclusion, chlorinated pesticides and PCBs proved of immense benefit to society but are now no longer used in most countries. The realization that their poor metabolism and lipophilicity could lead to bioaccumulation up the food chain to the detriment of wildlife and possibly human health has led to a dramatic decline or halt in their production. Coupled to this was

the recognition that highly toxic dioxins and dibenzofurans were inadvertantly formed either in the manufacture of chlorinated products or in their incineration. However, organochlorine chemicals still constitute a major source of persistent chemical contaminants present in the environment including the sea and fish, despite the regulatory ban or control on their continued use and production in most countries. These relatively stable lipophilic compounds, resistant to biodegradation, have been found dispersed throughout the biosphere. Their progression through the food chain into the human diet has been well established. Although these chemicals have a relatively low water solubility, their lipophilicity enables crustaceans such as crabs, mussels, shellfish and other bottom feeders to absorb and concentrate them in their fatty tissues. Thus the organochlorine chemicals eventually pass higher up the marine life food chain to fish and eventually to sea mammals such as seals and whales, some species serving as food for humans. Surveys conducted in a number of countries have shown that the principal source of human exposure to these organochlorine chemicals occurs via the diet (well over 90%). Seafood and meat (including milk) are the major dietary sources of organochlorine contaminants for many people around the world.

Much of the current concern about organochlorines is centred on the dioxins and PCBs, both the dioxin-like and non-coplanar congeners. The toxicology of dioxin-like compounds is largely based on data derived from studies in experimental animals. Much of the limited human data available have been obtained from studies carried out following industrial accidents or at the workplace. As human exposure to these compounds occurs throughout man's lifespan from the diet, it is essential for studies to be directed at elucidating the long-term consequences of chronic exposure at low levels. Data generated from appropriate epidemiological and other studies would clearly be of value for the realistic risk assessment of these compounds to man.

Although the manufacture and use of these compounds is banned or highly restricted, residues of polychlorinated compounds continue to detected in blood and breast milk of humans, particularly in populations whose major source of protein intake is from fish, crustaceans and sea mammals. Despite the fact that these chemicals accumulate in the body, so far there is no clear and unequivocal evidence that, at the levels encountered in the human diet, they constitute a long-term human health hazard for the majority of the population. However, general dietary intake levels in many countries are close to the new the TDIs estimated by the EU, UK and WHO, and there are subpopulations that may be at greater risk. For small children or high consumers of fish the intakes will exceed the advised TDIs and it is some aspects of impairment of cognitive development and the developing immune response that have been of concern. It is important to remember that TDIs have built-in margins of safety as judged from experimental evidence. In the short term there is little that can be done to reduce levels, other than to continue the policies of restriction of use and lowering of release into the environment of organochlorine chemicals. In fact there are clear signs that general levels in food are steadily declining (MAFF, 1997a) and levels in fish consumed probably reflect this although data are less readily available. Meanwhile, more information should be gained on potential effects of these chemicals on humans at low exposure levels, particularly neurodevelopment.

Acknowledgements

We are grateful to Dr. J.R.P. Caloral for encouragement and to Dr. D. Benford and Dr. S. Barlow for their critical comments and suggestions.

References

Ali, I.B., Joiris, C.R., Holsbeek, L., 1997. Polychlorinated biphenyls in Barents and Greenland seas fish. Bulletin of Environmental Contamination and Toxicology 58, 885–892.

Atuma, S.S., Linder, C.E., Wicklund-Glynn, A., Andersson, O., Larsson, L., 1996. Survey of consumption fish from Swedish waters for chlorinated pesticides and polychlorinated biphenyls. Chemosphere 33, 791–799.

Albaigés, J., Farrán, A., Solar, M., Gallifa, A., 1987. Accumulation and distribution of biogenic and pollutant hydrocarbons, PCBs and DDT in tissues of western Mediterranean fishes. Marine Environment Research 22, 1–18.

Anderson, H.A., Falk, C., Hanrahan, L., Olson, J., Burse, V.W., Needham, L., Paschal, D., Patterson, H.R., Hill Jr., R.H., 1998. Profiles of great lakes critical pollutants: a sentinel analysis of human blood and urine. Environmental Health Perspectives 106, 279–289 (and the great lakes consortium).

Anon., 1998. Unfit to eat; the world's pollutants end up in Inuits' food. New Scientist 159 (2153), 13.

Asplund, L., Svensson, B.-G., Nilsson, A., Eriksson, U., Jansson, B., Jensen, S., Wideqvist, U., Skerfving, S., 1994. Polychlorinated biphenyls, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (p,p′-DDT) and 1,1-dichloro-2.2-bis(p-chlorophenyl)-ethylene (p,p′-DDE) in human plasma related to fish consumption. Archives of Environmental Health 49, 477–486.

Becher, G., Rebecka, J.H., Alexander, J., Løvvik, M., Gaarder, P.I., Gdynia, W., 1995. Consumption of crabs and body burden of PCDDs/PCDFs: A study of male crab consumers from a polluted fjord area in Norway. Organohalogen Compounds 26, 39–43.

Beck, H., Dross, A., Mathar, W., 1992. PCDDs, PCDFs and related compounds in the German food supply. Chemosphere 25, 1539–1550.

Bjerk, J.E., Brevik, E.M., 1980. Organochlorine compounds in aquatic environments. Archives of Environmental Contamination and Toxicology 9, 743–750.

Birnbaum, L.S., 1995. Workshop on perinatal exposure to dioxin-like compounds. V. Immunologic effects. Environmental Health Perspectives 103 (Suppl.2), 157–160.

Birmingham, B., Gilman, A., Grant, D., Salminen, J., Boddington, M., Thorpe, B., Wile, I., Toft, P., Armstrong, V., 1989. PCDD/PCDF multimedia exposure analysis for the Canadian population: detailed exposure estimation. Chemosphere 19, 507–512.

Brouwer, A., Van Den Berg, K.J., 1986. Binding of a metabolite of 3,4,3′,4″-tetrachlorobiphenyl to transthyretin reduced vitamin A transport by inhibiting the formation of the protein complex carrying both retinol and thyroxin. Toxicology and Applied Pharmacology 88, 301–312.

Burnett, R., 1971. D.D.T. residues: Distribution of concentrations in *Ementa analoga* (Stimpson) along coastal California. Science 174, 606–608.

Carson, R., 1962. Silent Spring. Houghton-Mifflin Co, Boston.

COMA (Committee on the Medical Aspects of Food Nutrition Policy), 1994. Nutritional Aspects of Cardiovascular Disease. Report of the Cardiovascular Review Group. Health and Social Subjects No. 46. Department of Health, UK.

Cooper, K., 1991. Effects of pesticides in wildlife. In: Hayes, W.J., Lawes, E.R. (Eds.), Handbook of Pesticide Toxicology. Academic Press, San Diego.

CoT, 2001, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls. Available at http://www.foodstandards.gov.uk/committees/cot/cot_dioxin_stat.pdf.

Daston, G.P., Gooch, J.W., Breslin, W.J., Shuey, D.L., Nikiforov, A.I., Fico, T.A., Gorsuch, J.W., 1997. Environmental estrogens and reproductive health: A discussion of the human and environmental data. Reproductive Toxicology 11, 465–481.

De Boer, J, Stronck, C.J.N., Traag, W.A., Van Der Meer, J., 1993. Non-ortho and mono-ortho substituted chlorobiphenyls and chlorinated dibenzo-p-dioxins and dibenzofurans in marine and freshwater fish and shellfish from the Netherlands. Chemosphere 26, 1823–1842.

De Boer, J., Wester, P.G., Klamer, H.J.C., Lewis, W.E., Boon, J.P., 1998. Do flame-retardants threaten ocean life? Nature 394, 28–29.

Devoto, E., Kohlmeier, L, Heeschen, W., 1998. Some dietary predictors of plasma organochlorine concentrations in an elderly German population. Archives of Environmental Health 53, 147–155.

Dewailly, E.A., Nantel, A., Weber, J.-P., Meyer, F., 1989. High levels of PCBs in breast milk of Inuit women from Arctic Quebec. Bulletin of Environmental Contamination. and Toxicology 47, 491–498.

Dewailly, E., Ryan, J.J., Laliberte, C., Bruneau, S., Weber, J.-P., Gingras, S., Carrier, G., 1994. Exposure of remote maritime populations to coplanar PCBs. Environmental Health Perspectives 102 (Suppl.), 205–209.

Duarte-Davidson, R., Jones, K.C., 1994. Polychlorinated biphenyls (PCBs) in the UK population: estimated intake, exposure and body burden. Science of the Total Environment 151, 131–152.

Elijarrat, E., Caiyach, J., Rivera, J., De Torres, M., Cinebrada, A., 2001. Toxic potency assessment of non- and mono—or the PCBs, PCDDs, PCDFs and PAHs in Northwest Mediterranean sediments (Catlonia, Spain). Environmental Science and Technology 35, 3589–3594.

Ernst, W., 1986. Hexachlorobenzene in the marine environment: distribution, fate and ecotoxicological aspects. In: Morris, C.R., Cabral, J.R.P. (Eds.), Hexachlorobenzene: Proceedings of an International Symposium. IARC Scientific Publications no. 77. International Agency for Research on Cancer, Lyon, pp. 211–222.

Falandysz, J., 1994. Polychlorinated biphenyl concentrations in cod-liver oil: evidence of a steady-state condition of these compounds in the Baltic area oils and levels noted in Atlantic oils. Archives of Environmental Contamination and Toxicology 27, 266–271.

Fein, G.G., Jacobson, J.L., Jacobson, S.W., Schwartz, P.M., Dowler, J.K., 1984. Prenatal exposure to polychlorinated biphenyls:effects on birth size and gestational age. Journal of Pediatrics 105, 315–320.

Fujiwara, K., 1975. Environmental and food contaminations with PCBs in Japan. Science of the Total Environment 4, 219–247.

Golden, R.J., Noller, K.L., Ernstoff, L.T., Kaufman, R.H., Mittendorf, R., Stillman, R., Reese, E.A., 1998. Environmental endocrine modulators and human health: an assessment of the biological evidence. Critical Reviews in Toxicology 28, 109–227.

Gosset, R., Wikholm, G., Lyubenkor, J., Steinman, D., 1989. Human serum DDT levels related to consumption of fish from the coastal waters of Los Angeles. Environmental Toxicology and Chemistry 8, 951–955.

Grandjean, P., Weihe, P., Needham, L.L., Burse, V.W., Patterson Jr., D.G., Sampson, E.J., Jorgensen, P.J., Vahter, M., 1995. Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. Environmental Research 71, 29–38.

Grimvall, E., Rylander, L., Nilsson, P., Stromberg, U., Hagmar, L., Ostman, C., 1997. Monitoring of polychlorinated biphenyls in human blood plasma: methodological developments and influence of age, lactation and fish consumption. Archives of Environmental Contamination and Toxicology 32, 329–336.

Guzelian, P.S., 1982. Comparative toxicology of chlordecone (kepone) in humans and experimental animals. Annual Review of Pharmacology and Toxicology 22, 89–113.

Hansen, P.D., 1985. Chlorinated hydrocarbons and hatching success in Baltic herring spring spawners. Marine Environmental Research 25, 59–76.

Hayes, W.J., 1991. Introduction. In: Hayes, W.J., Lawes, E.R. (Eds.), Handbook of Pesticide Toxicology. Academic Press, San Diego, pp. 1–37.

IARC, 1997. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 69. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. International Agency for Research on Cancer, Lyon.

IPCS, 1989. Environmental Health Criteria 88. Polychlorinated Dibenzo-*para*-dioxins and Dibenzofurans. WHO, Geneva.

IPCS, 1993. Environmental Health Criteria 140. Polychlorinated Biphenyls and Terphenyls. WHO, Geneva.

IPCS, 1997. Environmental Health Criteria 195. Hexachlorobenzene. WHO, Geneva.

Jacobson, J.L., Jacobson, S.W., 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. New England Journal of Medicine 335, 783–789.

JECFA (Joint FAO/WHO Expert Committee on Food Additives) 2001 57th meeting, Rome, 5–14 June, 2001. Summary and conclusions. Available at http://www.who.int/pcs/jecfa/Summary57-corr.pdf.

Jensen, S., Johnels, A.G., Olssen, M., Otterlind, G., 1969. DDT and PCB in marine animals from Swedish waters. Nature 224, 247–250.

Jimenez, B., Wright, C., Kelly, M., Startin, J.R., 1996. Levels of PCDDs, PCDFs and non-ortho PCBs in dietary supplement fish oil obtained in Spain. Chemosphere 32, 461–467.

Johansen, H.R., Alexander, J., Rossland, O.J., Planting, S., Lovik, M., Gaarder, P.I., Gdynia, W., Bjerve, K.S., Becher, G., 1996. PCDDs, PCDFs, and PCBs in human blood in relation to consumption of crabs from a contaminated fjord area in Norway. Environmental Health Perspectives 104, 756–764.

Kannan, K., Tanabe, S., Williams, R.J., Tatsukawa, R., 1994. Persistant organochlorine residues in foodstufffs from Australia, Papua New Guinea and the Solomon Islands: contamination levels and human dietary exposure. Science of the Total Environment 153, 29–49.

Kelce, W.R., Christy, R.S., Laws, S.C., Gray, L.E., Kemppaven, J.A., Wilson, E.M., 1995. Persistent DDT metabolite p,p-DDE is a potent androgen receptor antagonist. Nature 375, 581–585.

Kelly, A.G., Campbell, A., 1999. Organochlorine contaminants in liver of cod (*Gadus morhua*) and muscle of herring (*Clupea harengus*) from Scottish waters. Marine Pollution Bulletin 28, 103–108.

Key, T., Reeves, G., 1994. Organochlorines in the environment and breast cancer. The data so far produced provide reassurance rather than anxiety. British Medical Journal 308, 1520–1521.

Kuhnlein, H.V., Receveur, O., Muir, D.C.G., Chan, H.M., Soueida, X., 1995. Arctic indigenous women consume greater than acceptable levels of organochlorines. Journal of Nutrition 125, 2501–2510.

Kuwabara, K., Yakushiji, T., Watanabe, I., Yoshida, S., Yoyama, K., Kunita, N., 1979. Increase in the human blood PCB levels promptly following ingestion of fish containing PCBs. Bulletin of Environmental Contamination Toxicology 21, 273–278.

Lohse, J., 1991. Distribution of organochlorine pollutants in North Sea sediments. Water Science Technology 24, 107–111.

MAFF/HSE (Ministry of Agriculture, Fisheries and Food/Health and Safety Executive), 1994. Report of the Working Party on Pesticide Residues, 1993—Supplement to the Pesticides Register. HMSO, London.

MAFF, 1997a. Dioxins and Polychlorinated Biphenyls in Foods and Human Milk. Food Surveillance Sheet, No. 105. Ministry of Agriculture, Fisheries and Food, UK.

MAFF, 1997b. Dioxins and Polychlorinated Biphenyls in Fish Oil Dietary Supplements and Licensed Medicines. Food Surveillance Sheets, No. 106. Ministry of Agriculture, Fisheries and Food, UK.

MAFF, 1999. Dioxins and PCBs in UK and Imported Marine Fish. Food Surveillance Information Sheet, No. 184. Ministry of Agriculture, Fisheries and Food, UK.

Marien, K., Laflamme, D.M., 1995. Determination of a tolerable daily intake of DDT for consumers of DDT contaminated fish from the lower Yakima river, Washington. Risk Analysis 15, 709–717.

McDowell Capuzzo, J., Farrington, J.W., Rantamki, P., Hovey Clifford, C., Lacaster, B.A., Leavitt, D.F., Jia, X., 1989. The relationship between lipid composition and seasonal difference in the distribution of PCBs in *Mytilus edulis* L. Mar. Environmental Research 28, 259–264.

Mes, J., Newsome, W.H., Conacher, H.B.S., 1991. Levels of specific polychlorinated biphenyl congeners in fatty foods from five Canadian cities between 1986 and 1988. Food Additives and Contaminants 8, 351–361.

Mussalo-Rauhamaa, H., Pyysalo, H., Moilanen, R., 1984. Influence of diet and other factors on the levels of organochlorine compounds in human adipose tissue in Finland. Journal of Toxicology and Environmental Health 13, 689–704.

Oehm, M., Mano, S., Brevik, E.M., Knutzen, D.J., 1989. Determination of polychlorinated dibenzofuran (PCDF) and dibenzo-p-dioxin (PCDD) levels and isomers in fish, crustaceans, mussels and sediment samples from a fjord region polluted by Mg-production. Fres. Zeitschrift fur Analytische Chemie 335, 987–997.

Ostfeldt, P., Gustavson, K., Jansson, B., Honsson, P., Miettinen, V., Ringstad, O., Wesen, D.C., 1994. Halogenated organic compounds in the marine environment. TemaNord 124, 591.

Pastor, D., Boix, J., Fernandez, V., Albaiges, J., 1996. Bioaccumulation of organo chlorinated contaminants in three estuarine fish species (*Mullus babatus, Mugil chephalus* and *Dicentrarcus labrax*). Marine Pollution Bulletin 32, 257–262.

Patandin, S., Lanting, C.I., Mulder, P.G.H., Boersma, E.R., Sauer, P-J.J., Weisglas-Kuperus, N., 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. Journal of Pediatrics 134, 33–41.

Pohjanvirta, R., Tuomisto, J., 1994. Short term toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals: effects, mechanisms, and animals models. Pharmacological Reviews 46, 483–549.

Porte, C., Albaigés, J., 1993. Bioaccumulation patterns of hydrocarbons and polychlorinated biphenyls in bivalves, crustaceans, and fishes. Archives of Environmental Contamination and Toxicology 26, 273–281.

Risebrough Rieche, R.W.P., Peakall, D.B., Herman, S.G., Kirven, M.N., 1968. Polychlorinated biphenyls in the global ecosystem. Nature 220, 1098–1102.

Risebrough, R.W., Walker, W., Schmidt, T.T., De Lappe, B.W., Connors, C.W., 1976a. Transfer of chlorinated biphenyls to Antartica. Nature 264, 738–739.

Risebrough, R.W., De Lappe, B.W., Schmidt, T.T., 1976b. Bioaccumulation factors of chlorinated hydrocarbons between mussels and seawater. Marine Pollution Bulletin 7, 225–228.

Rylander, L.L., Hagmar, L.L., 1995. Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochlorine compounds. Scandinavian Journal of Work Environment and Health 21, 419–426.

Rylander, L., Stromberg, U., Hagmar, L., 1996. Dietary intake of fish contaminated with persistent organochlorine compounds in relation to low birthweight. Scandinavian Journal of Work Environment and Health 22, 260–266.

Salama, A.A., Mohamed, M.A.M., Duval, B., Potter, T.L., Levin, R.E., 1998. Polychlorinated biphenyl concentation in raw and cooked North Atlantic bluefish (*Pomatomus saltatrix*) fillets. Journal of Agricultural and Food Chemistry 46, 1359–1362.

SCF, 2001, Opinion of the Scientific Committee on Food on the Risk assessment of dioxins and dioxin-like PCBs in food.30/5/2001. Available at http://europa.eu.int/comm/food/fs/sc/scf/out90_en.pdf.

Schade, G., Heinzow, B., 1998. Organochlorine pesticides and polychlorinated biphenyls in human milk of mothers living in Northern Germany:current extent of contamination, time trend from 1986 to1997 and factors that influence the levels of contamination. Science of the Total Environment 215, 31–39.

Schaum, J., Cleverly, D., Lorber, M., Philips, L., Schweer, G., 1994. Updated analysis of U.S. sources of dioxin-like compounds and background exposure levels. Organohalogen Compounds 20, 237–243.

Sladen, W.J.L., Menzie, C.M., Reichel, W.L., 1966. DDT residues in Adelie penguins and crab eater seal from Antarctica. Nature 210, 670–673.

Smith, A.G., 1991. Chlorinated hydrocarbon insecticides. In: Hayes, W.J., Lawes, E.R. (Eds.), Handbook of Pesticide Toxicology. Academic Press, San Diego.

Smith, A.G., 2000. How toxic is DDT. Lancet 356, 267–268.

Smith, A.G., Dinsdale, D., Cabral, J.R.P., Wright, A.L., 1987. Goitre and wasting induced in hamsters by hexachlorobenzene. Archives of Toxicology 60, 343–349.

Strandberg, B., Strandberg, L., Van Bavel, B., Bergqvist, P.A., Broman, D., Falanysz, J., Naf, C., Papakosta, O., Rolff, C., Rappe, C., 1998. Concentrations and spatial variations of cyclodienes and other organochlorines in herring and perch from the Baltic Sea. Science of the Total Environment 215, 69–83.

Stout, V.F., 1980. Organochlorine residues in fishes from the Northwest Atlantic Ocean and Gulf of Mexico. Fishery Bulletin 78, 51–57.

Stringer, R., Jacobs, L.M.N., Johnston, P.A., Wyatt, C.L., Santillo, D., 1996. Organochlorine residues in fish oil dietary supplements. Organohalogen Compounds 28, 551–556.

Svensson, B.-G., Nilsson, A., Hansson, M., Rappe, C., Akesson, B., 1991. Exposure to dioxins and dibenzofurans through the consumption of fish. New England Journal of Medicine 324, 8–12.

Svensson, B.-G., Nilsson, A., Jonsson, E., Schütz, A., Akesson, B., Hagmar, L., 1995. Fish consumption and exposure to persistent organochlorine compounds, mercury selenium and methylamines among Swedish fisherman. Scandinavian Journal of Work Environment and Health 2, 96–105.

Tanabe, S., Tasukawa, R., 1987. Mussels as bioindicators of PCB pollution: A case study on uptake and release of PCB isomers and congeners in green-lipped mussels (*Perna viridis*) in Hong Kong waters. Environmental Pollution 47, 41–62.

Theelen, R.M.C., 1991. Modelling of human exposure to TCDD and I-TEQ in the Netherlands: background and occupational. In: Gallo, M.A., Scheuplein, R.J., van der Heijden, K.A. (Eds.), Banbury Report 35., Biological Basis for Risk Assessment of Doxins and Related Compounds. Cold Spring Harbor Laboratory Press, New York, pp. 277–290.

Trotter, W.J., Corneliussen, P.E., 1989. Levels of polychlorinated biphenyls and pesticides in bluefish before and after cooking. Journal of the Association of Official Analytical Chemists 72, 501–503.

Tryphonas, H., 1998. The impact of PCBS and dioxins on children's health: immunological considerations. Canadian Journal of Public Health 89, S49–S52.

Tsutsumi, T., Yanagi, T., Nakamura, M., Konon, Y., Uchibe, H., Iida, T., Huri, T., Nakagawa, R., Tubiishi, K., Matsuda, R., Sasaki, K., Toyoda, M., 2001. Update of daily intake of PCDDs, PCDFs, and dioxin-like PCBVs from food in Japan. Chemosphere 45, 1129–1137.

Van Den Berg, R., Peterson, R.E., Schrenk, D., 2000. Human risk assessment and TEFs. Food Additives and Contaminants 17, 347–358.

Van Leeuwen, F.X.R., Younes, M.M., 2000. Assessment of the health risk of dioxins: re-evaluation of the tolerable daily intake (TDI) Papers presented at meeting organized by WHO-ECEH and IPCS, Geneva, Switzerland, May 1998. Food Additives and Contaminants 17, 223–369.

Vassilopoulou, V., Georgakopoulos-Gregoriades, E., 1993. Factors influencing the uptake of PCBs and DDTs in red mullet (*Mullus barbatus*) from Pagassitikos Gulf, Central Greece. Marine Pollution Bulletin 26, 285–287.

Voss, J.G., De Heer, C., Van Loveren, H., 1997/1998. Immunotoxic effects of TCDD and toxic equivalency factors. Teratogenesis, Carcinogenesis, and Mutagenesis 17, 275–284.

Weihe, P., Grandjean, P., Debes, F., White, R., 1996. Health implications for Faroe islanders of heavy metals and PCBs from pilot whales. Science of the Total Environment 186, 141–148.

Weisglas-Kuperus, N., Patandin, S., Berbers, G.A., Sas, T.C., Mulder, P.G., Sauer, P.J., Hooijkass, H., 2000. Immunlogic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Environmental Health Perspectives 108, 1203–1207.

West, T.F., Campbell, G.A., 1946. DDT, The Synthetic Insecticide. Chapman and Hall, London.

Westoo, G., Noren, K., 1978. Organochlorine contaminants in human milk. Stockholm 1967–1977. Ambio 7, 62–64.

WHO/EURO, 1991. Consultation on tolerable daily intake from food of PCDDs and PCDFs: Summary report. Bilthoven, The Netherlands, 4–7 December 1990. EUR/IPC/PCS 030(5). World Health Organization, Regional Office for Europe, Copenhagen.

Yamagishi, T., Miyazaki, T., Akiyama, K., Kaneko, S., Horii, S., 1981. Residues of chlordane in fish and shellfish from Kanto area and its vicinity. Journal of the Food Hygienic Society of Japan 22, 270–278.

Yoshida, K., Ikeda, S., Nakanishi, J., 2000. Assessment of human health risks of dioxins in Japan. Chemosphere 40, 177–185.

Young, D.R., Mcdermott, D.J., Heesen, T.C., 1976. DDT in sediments and organisms around southern California outfalls. Journal of Water Pollution and Toxicology Federation 48, 1919–1928.

Zabik, M.E., Harte, J.B., Zabik, M.J., Dickmann, G., 1992. Effect of preparation and cooking on contaminants distribution in crustaceans: PCBs in blue crab. Journal of Agricultural and Food Chemistry 40, 1197–1203.

Zabik, M.E., Booren, Al., Zabik, M.J., Welch, R., Humphrey, H., 1996. Pesticide residues, PCBs and PAHs in baked, charbroiled, salt boiled and smoked Great Lakes lake trout. Food Chemistry 55, 231–239.