POLYCHLORINATED DIBENZOFURANS

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature and molecular formulae and weights*

Chemical Abstracts Service (CAS) names and synonyms, CAS Registry numbers, molecular formulae and molecular weights for selected polychlorinated dibenzofurans (PCDFs) are presented in **Table 1**. The tetra-, penta-, hexa- and hepta-chlorinated compounds are referred to here as TCDFs, PeCDFs, HxCDFs and HpCDFs, or collectively as, for example, Cl_4–Cl_7 PCDFs or hepta/octa-CDFs.

Table 1. Nomenclature, molecular formulae and molecular weights of selected polychlorinated dibenzofurans

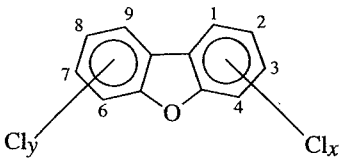
CAS Registry No.	CAS name and synonyms[a]	Molecular formula	Molecular weight
51207-31-9	**2,3,7,8-Tetrachlorodibenzofuran**; F83; TCDF; 2,3,7,8-TCDF; 2,3,7,8-tetra-CDF	$C_{12}H_4Cl_4O$	305.98
57117-41-6	**1,2,3,7,8-Pentachlorodibenzofuran**; F94; 1,2,3,7,8-PeCDF; 1,2,3,7,8-penta-CDF	$C_{12}H_3Cl_5O$	340.42
57117-31-4	**2,3,4,7,8-Pentachlorodibenzofuran**; F114; 2,3,4,7,8-PeCDF; 2,3,4,7,8-PnCDF; 2,3,4,7,8-penta-CDF	$C_{12}H_3Cl_5O$	340.42
70648-26-9	**1,2,3,4,7,8-Hexachlorodibenzofuran**; F118; 1,2,3,4,7,8-HxCDF; 1,2,3,4,7,8-hexa-CDF	$C_{12}H_2Cl_6O$	374.87
57117-44-9	**1,2,3,6,7,8-Hexachlorodibenzofuran**; F121; 1,2,3,6,7,8-HxCDF; 2,3,4,7,8,9-hexachlorodibenzofuran; 1,2,3,6,7,8-hexa-CDF	$C_{12}H_2Cl_6O$	374.87
72918-21-9	**1,2,3,7,8,9-Hexachlorodibenzofuran**; F124; 1,2,3,7,8,9-HxCDF; 1,2,3,7,8,9-hexa-CDF	$C_{12}H_2Cl_6O$	374.87
60851-34-5	**2,3,4,6,7,8-Hexachlorodibenzofuran**; F130; 2,3,4,6,7,8-HxCDF; 2,3,4,6,7,8-hexa-CDF	$C_{12}H_2Cl_6O$	374.87
67562-39-4	**1,2,3,4,6,7,8-Heptachlorodibenzofuran**; F131; 1,2,3,4,6,7,8-HpCDF; 1,2,3,4,6,7,8-hepta-CDF	$C_{12}HCl_7O$	409.31
55673-89-7	**1,2,3,4,7,8,9-Heptachlorodibenzofuran**; F134; 1,2,3,4,7,8,9-HpCDF; 1,2,3,4,7,8,9-hepta-CDF	$C_{12}HCl_7O$	409.31
39001-02-0	**Octachlorodibenzofuran**; F135; OCDF; octa-CDF; perchlorodibenzofuran	$C_{12}Cl_8O$	444.76

[a] Names in bold letters are the Chemical Abstracts Service (CAS) names

1.1.2 *Structural formulae*

The general structure of the PCDFs is shown in **Table 2**. Any or all of the eight hydrogen atoms on dibenzofuran can be replaced with chlorine, giving rise to 135 possible chlorinated dibenzofuran structures. All of the 135 are referred to as congeners (members of a like group) of one another, and congeners having the same number of chlorines are isomers (Clement, 1991).

Table 2. Dibenzofuran structural formula and numbers of chlorinated isomers

Formula	
	
No. of chlorines ($x + y$)	No. of isomers
1	4
2	16
3	28
4	38
5	28
6	16
7	4
8	1
Total	135

1.1.3 *Chemical and physical properties*

Knowledge of basic chemical and physical properties is essential to understanding and modelling environmental transport and fate as well as pharmacokinetic and toxicological behaviour. The most important parameters for the PCDFs appear to be water solubility, vapour pressure, and octanol/water partition coefficient (K_{ow}). The ratio of vapour pressure to water solubility yields the Henry's Law constant for dilute solutions of organic compounds, an index of partitioning for a compound between the vapour and aqueous solution phases (Mackay *et al.*, 1991). Chemical and physical properties of selected PCDFs are presented in **Table 3**.

Limited research has been carried out to determine physical and chemical properties of PCDFs. As with the polychlorinated dibenzo-*para*-dioxins (PCDDs), the tetra- to octachloro congeners with 2,3,7,8-chlorination have received the most attention. Of the large number of possible congeners, only the 2,3,7,8-chlorinated compounds and a few others are available commercially, and preparation and synthesis can be both time-consuming

and difficult. Some of the PCDF congeners have not yet been prepared in pure form. Like the PCDDs, the PCDFs are intentionally prepared only for research purposes.

Table 3. Chemical and physical properties of selected PCDFs[a]

Chemical	Melting point (°C)	Water solubility (mg/L)	Vapour pressure (Pa) at 25 °C	Henry's Law constant (Pa × m^3/mol)[b]	log K_{ow}
2,3,7,8-TCDF	227–228	4.19×10^{-4} at 22.7 °C	2×10^{-6}	1.5	6.53
1,2,3,7,8-PeCDF	225–227		2.3×10^{-7}		6.79
2,3,4,7,8-PeCDF	196–196.5	2.36×10^{-4} at 22.7 °C	3.5×10^{-7}	[0.5]	6.92
1,2,3,4,7,8-HxCDF	225.5–226.5	8.25×10^{-6} at 22.7 °C	3.2×10^{-8}	[1.43]	
1,2,3,6,7,8-HxCDF	232–234	1.77×10^{-5} at 22.7 °C	2.9×10^{-8}	[0.6]	
1,2,3,7,8,9-HxCDF	246–249		2.4×10^{-8}		
2,3,4,6,7,8-HxCDF	239–240		2.6×10^{-8}		
1,2,3,4,6,7,8-HpCDF	236–237	1.35×10^{-6} at 22.7 °C	4.7×10^{-9}	[1.4]	7.92
1,2,3,4,7,8,9-HpCDF	221–223		6.2×10^{-9}		
OCDF	258–260	1.16×10^{-6} at 25 °C	5×10^{-10}	[0.2]	8.78

[a] From Burkhard & Kuehl (1986); Rordorf (1989); Sijm *et al.* (1989); Friesen *et al.* (1990); Mackay *et al.* (1991)

[b] Values in brackets have been calculated by the Working Group.

The concept of toxic equivalency factors (TEFs) was developed by several agencies and national and international organizations (Ahlborg, 1989; Safe, 1990; Ahlborg *et al.*, 1992; Birnbaum & De Vito, 1995) to aid in the interpretation of the complex database and in the evaluation of the risk of exposure to mixtures of structurally related PCDDs and PCDFs. TEF values are derived by evaluating the potency of each PCDD and PCDF isomer relative to that of tetrachlorodibenzo-*para*-dioxin (2,3,7,8-TCDD). TEFs are order-of-magnitude estimates that are based on the evaluation of all available information, including binding to the Ah receptor (see Section 4) and other in-vitro responses as well as in-vivo effects ranging from enzyme induction to tumour formation (Ahlborg *et al.*, 1992; Birnbaum & De Vito, 1995).

The levels of all the individual PCDDs and PCDFs in a mixture may be converted into one value of toxic equivalents (TEQs), as follows:

$$\text{TEQ} = \Sigma \text{ (TEF} \times \text{concentration)}$$

Assignment of relative potencies in a quantitative sense imposes appreciable demands on the experimental data. All congeners must exhibit parallel dose–response curves for the effects studied to be treated as additive. Additivity is an implicit assumption of the TEF concept. Many in-vitro and in-vivo studies have supported the hypothesis that the toxic effects of combinations of PCDDs and PCDFs are additive and have supported the applicability of the TEF concept in practice (Ahlborg *et al.*, 1992a).

Toxicologists have widely adopted the set of TEFs shown in **Table 4** (I-TEFs, also adopted by NATO (North Atlantic Treaty Organization)). Other sets of TEFs have been used in the past (e.g. BGA (German), Nordic, Swiss, Eadon (american)), but TEQs

calculated with these TEFs normally do not differ from those based on I-TEFs by more than a factor of 2 (Ahlborg *et al.*, 1988; Rappe *et al.*, 1993).

Table 4. I-TEFs for 2,3,7,8-substituted PCDFs[a]

Congener	I-TEF
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-HpCDF	0.01
OCDF	0.001
All other PCDFs	0

[a]From Ahlborg *et al.* (1992a); Rappe *et al.* (1993)
I-TEF, international toxic equivalency factor

1.1.4 *Methods of analysis*

Analysis for PCDFs in the environmental and biological matrices uses essentially the same methods as those developed for PCDDs. In fact, analyses for PCDFs and PCDDs are very frequently performed concurrently. Thus, methods of analysis for both classes of compounds are discussed in the monograph on PCDDs, and the designations A-W used here are those given in Table 5 of the PCDD monograph on page 39.

1.2 Formation and destruction

PCDFs can be formed by a number of different reactions including synthetic chemical, thermal, photochemical and biochemical; analogous pathways can be used for their destruction. PCDFs already present in reservoir sources such as sediments, soil and sewage sludge are significant contributors to current environmental levels.

1.2.1 *Formation of PCDFs*

(*a*) *Chemical reactions*

(i) *Polychlorinated biphenyls (PCBs)*

Mixtures of PCBs (see IARC, 1987d) have been widely used since the 1930s as dielectric fluids in electrical equipment such as cables, transformers and capacitors. They have also been used as non-flammable heat-exchange liquids and as additives to plastics and in cutting oil. The total world production is estimated to exceed 500 000 tonnes

(Rappe *et al.*, 1979a). Primarily due to environmental problems, use of PCBs has now been phased out in most European countries and in many others.

Vos *et al.* (1970) identified PCDFs (tetra- and penta-CDFs) in samples of European PCBs (Phenoclor DP-6 and Clophen A60) but not in a sample of American Aroclor 1260. The toxic effects of these PCBs were found to parallel the levels of PCDFs present. Bowes *et al.* (1975) examined a series of Aroclors as well as the same samples of Aroclor 1260, Phenoclor DP-6 and Clophen A60 previously analysed by Vos *et al.* (1970). They used packed column gas chromatography (GC) with low-resolution mass spectrometry and very few standard compounds and reported that the most abundant PCDFs were PeCDFs (**Table 5**). Using a complete set of PCDF standards and high-resolution GC, Rappe *et al.* (1985a) determined the levels of 2,3,7,8-substituted PCDFs in commercial PCB products (see **Table 6**).

Table 5. Concentrations of PCDFs in PCBs (mg/kg)

PCB[a]	TCDFs	PeCDFs	HxCDFs	Total
Aroclor 1248 (1969)	0.5	1.2	0.3	2.0
Aroclor 1254 (1969)	0.1	0.2	1.4	1.7
Aroclor 1254 (1970)	0.2	0.4	0.9	1.5
Aroclor 1260 (1969)	0.1	0.4	0.5	1.0
Aroclor 1260 (lot AK3)	0.2	0.3	0.3	0.8
Aroclor 1016 (1972)	ND	ND	ND	
Clophen A 60	1.4	5.0	2.2	8.4
Phenoclor DP-6	0.7	10.0	2.9	13.6

From Bowes *et al.* (1975)
ND, not detected at 0.001 mg/kg
[a] Production year in parentheses

(ii) *Chlorophenols*

Chlorophenols (see IARC, 1986b; 1987c) have been used extensively since the 1950s as insecticides, fungicides, mould inhibitors, antiseptics and disinfectants. In 1978, the annual world production was estimated to be approximately 150 000 tonnes (Rappe *et al.*, 1979a). Due to occupational and environmental risks, the use of chlorophenols has now been phased out in most European countries and in a few countries outside Europe. The most important use of 2,4,6-tri-, 2,3,4,6-tetra- and pentachlorophenol (PCP) and their salts is for wood preservation. PCP is also used as a fungicide for slime control in the manufacture of paper pulp and for a variety of other purposes such as in cutting oils and fluids, for tanning leather and in paint, glues and outdoor textiles. **Table 7** summarizes a number of relevant analyses of the levels of PCDFs in commercial chlorophenol formulations (Rappe *et al.*, 1978b).

Buser and Bosshardt (1976) reported the results of a survey of the PCDF and PCDD content of PCP and its sodium salt from commercial sources in Switzerland (analytical method AC). On the basis of the results, the samples could be divided into two groups:

Table 6. Concentrations of PCDFs in commercial PCBs (μg/kg)

PCB type	Tri-CDF	TCDFs		PeCDFs			HxCDFs					HpCDFs
	Total	2378-	Total	12348-/ 12378-	23478-	Total	123479-/ 123478	123678-	123789-	234678-	Total	Total
Pyralene	700	53	630	10	T	35	ND	ND	ND	ND	ND	ND
Aroclor 1254	63	19	1 400	690	490	4 000	2 500	2 100	190	130	10 000	960
Aroclor 1260	10	13	110	48	56	260	500	120	190	27	1 500	1 300
Aroclor 30	500	35	573	14	28	160	50	59	ND	ND	220	T
Aroclor 40	1 300	180	2 600	96	8	1 700	79	68	ND	T	310	ND
Aroclor 50	7 400	3 300	20 000	760	1 100	8 000	700	360	18	98	3 100	75
Clophen A60	770	840	6 900	1 100	990	8 100	1 600	330	170	330	6 800	2 000
Clophen T64	47	23	360	97	122	840	520	390	58	41	2 600	220
Clophen	710	54	1 200	34	30	270	ND	T	ND	ND	T	ND

T, traces; ND, not detected
From Rappe *et al.* (1985a)

a first series with generally low levels (HxCDD, < 1 mg/kg) and a second series with much higher levels (HxCDD, > 1 mg/kg) of PCDDs. Samples with high PCDD levels also had high levels of PCDFs. The ranges of the combined levels of PCDFs were 1–26 mg/kg for the first series of samples and 85–570 mg/kg for the second series of samples. The levels of OCDF were as high as 300 mg/kg and this congener dominated the PCDF content of the samples.

Table 7. Levels of PCDFs in commercial chlorophenols (mg/kg)

	2,4,6-Tri-chlorophenol	2,3,4,6-Tetra-chlorophenol	Pentachlorophenol	
			Sample A	Sample B
TCDFs	1.5	0.5	0.9	≤ 0.4
PeCDFs	17.5	10	4	40
HxCDFs	36	70	32	90
HpCDFs	4.8	70	120	400
OCDF	< 1	10	130	260

From Rappe *et al.* (1978b); Rappe & Buser (1981)

(iii) *Pulp bleaching*

During the 1950s, free chlorine gas was introduced for the bleaching of pulp in pulp and paper mills. In 1986–87, it was first reported that bleaching pulp using free chlorine gas produced 2,3,7,8-TCDF (Rappe *et al.*, 1987a). A survey performed in 1987 in the United States showed that the concentrations of 2,3,7,8-TCDF in bleached pulp ranged from undetectable (at a detection limit of 1.2 ng/kg) up to 330 ng/kg, with a median concentration of 50 ng/kg and a mean of 93 ng/kg (Gillespie & Gellman, 1989).

New technology has been developed for pulp bleaching using chlorine dioxide (ECF, elemental chlorine free) or non-chlorinated reagents (TCF, total chlorine free). 2,3,7,8-TCDF at a level of about 0.2 ng/kg was found in ECF- and TCF-bleached pulp (Rappe & Wågman, 1995).

(iv) *Production of chlorine*

Chlorine is produced primarily by the electrolysis of brine. The annual world production in 1995 was estimated to be 40 million tonnes (Fauvarque, 1996). Rappe *et al.* (1991) reported that residues from the production of chlorine using the chloralkali process were highly contaminated with PCDFs. The problem is particularly associated with the use of graphite electrodes in the process. The graphite electrode process was for a long time the dominant technology and is still very widespread. Chlorine butter, a by-product from this process, was already identified as a chloracnegen 100 years ago. Only a few samples from chloralkali plants have been analysed, primarily from landfills. Total PCDF concentrations of 0.6–0.7 mg/kg have been found. The pattern of PCDFs is dominated by the 2,3,7,8-substituted tetra- to hepta-CDFs, resulting in a nordic TEQ value of 10–30 µg/kg (see **Table 8**).

Table 8. Levels of PCDFs (ng/kg) in three samples of electrode sludge from chloralkali plants

	Sample 1	Sample 2	Sample 3
2,3,7,8-TCDF	26 000	56 000	57 000
Total TCDFs	64 000	150 000	140 000
1,2,3,4,8-/1,2,3,7,8-PeCDF	25 000	55 000	56 000
2,3,7,8-PeCDF	12 000	25 000	24 000
Total PeCDFs	75 000	240 000	240 000
1,2,3,4,7,9-/1,2,3,7,8-HxCDF	32 000	71 000	73 000
1,2,3,6,7,8-HxCDF	7 000	16 000	15 000
Total HxCDFs	68 000	140 000	140 000
1,2,3,4,6,7,8-HpCDF	9 100	19 000	19 000
1,2,3,4,7,8,9-HpCDF	8 100	19 000	20 000
Total HpCDFs	24 000	53 000	54 000
OCDF	31 000	76 000	71 000
TEQ (nordic)	13 000	28 000	28 000

From Rappe *et al.* (1991)

(v) *Production of vinyl chloride*

Stringer *et al.* (1995) reported the analyses of three samples of residues from the production of vinyl chloride (see IARC, 1987e), an intermediate in the production of polyvinyl chloride (PVC) (analytical method ACS). In all samples, the concentrations of PCDFs were much higher than those of PCDDs and the higher chlorinated 2,3,7,8-substituted congeners constituted a substantial proportion (see **Table 9**).

(b) Thermal reactions

(i) *Incineration of municipal waste*

Olie *et al.* (1977) reported the occurrence of PCDDs and PCDFs in fly ash from three municipal incinerators in the Netherlands. Their results indicated only the presence of PCDFs, without isomer identification or quantification. Buser *et al.* (1978a) quantified PCDDs and PCDFs in fly ash from a municipal incinerator and an industrial heating facility in Switzerland. In the former, the level of total PCDFs was 0.1 mg/kg. In the industrial incinerator fly ash, the level was 0.3 mg/kg.

In 1986, a working group of experts convened by the World Health Organization Regional Office for Europe (WHO/EURO, 1987) reviewed the available data on emissions of PCDDs from municipal solid-waste incinerators. They concluded that, because of their high thermal stability, PCDFs were destroyed only after adequate residence times (> 2 s) at temperatures above 800 °C. Total emissions of PCDFs from tests on municipal solid-waste incinerators were reported to range between a few and several thousand ng/m^3 dry gas at 10% carbon dioxide. The WHO working group prepared a table giving a range of estimated isomer-specific emissions for those isomers of major concern with respect to municipal solid-waste incinerators operating under various conditions (**Table 10**).

Table 9. Concentrations of PCDFs in still bottoms and residues from vinyl chloride production (μg/kg)

	Sample 1[a]	Sample 2[b]	Sample 3[c]
2,3,7,8-TCDF	0.91	680	0.44
Total TCDF	15	20 600	6
1,2,3,7,8-PeCDF	9.5	975	1.8
2,3,4,7,8-PeCDF	1.6	1 050	0.58
Total PeCDFs	65	45 300	11
1,2,3,4,7,8-HxCDF	110	10 100	11
1,2,3,6,7,8-HxCDF	24	9 760	2.4
1,2,3,7,8,9-HxCDF	9.5	21 800	1.3
2,3,4,6,7,8-HxCDF	3.1	930	0.89
Total HxCDFs	300	63 700	27
1,2,3,4,6,7,8-HpCDF	250	13 400	38
1,2,3,4,7,8,9-HpCDF	51	1 340	6
Total HpDFs	450	16 600	58
OCDF	390	43 500	650
I-TEQ	20	6 370	3.9

From Stringer *et al.* (1995)

[a] Sample 1 is a process waste including, but not limited to, distillation residues, heavy ends, tars and reactor clean-out wastes, from the production of certain chlorinated aliphatic hydrocarbons by free radical catalysed processes.

[b] Sample 2 is a waste from heavy ends from the distillation of ethylene in ethylene dichloride production.

[c] Sample 3 is a waste from heavy ends from the distillation of vinyl chloride in vinyl chloride monomer production.

The emissions tabulated in column 1 are those which the working group considered to be achievable in modern, highly controlled and carefully operated plants in use in 1986. The results given in column 1 are not representative of emissions that might be expected from such plants during start-up or during occasional abnormal conditions. Emission levels listed in column 2 were considered by the working group to be indicative of the upper limit of emissions from modern municipal solid-waste incinerators. These plants might experience such emissions during start-up or during occasional abnormal conditions, although some of the data reviewed have shown that the figures in column 2 should not be considered to be an absolute maximum. However, most plants existing in 1986, if carefully operated, will have had PCDF emissions in the range between columns 1 and 2. The highest values for municipal solid-waste incinerators (column 3) were obtained by multiplying the values in column 2 by a factor of 5. Emission data that were reported to the working group from all tests and under all circumstances were no greater than these values. Generally, these emission levels are associated with irregular or unstable operating conditions, high moisture content of the municipal solid waste or low combustion or afterburner temperatures. Of special importance is the observation that the major contributor to the TEQ was 2,3,4,7,8-PeCDF.

Table 10. Estimated range of emissions of PCDFs from municipal solid-waste (MSW) and municipal sewage sludge (MSS) incinerators

	Emissions from MSW combustion (ng/m^3)				Emissions from MSS combustion (ng/m^3)
	Achievable with modern plants with no gas cleaning	Maximum from average operation	High emissions[a]	Achievable with modern plants with gas cleaning[b]	Most probably highest emissions
	(1)	(2)	(3)	(4)	(5)
2,3,7,8-TCDF	0.9	10	50	0.1	0.9
1,2,3,7,8-/1,2,3,4,8-PeCDF	2.3	52	260	0.2	2.3
2,3,4,7,8-PeCDF	2.0	40	200	0.2	2.0
1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF	1.1	48	240	0.1	1.1
1,2,3,6,7,8-HxCDF	1.3	40	200	0.1	1.3
1,2,3,7,8,9-HxCDF	0.06	52	260	–	0.06
2,3,4,6,7,8-HxCDF	2.0	36	180	0.2	2.0

From WHO/EURO (1987) excepted when noted

[a] Values obtained by multiplying values in column 2 by a factor of 5

[b] Adapted from ECETOC (1992)

During the second half of the 1980s and 1990, regulatory agencies in several countries, such as Germany, the Netherlands and Sweden, announced strict regulations for municipal solid-waste incinerators. The European Union value is 0.1 ng TEQ/m^3 (European Union, 1994) (see column 4, **Table 10**). This directive has resulted in the introduction of modern air pollution control devices and, together with improved burning conditions, has led to a decrease in PCDF emissions from municipal solid-waste incinerators, which had been considered to be major sources.

(ii) *Incineration of sewage sludge*

Sludge from municipal waste-water treatment plants may be incinerated after being dehydrated. The WHO working group in 1986 reviewed the available data from municipal sewage sludge incinerators and found that PCDD and PCDF emissions from this type of plant were generally lower than emissions from municipal solid-waste incinerators (see Table 10, column 5) (WHO/EURO, 1987).

(iii) *Incineration of hospital waste*

Doyle *et al.* (1985) claimed that the incomplete combustion of certain hospital wastes containing halogenated compounds could produce high emissions of PCDFs. They found the mean levels of total PCDFs to be 156 ng/m^3, but no isomer-specific data were available. Data cited by the United States Environmental Protection Agency indicate that flue gas emissions from hospital waste incinerators are in the range of 10–100 ng I-TEQ/m^3, higher than the levels achievable with modern municipal solid-waste incinerators (United States Environmental Protection Agency, 1994; Thomas & Spiro, 1995). [The Working Group noted that, due to smaller emission volumes, the overall emissions from hospital waste incinerators are generally lower than those from the municipal solid-waste incinerators.]

(iv) *Incineration of polyvinyl chloride (PVC)*

The extent to which PCDFs are formed during the combustion of PVC is a controversial issue. However, the incineration conditions appear to be quite important. On the basis of laboratory experiments, Christmann *et al.* (1989a) considered PVC to be an important source of PCDFs. However, experiments performed in incinerators showed the effect of PVC on the formation of PCDFs to be minimal (Frankenhaeuser *et al.*, 1993; Wikström *et al.*, 1996).

(v) *Combustion of wood*

Schatowitz *et al.* (1994) studied PCDD/PCDF emissions from small-scale laboratory studies of combustion of wood and household waste (analytical method ABS). The results (in ng I-TEQ/m^3) are summarized in **Table 11**. Data on PCDDs and PCDFs are not separated.

(vi) *Automobile emissions*

Hagenmaier *et al.* (1990) reported on the emissions of PCDFs and the lower chlorinated congeners and brominated analogues in automobile emissions from four representative experiments using leaded gasoline, unleaded gasoline with or without catalytic

converters and diesel fuel (analytical method ABS). The results are summarized in **Table 12**.

Table 11. PCDD/PCDF emissions from wood and household waste combustion

Fuel	Furnace	PCDD/PCDFs (ng I-TEQ/m^3)
Beech wood sticks	Fireplace	0.064
Beech wood sticks	Stick wood boiler	0.019–0.034
Wood chips	Automatic chip furnace	0.066–0.214
Uncoated chipboard	Automatic chip furnace	0.024–0.076
Waste wood chips	Automatic chip furnace	2.70–14.42
Household waste	Household stove, closed	114.4

From Schatowitz *et al.* (1994)

Table 12. PCDFs from automobile emissions (pg/m^3)

	Leaded gasoline	Unleaded gasoline	Unleaded gasoline with catalytic converter	Diesel engine
TCDFs	6 628	110	6.8	3.9
2,3,7,8-TCDF	201.4	8.5	0.55	1.04
PeCDFs	1 514	180	6.9	2.0
1,2,3,7,8-PeCDF	141.2	8.6	0.43	< 0.26
2,3,4,7,8-PeCDF	58.4	4.0	0.31	0.36
HxCDFs	824	73	4.3	1.3
1,2,3,4,7,8-HxCDF	111.8	8.1	0.62	0.33
1,2,3,6,7,8-HxCDF	111.8	4.1	0.81	0.34
1,2,3,7,8,9-HxCDF	< 10.0	7.3	0.02	< 0.26
2,3,4,6,7,8-HxCDF	35.7	10.5	0.59	< 0.26
HpCDFs	737	92	3.5	4.1
1,2,3,4,6,7,8-HpCDF	529.2	5.4	2.11	2.07
1,2,3,4,7,8,9-HpCDF	< 10.0	3.2	< 0.02	0.43
OCDF	30	23	3.6	4.8
Total tetra- to octaCDFs	**9 733**	**478**	**25.1**	**16.1**
I-TEQ pg/m^3	141.5	9.8	0.93	1.20
I-TEQ pg/L fuel	1 083.3	50.7	7.20	23.60

From Hagenmaier *et al.* (1990)

(vii) *Metal production*

Steel mills and the manufacturing of iron and steel are considered to be major sources of PCDDs and PCDFs in the environment. The concentrations of PCDFs are much higher than the concentrations of PCDDs in these samples (Rappe, 1994). Jager (1993)

reported on the contamination of scrap samples and I-TEQ levels in flue gas emissions from German steel mills (see **Table 13**) (analytical method ABS).

Table 13. PCDD/PCDF contamination of flue gas, clean gas and flue dust from a steel mill

Proportion of non-metals in scrap added	Flue gas (ng I-TEQ/m^3)	Clean gas (ng I-TEQ/m^3)	Flue dust (ng I-TEQ/g)
Low	0.9	0.02	4.8
Average	1.7	0.04	5.1
High	2.7	0.06	6.0

From Jager (1993)

(viii) *Accidents with electrical equipment containing PCBs*

Buser *et al.* (1978b) reported that pyrolysis of PCBs could cause formation of PCDFs and they issued a warning for this risk. Such an accident occurred in 1981 in the State Office building in Binghamton, NY (United States), when a transformer in the basement exploded and contaminated soot was spread throughout the building (O'Keefe *et al.*, 1985; Schecter, 1986). In the 1980s, following similar accidents involving both transformers and capacitors, people were evacuated from houses and workplaces in the United States, Canada, Sweden, Finland and France (Rappe *et al.*, 1985b; Hryhorczuk *et al.*, 1986; Rappe *et al.*, 1986b). In many cases, analyses showed elevated concentrations of PCDFs in the soot (as high as 2168 mg/kg; the major constituents being 2,3,6,7-/2,3,7,8-TCDFs, 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-/1,2,3,6,7,8-HxCDFs) (Rappe *et al.*, 1985b).

(*c*) *Photochemical reactions*

The photochemical dechlorination of OCDF on soil has been studied by Tysklind *et al.* (1992). Dechlorination occurs preferentially in the lateral (2,3,7,8) positions. Consequently, no 2,3,7,8-substituted PCDFs could be identified in the dechlorination products. Similar results were obtained by Friesen *et al.* (1996) for the photochemical degradation of 2,3,4,7,8-PeCDF, where no 2,3,7,8-TCDF was found.

(*d*) *Biochemical reactions*

Öberg *et al.* (1990) showed that chlorinated phenols could be transformed *in vitro* to PCDFs by peroxidase-catalysed oxidation.

1.2.2 *Destruction of PCDFs*

Although PCDFs are considered to be very stable, they can undergo a series of chemical degradation reactions. Peterson and Milicic (1992) and Oku *et al.* (1995) reported the degradation of a series of PCDFs using a mixture of potassium hydroxide in polyethylene glycol or sodium or potassium hydroxide in 1,3-dimethyl-2-imidazolidinone.

Vollmuth and Niessner (1995) reported no significant degradation of PCDFs by ultraviolet radiation, ozone or a combination of the two.

Thermal degradation of PCDFs occurs at temperatures above 800 °C and at residence times of longer than 2 s (WHO/EURO, 1987), but the conditions required for thermal degradation are matrix-dependent.

Adriaens *et al.* (1995) reported on the biologically mediated reductive dechlorination of 2,3,4,7,8-PeCDF in sediments using inocula derived from contaminated environments.

1.3 Occurrence

All tissue concentrations reported in this section are lipid-based (as ng/kg fat), unless otherwise stated.

1.3.1 *Occupational and accidental exposures to PCDFs*

(*a*) *Occupational exposures*

(i) *Exposure during production of PCBs*

Although several cohorts of PCB workers have been studied, no study has taken PCDFs into account.

(ii) *Exposure during production of TCP and 2,4,5-T*

In the Boehringer-Ingelheim plant in Hamburg manufacturing a range of herbicides, Flesch-Janys *et al.* (1996a) studied 48 workers (45 men and 3 women) (see also monograph on PCDD, p. 55). The blood concentrations of PCDFs in these workers are given in **Table 14**.

Table 14. Concentrations of PCDFs (ng/kg fat) in blood of workers at a German herbicide plant (Boehringer-Ingelheim plant)

		First blood sample[b]		Last blood sample[c]	
	No.[a]	Median	Range	Median	Range
2,3,4,7,8-PeCDF	5	105.9	76.4–406.7	71.3	47.9–108
1,2,3,4,7,8-HxCDF	42	116.7	37.5–1035	61.5	21.9–489.4
1,2,3,6,7,8-HxCDF	31	50.4	28.5–374	30.2	13.6–205.9
2,3,4,6,7,8-HxCDF	6	16.3	10.1–38	8.8	6.1–14.8
1,2,3,4,6,7,8-HpCDF	22	123.1	47.3–1028	45.8	24.7–243
1,2,3,4,7,8,9-HpCDF	6	14.8	3.6–26	3	1.6–5.4

From Flesch-Janys *et al.* (1996a)

[a] Number of persons whose levels exceeded upper background concentrations at all points in time

[b] Mean, 5.4 years after end of employment

[c] Mean, 5.6 years after the first blood sample

(iii) *Exposure during handling and spraying of 2,4,5-T*

Professional pesticide applicators involved in ground-level spraying of 2,4,5-T in New Zealand are claimed to be the group most heavily exposed to agricultural use of 2,4,5-T in the world (Smith *et al.*, 1992a). Many of the applicators sprayed for more than six months per year and some were spraying for more than 20 years. Measurements of PCDFs in blood serum of nine of these workers are given in **Table 15** (see also monograph on PCDDs, p. 57).

Table 15. Levels of PCDFs in serum of nine 2,4,5-T applicators and nine matched control subjects in New Zealand

Congener	Average level (ng/kg fat ± SE)[a]		Ratio[b]
	Applicator	Matched control	
2,3,7,8-TCDF	1.6 ± 0.3	1.7 ± 0.3	0.9
1,2,3,7,8-PeCDF	< 2.1 ± 0.2	< 2.0 ± 0.2	1.1
2,3,4,7,8-PeCDF	8.0 ± 0.9	7.4 ± 0.8	1.1
1,2,3,4,7,8-HxCDF	5.4 ± 0.3	5.1 ± 0.5	1.1
1,2,3,6,7,8-HxCDF	5.5 ± 0.4	5.6 ± 0.6	1.0
1,2,3,7,8,9-HxCDF	< 0.8 ± 0.1	< 0.8 ± 0.1	1.0
2,3,4,6,7,8-HxCDF[c]	< 1.1 ± 0.4	< 1.7 ± 0.2	1.1
1,2,3,4,6,7,8-HpCDF	14.2 ± 0.7	16.0 ± 2.3	0.9
1,2,3,4,7,8,9-HpCDF[c]	< 1.6 ± 0.1	< 1.9 ± 0.3	0.8

From Smith *et al.* (1992a)

[a] Values are adjusted for total lipids in serum.

[b] Ratio, average for applicators/average for matched control subjects

[c] A number of positive signals were below the limit of quantification.

Military personnel in Viet Nam: Nygren *et al.* (1988) analysed adipose tissue and blood samples collected 15–20 years after military service from 27 men, 10 of whom were heavily exposed during their service in Viet Nam, 10 of whom had marginal exposure during service and served as Viet Nam controls and seven veterans who did not serve in Viet Nam and were used as 'era' controls. The results for PCDFs levels are summarized in **Table 16** (see also Section 1.3.1(*a*)(ii) of the monograph on PCDDs).

(iv) *Exposure at incinerators*

Studies of workers at incinerators have not found elevated tissue levels of PCDFs. Rappe *et al.* (1992), Päpke *et al.* (1993a) and Böske *et al.* (1995) found only elevated tissue levels of PCDDs.

(v) *Metal production and recycling*

Triebig *et al.* (1996) analysed the concentrations of PCDFs in the blood of 76 workers in a non-iron recycling plant in the south-western part of Germany. The results were compared with those from a group of 102 controls. Elevated concentrations of PCDFs

Table 16. Concentrations of PCDFs in blood plasma of exposed and unexposed groups of United States Army veterans (ng/kg fat)

Isomers	Arithmetic means						Geometric means		
	Exposed Viet Nam veterans		Viet Nam controls		Era controls[a]		Exposed Viet Nam veterans	Viet Nam controls	Era controls
	Mean	SEM[b]	Mean	SEM	Mean	SEM	Mean	Mean	Mean
2,3,7,8-TCDF	4.0	2.1	3.6	0.9	3.4	1.7	2.3	2.1	1.0
2,3,4,7,8-PeCDF	14.0	2.5	15.2	2.4	19.2	5.9	11.9	13.4	15.2
1,2,3,4,7,8-HxCDF[c]	13.5	1.5	9.3	1.7	11.5	3.0	12.8	7.6	9.2
1,2,3,6,7,8-HxCDF	9.1	1.3	5.4	1.3	7.5	2.6	8.2	3.7	5.7
2,3,4,6,7,8-HxCDF	2.9	0.7	1.9	0.4	1.7	1.7	2.3	1.7	1.5
1,2,3,4,6,7,8-HpCDF	27.2	4.4	20.5	3.6	19.6	2.6	24.6	13.3	16.6

From Nygren *et al.* (1988)

[a] Era controls are veterans who served outside Viet Nam during the period of the Viet Nam conflict.

[b] SEM, standard error of mean

[c] 1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF

were found in the exposed group (up to 1138 ng/kg), around six times above the maximal blood concentrations in controls. Elevated levels were found particularly for 2,3,4,7,8-PeCDF and for HxCDFs (analytical method ACS). In another study, Bergschicker *et al.* (1994) found elevated concentrations of the same PCDFs in a group of 34 workers employed in a primary and secondary copper smelter (analytical method ACS).

Menzel *et al.* (1996) reported elevated blood concentrations of PCDDs/PCDFs in a group of 14 workers employed in welding and cutting of metals (welders: median, 29.9; burners: median, 46.7; referents, 28.3 ng I-TEQ/kg).

Hansson *et al.* (1995) reported a significant increase in Cl_5–Cl_8 PCDFs in the blood of nine workers from a magnesium plant in Norway. They analysed blood samples from workers employed at the plant for 10–36 years and from a control group of nine non-production workers. OCDF was the congener with the highest exposure levels (see **Table 17**).

Table 17. Mean concentrations of PCDFs (expressed in ng/kg fat) in blood plasma from metal workers and controls

PCDF	Controls (n = 9)		Workers (n = 9)		p value[a]
	Mean	Range	Mean	Range	
2,3,7,8-TCDF	2.9	1.2–4.7	3.5	1.5–6.1	0.5
1,2,3,7,8-PeCDF	2.2	< 1–3	5.4	< 1–11	0.06
2,3,4,7,8-PeCDF	20	14–29	51	19–170	0.02
1,2,3,4,7,8-HxCDF	22	5.9–94	59	23–150	0.01
1,2,3,6,7,8-HxCDF	12	5.7–31	59	19–190	0.002
2,3,4,6,7,8-HxCDF	3.4	< 1–6.8	5.4	2–9.6	0.09
1,2,3,4,6,7,8-HpCDF	14	4.7–32	85	21–150	0.0007
1,2,3,4,7,8,9-HpCDF	< 2		6.9	< 2–16	0.0005
OCDF	7.5	< 3–18	216	17–560	0.0005
I-TEQ	25	17–42	60	27–190	0.007

From Hansson *et al.* (1995)

[a] Mann-Whitney U test for comparison between groups (two-tailed)

(vi) *Exposure during production of chlorine gas*

Svensson *et al.* (1993) reported that in a small cohort of workers at a chloralkali plant in Sweden, handling sludge from graphite electrodes had caused exposure to 2,3,7,8-substituted PCDFs (2,3,4,7,8-PeCDF and HxCDFs). However, exposure to contaminated soil did not result in elevated concentrations of PCDFs (analytical method ACS).

(vii) *Exposure in bleached pulp mills*

Rosenberg *et al.* (1995) analysed 34 blood samples from workers at a pulp mill and 14 controls. They found no statistically significant differences in lipid-adjusted concentrations of PCDFs between the two groups.

(viii) *Exposure during production of PVC*

Hansson *et al.* (1997) reported a weak correlation between length of employment in production of PVC (or vinyl chloride monomer) and concentrations of PCDFs in the blood, especially 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs and 1,2,3,4,6,7,8-HpCDF.

(*b*) *Accidental exposure*

Repeated heating of PCBs in the presence of oxygen can result in formation of PCDFs, polychlorinated quaterphenyls (PCQs) and other compounds. In Japan and Taiwan, the use of PCBs as heat exchangers during the deodorizing of cooking oil resulted in contamination of cooking oil, presumably when the processing machines leaked. These incidents caused thousands of cases of PCB/PCDF poisoning when the contaminated oil was distributed and consumed.

(i) Yusho *incident, Japan, 1968*

A mass poisoning, called the *yusho* ('oil disease') incident, occurred in western Japan in 1968. The disease was caused by ingestion of a specific brand of rice oil that was contaminated not only with PCBs but also with PCDFs, PCQs and other substances. About 2000 affected individuals (Chen *et al.*, 1985a) were identified (1870 had been registered by 31 May 1990), primarily in the Fukuoka and Nagasaki prefectures on the island of Kyushu (Ikeda & Yoshimura, 1996). Although *yusho* patients had ingested more than 40 different PCDF congeners, Rappe *et al.* (1979b) found that only a few congeners had been retained by the patients. Most of the retained congeners were found to have the 2, 3, 7 and 8 positions chlorinated. The missing congeners, apparently metabolized and excreted, were those with two vicinal hydrogenated carbon atoms in at least one of the rings. Masuda (1994) determined concentrations of the major PCDF congeners identified in tissues and blood at different sampling times (**see Table 18**). The highest concentrations were found for 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-/1,2,3,6,7,8-HxCDFs. Five years after exposure ended, the mean concentrations of PCBs in the adipose tissue, liver and blood of *yusho* cases were 1.9 mg/kg (ppm), 0.08 mg/kg and 6.7 μg/kg, respectively (Masuda *et al.*, 1985), which were about twice the levels in the control group. Levels of PCDFs in adipose tissue ranged from 6 to 13 μg/kg (Masuda *et al.*, 1985). Sixteen years after exposure, the mean level of PCQs in adipose tissue of *yusho* cases was 207 μg/kg, approximately 100 times the level in Japanese controls (Kashimoto *et al.*, 1985).

(ii) Yucheng *incident, Taiwan, 1979*

In 1979, 11 years after the Japanese *yusho* incident, a similar incident occurred in central Taiwan. About 2000 persons were identified as *yucheng* patients, primarily from Taichung and Changhwa counties (Chen & Hites, 1983; Chen *et al.*, 1985a). Oil samples were found to be contaminated with PCBs, PCDFs and PCQs, like the *yusho* oil. However, the average chlorination level seemed to be higher in the Taiwanese oil than in

Table 18. Concentrations of PCDF congeners in tissues of *yusho* patients

Year of sampling	Tissue	PCBs (mg/kg)	PCDFs (μg/kg wet weight)			
			2,3,7,8-TCDF	2,3,4,7,8-PeCDF	1,2,3,4,7,8-/1,2,3,6,7,8-HxCDF	1,2,3,4,6,7,8-HpCDF
1969	Liver	1.4	0.3	6.9	2.6	
1969	Liver	0.2	0.02	1.2	0.3	
	Adipose	2.8	0.3	5.7	1.7	
1972	Liver	0.03	< 0.01	0.3	0.03	
	Adipose	4.3	ND	0.8	0.2	
1975	Adipose	0.2	ND	0.1	0.5	
1977	Liver	0.06	ND	1.49	5.31	1.39
	Adipose	3.0	0.002	1.45	1.99	0.22
	Lung	0.016	0.002	0.365	0.41	0.05
1985	Uterus	0.005	ND	0.026	0.031	ND
1982	Comedo	0.2	ND	0.36	0.39	0.1
1986	Adipose[a]	2.2	0.003	1.4	0.51	
1986	Adipose[b]	2.3	0.028	0.77	0.66	0.036
	Blood[b]	0.0085	0.0025	0.0025	0.0004	
	Control subject					
1986	Adipose[c]	1.1	0.007	0.02	0.02	0.0009
	Blood[c]	0.0033	0.00007	0.00006	0.0009	

From Masuda (1994)

[a] Average of seven patients

[b] Average of six patients

[c] Average of three controls

the Japanese oil. The major PCDF was 1,2,3,4,7,8-HxCDF. Chen & Hites (1983) analysed tissue samples from a deceased patient (see **Table 19**). PCDFs in the blood of 10 patients were analysed by GC with negative chemical ionization–mass spectrometry. The blood samples were collected 9–27 months after the onset of poisoning. The total PCDFs in the blood of 10 patients ranged from 0.02 to 0.20 μg/kg, the major components being 1,2,3,4,7,8-HxCDF and 2,3,4,7,8-PeCDF. Minor amounts of 1,2,3,4,6,7,8-HpCDF and 1,2,4,7,8-PeCDF were also found (Chen *et al.*, 1985b). In *yucheng* patients, within the first year of exposure, mean serum PCB, PCDF and PCQ levels for 15 cases were 60 mg/kg (range, 4–188 mg/kg, 0.14 μg/kg (range, < 0.005–0.27 μg/kg) and 19.3 μg/kg (range, 0.9–63.8 μg/kg), respectively (Kashimoto *et al.*, 1985). Analysis of PCB levels in 1980–81 in 165 cases (mean, 38 μg/kg; range, 10–720 μg/kg) (Rogan, 1989) and in 1985 in 32 cases (mean, 15.4 μg/kg; range, 0.6–86.8 μg/kg) (Lundgren *et al.*, 1988) suggested that some PCBs were being eliminated. [The Working Group noted that it was not clear from the reports if the samples were drawn from distinctly different individuals or included some of the same individuals.]

Table 19. Concentrations of PCDF congeners in the tissues of a deceased patient with *yucheng* in Taiwan

Tissue	Level of PCDF congener (μg/kg)		
	1,2,4,7,8-PeCDF	2,3,4,7,8-PeCDF	1,2,3,4,7,8-HxCDF
Liver	3.4	6.3	25.4
Intestinal fat	0.9	4.0	7.8
Bronchus	0.4	1.8	3.2
Large intestine	0.3	1.2	2.3
Heart	0.2	0.8	1.4
Stomach	0.05	0.23	0.4
Small intestine	0.05	0.21	0.34
Kidney	0.04	0.18	0.32
Lung	0.01	0.06	0.15
Brain	0.01	0.06	0.15
Spleen	0.01	0.08	0.1

From Chen & Hites (1983)

(*iii*) *PCB explosions and fires*

After the accident at Binghamton, NY (United States), in 1981 (see Section 1.2.1(*b*)(viii), 74.7 ng/kg 2,3,4,7,8-PeCDF, 149 ng/kg 1,2,3,4,7,8-HxCDF, 39.3 ng/kg 1,2,3,4,6,7,8-HpCDF and 25.9 ng/kg 1,2,3,4,7,8,9-HpCDF were found in the adipose tissue of an exposed person (Schecter *et al.*, 1985a). After an accident in Reims, France, in 1985, < 4 ng/kg 2,3,4,7,8-PeCDF, < 2 ng/kg 1,2,3,4,7,8-HxCDF, < 14 ng/kg total HpCDFs as well as < 12 ng/kg total HpCDDs and < 23 ng/kg OCDD were found in the blood of 6 exposed persons (Rappe *et al.*, 1986b).

1.3.2 *Environmental occurrence* (see also Appendix 2)

Most of the analytical data on environmental levels of PCDFs are from studies measuring PCDDs and PCDFs, often reported as a total I-TEQ (see the monograph on PCDDs as well as Appendix 1). However, in some studies, separate data on PCDFs were reported.

(*a*) *Air* (see Appendix 2, Table 1)

In a baseline study on PCDDs and PCDFs in ambient air (Eitzer & Hites, 1989), 55 samples were taken between 1985 and 1987 at three sites in Bloomington, IN (United States). A set of samples was also taken in the Trout Lake, WI, area, a much more rural area than Bloomington. There was consistency in the isomer pattern within a group of isomers, but overall levels of the various groups had somewhat more variation. Some of this variation was related to the atmospheric temperature; for example, more of the lower chlorinated PCDFs were found in the vapour phase at higher temperatures. The TCDF

distribution between vapour and particulate phases at various temperatures (with a detection limit of 1 fg/m^3 (femtogram = 10^{-15} g)) was as follows: at 3 °C, 50% vapour phase and 50% particulate phase; at 12 °C, 80% vapour phase and 20% particulate phase; and at 26 °C, > 95% vapour phase and < 5% particulate phase.

Airborne concentrations of PCDDs and PCDFs in office buildings and in ambient outdoor air in Boston, MA (United States), were measured by Kominsky and Kwoka (1989). Twelve of the 16 samples were collected inside the buildings and four samples were collected at the ambient air intake plenums of the buildings. PCDFs were generally not detected, except for three samples that showed detectable concentrations of TCDFs and PeCDFs. Two of these samples (one inside and one ambient air) contained 2,3,7,8-TCDF. The I-TEQs for the two samples containing 2,3,7,8-TCDF were 0.34 and 0.20 pg/m^3, respectively.

(*b*) *Water* (see Appendix 2, Table 2)

Muir *et al.* (1995) analysed water and other matrices downstream from a bleached kraft pulp mill on the Athabasca River (Alberta, Canada) in 1992. The 'dissolved phase' and the suspended particulates from centrifuged samples were analysed for 41 PCDDs/-PCDFs ranging from mono- to octa-chlorinated congeners. Most PCDD congeners (including 2,3,7,8-TCDD) were undetectable (< 0.1 pg/L) in the centrifugate; however, concentrations of 2,3,7,8-TCDF were above the detection limits at the 1 km site (Weldwood; 0.1 pg/L) and at 48 km (Emerson Lake; 0.09 pg/L). In 1993, 2,3,7,8-TCDF was not detected in the dissolved phase (< 0.1 pg/L) either 1 or 19 km downstream.

In a survey conducted in 1986 for PCDDs/PCDFs and other pollutants in finished water systems throughout New York State (United States), two TCDFs were found at concentrations of 1 pg/L in one finished drinking-water (Meyer *et al.*, 1989). Except for a trace of OCDF detected in one location, no other PCDD or PCDF was detected in any of the 19 other community water systems surveyed.

(*c*) *Soil* (see Appendix 2, Table 3; also Appendix 1, Tables 4, 5 and 8)

Topsoil samples were collected at six typical locations in Flanders, Belgium, including potential PCDD/PCDF source areas, and analysed [but not reported] isomer-specifically for PCDDs and PCDFs (Van Cleuvenbergen *et al.*, 1993). Concentrations in the 0–3-cm soil fraction, averaged per location, ranged between 2.1 ng/kg at a rural location and 8.9 ng/kg (both as I-TEQ) in an industrialized area. Generally, PCDFs made up 70 ± 6% of the I-TEQ, whereas they accounted for 34 ± 6% of the sum of the concentrations of the seventeen 2,3,7,8-substituted congeners.

At the end of 1990, high levels of PCDFs and PCDDs (10–100 µg I-TEQ/kg) were detected in the surface gravel of playgrounds and sports fields in Germany during routine monitoring. The source of this contamination was identified as a fine-grained copper slag which originated from a former copper smelter at Marsberg, Germany. This material had been used as a cover layer due to its red colour (*Kieselrot*), its reduced dust formation compared to other gravels and its quick drying after rain. The PCDDs/PCDFs in the copper slag were formed as by-products of a chlorinating roasting process when up to 8% sodium chloride and coal were added to a copper slag from an old mining process.

About 800 000 tonnes of red copper slag was produced by this process, and a large quantity was used. *Kieselrot* contains a large number of highly chlorinated aromatic compounds as its main organic components. It shows an unusual congener profile for PCDDs and PCDFs. The total amount of PCDFs was about one order of magnitude higher than that of PCDDs. Furthermore, the concentrations increased from TCDFs to OCDF by at least one order of magnitude. The levels of OCDF exceeded those of OCDD by more than a factor of 10. These concentration ratios are typical for metallurgical processes and have been found in the emissions from magnesium production. Typical OCDF and I-TEQ values in *Kieselrot* were 6311 and 64.5 μg/kg, respectively (Döring *et al.*, 1992; Theisen *et al.*, 1993).

In connection with analyses of highly contaminated samples related to the production and use of chlorine (e.g., chloralkali electrolysis sludge and chromate sludge) in Sweden, Rappe *et al.* (1991b) also found high PCDF levels in surface soil samples in the vicinity of the production plant. A typical PCDF congener pattern, called the 'chloralkali pattern', was identified in these soil samples.

(*d*) *Food* (see Appendix 2, Table 4)

All of the relevant data on PCDFs in foods derive from studies of both PCDFs and PCDDs. The monograph on PCDDs in this volume should be consulted for general remarks. The data included have been selected to meet a number of criteria, including: relevance to dietary intake rather than environmental monitoring, appropriate detection limits and appropriate analytical methodology. Some exceptions have, however, been made and some data that are available only as summed TEQs have been included where they seem to be of value. Additionally, the results included either were available on a lipid basis or could be so converted using either reported fat contents or reasonable assumptions. Some further results omitted from the tables are discussed in the text below. Certain entries in the Appendix 1 tables (for PCDDs) do not appear in Appendix 2, since PCDFs were either not determined, or not reported separately from the summed TEQ.

Summed TEQ concentrations are included in Tables 9–18 in Appendix 1 and these have, in most cases, been recalculated using I-TEF values and assuming that congeners that were not detected were present at the full value of the detection limit, unless limits of detection were not reported (indicated as 'ND').

Ryan *et al.* (1990) found an average concentration of 73.3 ng/kg 2,3,7,8-TCDF in cow's milk, much higher than in other reports (see Appendix 2, Table 4), and in a subsequent study showed this to be due to migration into milk from bleached paperboard containers (Ryan *et al.*, 1991). In Germany, Beck *et al.* (1990a) also found elevated levels of 2,3,7,8-TCDF in milk from cardboard containers, in the range 1.6–28 ng/kg (mean, 9.6 ng/kg), contrasting with a range of < 0.1–1.4 ng/kg (mean, 0.7 ng/kg) in other milk. The non-toxic 1,2,7,8-TCDF isomer also migrates. This congener is not normally present in milk but was found at a mean concentration of 4.9 ng/kg in milk from cardboard packages (Beck *et al.*, 1990a) and by Ryan *et al.* (1991) at a mean concentration of 80 ng/kg. Similar increases in 2,3,7,8-TCDF levels were found in studies in New Zealand (Buckland *et al.*, 1990b), the United Kingdom (Startin *et al.*, 1990) and the United States (Glidden *et al.*, 1990) and elsewhere. However, in Sweden, Rappe *et al.* (1990b) found

little or no such migration in cardboard-packaged milk from four out of five towns (5 ng/kg in one). Since 1990, the concentrations of PCDFs in pulp products have been substantially reduced. Thus, in samples from the United Kingdom Total Diet Study (Wright & Startin, 1995), a relatively high 2,3,7,8-TCDF level of 6.6 ng/kg was found in milk collected in 1982, together with 1,2,7,8-TCDF clearly indicating chlorine bleaching as the source, while neither congener was detected in milk collected in 1992.

If Ryan's atypical data are excluded, the samples of milk and dairy products from various locations, which are dominated by European samples from the late 1980s and early 1990s, have mean concentrations of individual PCDFs between about 0.2 and 2.8 ng/kg (Appendix 2, Table 4). The ratios between the lowest and highest measurements for different PCDF congeners vary from around 30 to several hundred. [The Working Group noted that data for OCDF should be treated with particular caution; at these concentrations, this congener is especially difficult to determine accurately and the range of reported concentrations is wide.] Apart from OCDF, 2,3,4,7,8-PeCDF tends to have the highest concentration in most European samples, but not in the single analysis presented of milk from the United States (Eitzer, 1995).

Milk produced close to sites associated with contamination from incineration and similar processes can contain relatively high concentrations of PCDFs (**Table 20**).

Analyses of meats and meat products indicate mean concentrations for most 2,3,7,8-chlorinated congeners of between 1 and 4 ng/kg, with 1,2,3,7,8,9-HxCDF and 1,2,3,4,7,8,9-HpCDF generally at lower concentrations. As with PCDDs, samples of animal liver show considerably higher concentrations.

The rather limited data on poultry meat and eggs suggest that concentrations are usually of the same order of magnitude as those seen in other animal products.

In fish, the pattern of concentrations of different congeners tends to be more extreme and more variable. It is unusual for 1,2,3,7,8,9-HxCDF to be detectable, while most of the tetra- and pentachlorinated congeners are present at higher concentrations than in terrestrial animal products. The predominant congener in fatty fish from the Baltic Sea is 2,3,4,7,8-PeCDF (Svensson *et al.*, 1991). 2,3,7,8-TCDF has been reported in retail samples of marine fish species at concentrations around 100 ng/kg (Beck *et al.*, 1989a; Liem *et al.*, 1991a).

1.4 Human tissue measurements (see Table 21)

Most of the analytical data on biological monitoring of PCDFs have been reported in studies in which both PCDDs and PCDFs were measured (see the monograph on PCDDs in this volume; Section 1.4 and Tables 24, 25 and 27).

In some studies, individual data on PCDFs are reported. All concentrations reported in this section are lipid-based (as ng/kg fat), unless otherwise stated.

Table 20. Concentrations of PCDFs in cow's milk from contaminated areas

Reference	Origin	Sample year	No.	PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Riss *et al.* (1990)	Austria, Brixlegg (metal reclamation)	1988	1	7.4	6.3	29.5	26.5	17.1	–	18.8	–	–	–
			1	9	6.5	57.6	26.8	17.8	–	9.4	–	–	–
Rappe *et al.* (1987b)	Switzerland, Hunzenschwil (MSWI)	–		[< 0.49]	[< 0.45]	[9.62]	[2.91]	[4.25]	ND	[6.26]	[11.0]	ND	[< 3.58]
	Rheinfelden (Cl compound manuf.)			[< 0.80]	[< 0.92]	[6.59]	[2.41]	[1.69]	ND	[1.40]	[< 5.16]	ND	[< 14.9]
	Suhr (MSWI)			[< 1.01]	[< 1.14]	[6.94]	[1.89]	[3.00]	ND	[3.79]	[8.83]	ND	[< 6.62]
Startin *et al.* (1990)	UK, incinerator	1989	1	[0.25]	[0.075]	[1.775]	[1.05]	[0.75]	[< 0.525]	[0.65]	[0.575]	[< 0.5]	[< 3.825]
			1	[0.275]	[< 0.6]	[2.625]	[1.25]	[1.025]	[< 0.55]	[0.925]	[< 1.8]	[< 0.85]	[< 3.05]
	UK, urban/industrial	1989	1	[0.525]	[0.3]	[6.1]	[1.375]	[0.9]	[< 0.425]	[0.725]	[0.425]	[< 0.25]	[< 1.95]
			1	[0.45]	[0.35]	[3.875]	[0.875]	[0.55]	[< 0.25]	[0.375]	[< 0.5]	[< 0.5]	[< 4]
Harrison *et al.* (1996)	UK, Derbyshire (Cl compd. Manuf.) (Farm A) (4% fat assumed)	1990	1	[0.5]	[0.5]	[7.75]	[2.75]	[3]	[< 0.25]	[3.25]	[1.5]	[0.25]	[0.75]
Eitzer (1995)	USA, Connecticut, (incineration) (4% fat assumed)	1993	12	[0.325]	[0.0325]	[0.0825]	[0.1725]	[0.0975]	[0.0675]	[0.1725]	[0.8]	[0.185]	[8.5]

Summed I-TEQs are given in the PCDD monograph in this volume.

–, not reported; ND, not detected and limit of detection not reported; [ ], calculated by the Working Group; MSWI, municipal solid-waste incinerator.

Table 21. Concentrations of PCDFs in human samples

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Austria														
Riss *et al.* (1990)	Brixlegg;	(1)	88	CSN	< 14	7.5	839	116	113	–	15	–	–	–
	blood from farmer	(1)			< 10	1.8	119	27.2	30	–	3.2	–	–	–
Canada														
Ryan *et al.* (1985b)	Kingston/Ottawa[a]; adipose	(8)	79–81	BSIW	2.9 ± 1.9 (6 pos.)	–	16.9 ± 21.4 (6 pos.)	–	–	–	–	–	–	–
Ryan *et al.* (1985c)	Adipose			BSIW										
	Québec	(5)	72		–	–	20.5 (4 pos.)		17.0 (1 pos.)	–	–	28.9	–	–
		(10)	76		–	–	21.7		2.8 (8 pos.)	–	–	23.5 (9 pos.)	–	–
	British Columbia	(5)	72		–	–	30.8		59.7	–	–	55.1	–	–
		(10)	76		–	–	18.3		21.8	–	–	38.3	–	–
	Maritimes	(10)	76		–	–	16.3		11.9 (2 pos.)	–	–	25.1	–	–
	Ontario	(6)	76		–	–	10.4		12.7	–	–	28.0	–	–
	Prairies	(10)	76		–	–	14.8		22.4 (6 pos.)	–	–	48.9 (8 pos.)	–	–
	E. Ontario[a]	(10)	80		–	–	18.4 ± 6.3		17.3 ± 6.9	–	–	39.4 ± 19.6	–	–
LeBel *et al.* (1990)	Adipose			BSO										
	Ontario	(76)	84		2.4 ± 2.6 (ND–10.8)	–	31.3 ± 19.1 (3.4–113)		35.6 ± 20.6 (6.1–107.6)	–	3.7 ± 3.1 (ND–15.2)	25.2 ± 15.0 (8.1–113)	–	4.7 ± 5.2 (ND–27.9)
	Kingston[a]	(13)	79–81		3.5	–	39.0		47.5	–	5.9	44.2	–	16.7
	Ottawa[a]	(10)	79–81		3.1	–	27.6		35.0	–	4.4	29.9	–	7.3
Teschke *et al.* (1992)	British Columbia; adipose, residents of forest industry region	(41)	90–91	CSO	2.2 (0.46–7.5)	1.9 (0.22–13)	10 (2.6–27)	11 (1.2–27)	10 (2.9–26)	3.3 (1.4–9.6)	0.80 (0.06–4.2)	19 (7.6–61)	0.60 (0.33–0.89)	3.7 (1.4–7.0)
China														
Ryan *et al.* (1987)	Shanghai; adipose[b]		84	BSOW										
	LC, 58%	(1)			9.7[c]	–	12			< 2		< 2	–	–
	LC, 50%	(1)			7.4[c]	–	5.8			< 2		< 2	–	–
	LC, 73%	(1)			6.4	–	15			< 2		< 2	–	–
	LC, 70%	(1)			2.7	–	12			16		< 2	–	–
	LC, 73%	(1)			< 2.8	–	14			25		< 2	–	–
	LC, 72%	(1)			< 2	–	9.9			18		< 2	–	–
	LC, 76%	(1)			< 1.8	–	14			14		< 2	–	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
China (contd)														
Schecter (1994)	Blood, general population;		92	BSOW										
	15–19 years	(50)			< 4.2	< 1.6	2.7	3.4	2.1	< 1.0	1.9	5.1	< 1.2	< 5.0
	> 40 years	(50)			2.7	< 1.0	2.7	4.7	3.0	< 1.0	2.7	7.7	< 2.3	< 5.0
Finland														
Rosenberg *et al.* (1995)	Plasma, general population; age, 28–60 years	(14)	89–90	BSIW	1.9 (0.4–5.3)	1.2 (0.3–2.7)	29 (7.8–60)	10 (3.8–17)	9.5 (4.4–18)	1.6 (1.4–1.8)	4.8 (2.6–10)	64 (14–136)	< 0.2	–
France														
Huteau *et al.* (1990a)	Paris; adipose; 6 patients, age, 54–82 years	(8)	< 90	BSO	5.7 (7 pos.) (2.4–12)	18.3 (3 pos.) (1–35.4)	104 (8 pos.) (19.3–242)	12.7 (4 pos.) (9.8–16.0)	11.5 (3 pos.) (9.8–14.4)	6 (1 pos.)	–	59.7 (2 pos.) (16.2–103)	–	–
Germany														
Beck *et al.* (1989b)	Hamburg residents; adipose	(20)	86	BSIW	2.5 (0.7–6.0)	0.4 (0.1–1.6)	40 (10–101)	15 (4.8–39)	16 (4.7–47)	–	4.7 (2.1–10)	20 (7.2–35)	–	0.4 (0.1–0.8)
Thoma *et al.* (1990)	Munich residents		< 89	BSO										
	Adipose	(28)			2.5 (0.7–12.8)	35.2 (7.6–93.3)			41.4 (15.8–146.0)			14.2 (3.8–45.6)		4.0 (1.2–13.5)
	Liver	(28)			5.5 (0.9–45.3)	173.7 (36.7–643)			398.5 (40.8–1801)			218.9 (12.2–757)		29.7 (4.3–65.8)
	Infants; adipose	(8)			2.1 (1.0–4.6)	16.1 (5.3–38.7)			10.4 (3.9–23.6)			4.2 (1.9–7.3)		4.8 (2.5–9.1)
Päpke *et al.* (1992)	General population; blood	(102)	89–90	BSOW	2.3 (0.5–6.7)	2.0 (0.5–7.1)	37 (6.3–99)	15.4 (3.6–49.0)	13.3 (2.7–53.0)	1.7 (0.5–9.4)	4.3 (0.5–14.0)	23.4 (4.8–55.0)	1.5 (0.5–4.0)	4.2 (1.0–15.0)
Kieselrot-studie (1991)	General population; blood	(56)	91	BSOW	4.2 (ND–12)	1.4 (ND–4.4)	34.5 (11–91)	13.9 (4.0–34)	15.9 (6.6–33)	0.5 (ND–4.7)	4.5 (ND–7.9)	22.4 (10–66)	0.4 (ND–4.2)	3.5 (ND–71)
Päpke *et al.* (1993b)	General population; blood	(44)	92	BSOW	1.2 (1.2–3.8)	0.4 (ND–2.5)	18.8 (6.8–48.2)	10.9 (4.4–24.5)	7.8 (3.1–20.7)	ND (ND–1.2)	2.9 (ND–9.9)	19.0 (8.5–38.4)	0.4 (ND–2.4)	0.4 (ND–2.4)

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Germany (contd)														
Schrey *et al.* (1992)	General population; blood	(95)	91	BSOW	1.37 (0.16–5.9)	0.64 (0.30–1.1)	34.3 (6.7–110)	11.5 (3.9–29)	16.5 (5.3–42)	–	3.67 (62–7.9)	15.4 (6.8–45)	0.48 (0.28–1.1)	1.10 (0.24–3.3)
Päpke *et al.* (1994b)	General population; blood	(70)	93	BSOW	2.2 (0.5–5.4)	0.7 (0.5–2.8)	15.3 (5.0–42.1)	8.8 (3.9–22.0)	6.5 (2.4–18.8)	ND	2.8 (1.0–5.6)	12.5 (5.1–36.3)	0.9 (0.5–3.1)	3.5 (1.9–6.1)
Päpke *et al.* (1996)	General population; blood	(134)	94	BSOW	1.9 (0.9–4.3)	0.5 (ND–1.8)	12.8 (3.2–41.3)	7.9 (2.5–19.4)	5.8 (1.8–16.3)	ND	2.6 (1.0–6.9)	11.4 (4.0–27.4)	0.6 (ND–2.0)	2.6 (ND–2.0)
	General population; blood		96	BSOW										
	18–71 years	(139)			1.2 (ND–2.0)	0.6 (ND–1.0)	10.9 (3.2–29.7)	6.5 (2.6–14.5)	4.7 (2.0–8.9)	ND	2.4 (0.5–4.8)	8.1 (4.1–18.3)	0.9 (0.5–0.9)	2.4 (1.5–3.2)
	18–30 years	(47)			1.2 (0.5–1.9)	0.6 (0.5–1.9)	8.2 (3.2–14.3)	5.8 (2.6–11.6)	4.1 (2.2–8.5)	ND	2.4 (1.4–4.1)	9.2 (4.2–18.3)	1.0 (0.7–1.6)	2.5 (1.8–2.5)
	31–42 years	(48)			1.3 (0.5–1.8)	0.6 (0.5–1.0)	10.9 (4.8–20.1)	6.4 (2.8–14.5)	4.8 (2.0–8.4)	ND	2.4 (0.5–4.4)	7.8 (4.7–16)	1.0 (0.8–1.8)	2.4 (1.6–3.1)
	43–71 years	(44)			1.2 (0.5–2.0)	0.5 (ND–1.0)	13.8 (5.2–29.7)	6.9 (3.0–13.3)	5.3 (2.2–8.9)	ND	2.5 (1.0–4.8)	7.1 (4.1–15.1)	0.8 (0.5–1.0)	2.4 (1.5–3.2)
Wittspiepe *et al.* (1993)	Marberg, near copper smelter; blood	(56)	91	BSOW	4.9 (ND–12)	1.8 (ND–10)	41.6 (13–240)	24.4 (5.1–120)	35.1 (6.5–280)	1.1 (ND–8.0)	5.6 (0.7–20)	42.1 (7.4–180)	0.5 (ND–3.2)	5.8 (ND–57)
Körner *et al.* (1994)	Mammary tumour tissue	(7)		BSO	3.2 (1.1–7.0)	1.3 (< 2–4.1)	39.3 (19.5–73.8)		33.5 (16.8–52.3)			14.4 (6.1–23.8)	–	8.1 (2.9–13.8)
Wuthe *et al.* (1990)	Near metal reclamation plant; blood	(22)	89	BSOW	4.9 (1.4–9.8)		72.9 (28–228)		108.6 (43.7–411)				48.3 (16–190)	4.3 (1.2–8.8)
Wuthe *et al.* (1993)	One woman		92	BSOW										
	Blood	(1)			1.8		9.7		19.1				15.4	< 4.4
	Milk	(1)			1.0		13.3		16.3				5.7	0.5
Ewers *et al.* (1994)	Allotment gardeners; blood	(21)	92	BSOW	1.1 (0.5–4.1)		32 (23–76)		27 (16–54)				12 (0.6–30)	2.7 (1.3–6.7)

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Germany (contd)														
Beck *et al.* (1994)	Infants, 3–23 months		< 93	BSOW										
	Adipose	(8)			1.1 (< 0.5–3.1)	< 0.5	8.7 (1.6–33)	4.4 (1.0–12)	2.8 (0.7–9.3)	–	1.0 (< 0.5–3.0)	5.2 (1.0–12)	–	< 0.5 (< 0.5–1.2)
	Liver	(8)			–	–	23 (3.3–82)	27 (< 2–107)	30 (2.9–85)	–	5.6 (< 1–14)	50 (< 4–169)	–	9.1 (4.5–15)
	Spleen	(8)			2.1 (< 1–< 10)	2.1 (< 1–< 10)	15 (< 5–68)	7.0 (1.4–28)	5.0 (1.3–16)	–	4.6 (1.0–20)	10 (1.9–31)	–	1.6 (< 1–< 5)
	Thymus	(8)			5.6 (3.2–7.5)	3.4 (< 1–7.5)	14 (6.1–37)	5.1 (2.2–< 15)	5.6 (3.5–< 15)	–	5.0 (2.1–< 15)	8.3 (2.6–19)	–	4.2 (< 1–< 15)
Jödicke *et al.* (1992)	Infant, 3 months		91	BSO										
	Stool	(1)			< 2	< 2	11.0	12.7		–	< 5	30.7	–	< 5
	Mother's milk	(2)			< 0.5–< 0.7	0.4–< 0.7	13.5–17.5	7.1–7.3		–	1.3–1.6	3.8–4.3	–	< 1–< 2
Welge *et al.* (1993)	Blood		92	BSOW										
	Vegetarians	(24)			0.94 (0.16–2.3)	0.64 (0.42–0.89)	25.8 (11–50)	8.1 (4.2–13)	11.8 (5.3–18)	–	3.16 (0.8–5.0)	14.2 (5.6–72)	0.40 (0.3–0.5)	2.0 (0.2–6.7)
	Non-vegetarians	(24)			1.3 (0.36–2.1)	0.66 (0.36–1.1)	25.5 (9.9–80)	9.1 (4.2–20)	12.9 (5.3–33)	–	3.16 (0.66–7.9)	14.6 (8.5–22)	0.38 (0.4–0.77)	1.4 (0.66–3.6)
Abraham *et al.* (1995a)	Mother's blood	(3)	93–94	BSOW	[< 2.2]	[< 1.0]	[8.5]	[4.7]	[3.2]	–	[1.0]	[4.8]	–	[< 2.4]
	Placenta	(3)			[< 2.4]	[< 1.0]	[8.0]	[2.5]	[1.7]	–	[< 1.0]	[2.2]	–	[< 3.0]
	Umbilical cord	(3)			[< 2.0]	[< 1.0]	[4.3]	[2.7]	[1.7]	–	[< 1.0]	[4.3]	–	[< 5.0]
	Meconium	(1)			[< 2.8]	[< 1.0]	[4.3]	[2.2]	[1.8]	–	[1.0]	[4.3]	–	[< 5.0]
Guam														
Schecter *et al.* (1992)	Whole blood	(10)	89	BSOW	3.9	0.5	9.3	6.3	5.4	0.5	1.2	34.1	0.9	6.4
Japan														
Miyata *et al.* (1977)	Omentum	(5)	75	CRO	< 5	ND–45.4				< 5.0		–	–	–
	Liver	(4)			< 5	ND–17.2				< 5.0		–	–	–
	Mamma	(1)			< 5	19.7				< 5.0		–	–	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Japan (contd)														
Ryan (1986)	Adipose		84	BSIW										
	Age 21; LC, 43%	(1)			–		17			20		–	–	–
	Age 33; LC, 37%	(1)			–		51			ND		–	–	–
	Age 46; LC, 67%	(1)			–		31			64		–	–	–
	Age 55; LC, 80%	(1)			–		29			41		–	–	–
	Age 64; LC, 71%	(1)			–		31			49		–	–	–
	Age 70; LC, 56%	(1)			–		36			168		–	–	–
	Mean; LC, 59%				–		33			68		–	–	–
Ono *et al.* (1986)	Cancer patients; adipose[b]	(13)	85	CSI	9 (3–12)	–	25 (4–71)	15 (4–24)	14 (3–28)	–	8 (4–16)	–	–	–
Okagi *et al.* (1987)	Big city; adipose	(1)	85	CRI	6	–	29	14	–	–	–	–	2	8
Hirakawa *et al.* (1991)	Controls; adipose	(8)	< 91	BSI	3 (1–7)	–	21 (8–30)	7 (3–13)	9 (3–20)	–	–	5 (2.8)	–	–
Masuda (1996)	Control; serum		91–92	BSIW	4.7	11.4	0.8	11.9	8.3	–	3.4	0.9	–	–
Netherlands														
van Wijnen *et al.* (1990)	Liver		< 90	BSIW										
	Fetus	(4)			–	–	0.12	0.12	0.10	–	–	0.10	–	–
	Infant not nursed	(1)			–	–	0.12	0.04	0.04	–	–	0.09	–	–
	Infant nursed	(1)			–	–	2.47	2.09	2.74	–	–	5.39	–	–
	Fat													
	Infant not nursed	(1)			–	–	5.20	ND	ND	–	–	1.80	–	–
	Infant nursed	(1)			–	–	14.66	2.61	2.05	–	–	4.43	–	–
	Placenta	(1)			–	–	1.01	0.17	0.12	–	–	0.18	–	–
New Zealand														
Smith *et al.* (1992a)	Control group for 2,4,5-T applicators; serum		88	BSIW	1.7 ± 0.3	< 2.0 ± 0.2	7.4 ± 0.8	5.1 ± 0.5	5.6 ± 0.6	< 0.8 ± 0.1	< 1.7 ± 0.2	16.0 ± 2.3	1.9 ± 0.3	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Norway														
Johansen *et al.* (1996)	Blood		93	BSO										
	Controls	(10)			2.8 (0.6–5.0)	1.8 (ND–10.9)	17.1 (4.9–34)	8.7 (1.9–21)	9.7 (2.3–22)	0.9 (ND–1)	4.3 (1.6–6.7)	18 (2.5–53)	1.0 (ND–0.9)	8.6 (1.3–30)
	Moderate crab intake	(15)			5.1 (ND–12.7)	7.2 (1.5–19.5)	54.0 (17.6–112)	55 (10.8–107)	45 (8.8–90)	3.6 (ND–34)	8.9 (ND–33)	44 (0.1–118)	4.8 (ND–4.6)	13.4 (ND–94)
	High crab intake	(9)			7.2 (1.7–16.5)	13.4 (1.3–35)	102 (52–148)	130 (34–233)	103 (27–217)	2.3 (ND–5.4)	14.3 (3.2–29)	93 (27–201)	26 (ND–5.3)	5.4 (2.1–8.8)
Russian Federation														
Schecter *et al.* (1992)	Whole blood		88–89	BSOW										
	Baikalsk	(8)			3.0	< 1.8	15	13	6.8	< 1.6	2.1	4.6	< 1.0	< 8
	St Petersburg (pool)	(60)			2.3	< 1.0	9.2	8.1	3.9	< 1.0	1.2	6.3	< 2.2	–
Spain														
Jiménez *et al.* (1995)	Madrid, unexposed; serum	(11)	93	BSO	4.7 ± 3.8 (9 pos.) (0.8–11.5)	1.4 ± 1.0 (9 pos.) (0.5–3.4)	7.0 ± 2.1 (10 pos.) (2.5–9.6)	5.8 ± 1.1 (10 pos.) (4.8–8.2)	5.1 ± 0.8 (10 pos.) (3.9–6.5)	1.8 ± 1.7 (5 pos.) (0.1–4.9)	2.6 ± 1.2 (9 pos.) (1.2–5.0)	12.8 ± 3.3 (11 pos.) (7.5–18.0)	5.0 ± 4.2 (9 pos.) (0.9–13)	20.6 ± 11.1 (9 pos.) (0.9–38.6)
Gonzáles *et al.* (1997)	Mataro; blood, 10 pools	(198)	95	BSOW	1.2		6.2			10.6			7.1	2.4
Sweden														
Rappe (1984b)	Background; adipose[b]	(6)	82	CS	3		40			22			50	3
Nygren *et al.* (1986)	Adipose[b]		84	BSIW										
	Unexposed	(18)			4.2 (0.3–11)	–	32 (9–54)	5 (1–6)	4 (1–5)	–	2 (1–4)	10 (1–18)	–	–
	Cancer patients	(17)			3.4 (0.3–7.2)	–	45 (9–87)	6 (1–15)	5 (1–13)	–	2 (1–7)	13 (1–49)	–	–
	Non-cancer patients	(14)			4.6 (0–11)	–	33 (11–65)	5 (2–7)	4 (2–7)	–	2 (1–4)	10 (5–16)	–	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Sweden (contd)														
Rappe (1992)	Blood		90	BSIW										
	No fish consumption				1.5	0.15	12	5.4	4.4	–	2.1	10	–	1.0
	Normal fish consumption				1.8	0.5	20	7.1	5.4	–	2.2	14	–	1.0
	High fish consumption				3.0	1.3	79	8.3	11	–	2.8	10	–	1.0
Svensson *et al.* (1995a)	Blood; pool[d]		95	BSI										
	South of Bothnia													
	Fishermen				4.8	ND	198	ND	ND	ND	5.0	16	–	ND
	Controls				ND	ND	40	5.9	6.8	ND	ND	19	–	ND
	Baltic Proper													
	Fishermen				ND	ND	110	9.7	12	ND	4.0	16	–	ND
	Controls				ND	ND	41	7.0	7.0	ND	2.6	15	–	3.2
	Baltic South													
	Fishermen				4.8	ND	163	19	23	ND	7.3	31	–	ND
	Controls				2.6	ND	59	10	10	ND	ND	20	–	6.8
	West Coast													
	Fishermen	(100)			ND	ND	47	8.0	8.0	ND	3.0	14	–	2.9
	Controls	(98)			ND	ND	42	8.9	9.6	ND	4.8	18	–	3.2
Hardell *et al.* (1995)	Blood													
	Cancer patients	(7)	> 86	BSI	3.3 (0.7–7.2)	1.0 (0.3–1.9)	59 (22–200)	8.6 (3.9–17)	7.9 (2.7–15)	2.0 (1–3)	2.7 (0.5–7)	16 (3–49)	0.8 (0.3–1)	< 3
	Non-cancer patients	(12)	> 86		5.0 (2.4–11.4)	< 1.0	35 (11–65)	5.3 (3–7)	3.8 (2–6)	–	2.1 (1–4)	9.9 (5–16)	< 1.0	–
Switzerland														
Wacker *et al.* (1990)	Background													
	Adipose[b]	(21)		CSO	0.8	3.3	48.5	8.3	7.4	–	8.0	1.2	–	0.4
	Liver[b]	(21)			0.2	2.3	7.3	3.7	4.7	–	1.8	1.6	–	0.2
Taiwan														
Ryan *et al.* (1994)	Control children; seum		91	BSW	< 5	–	19			25		34	–	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
United Kingdom														
Duarte-Davidson *et al.* (1993)	Wales, 5 pools; adipose	(5)	90/91	CSO	< 10	13	24 (20–27)	26 (18–42)	15 (9–27)	–	–	34 (24–49)	–	46 (36–62)
United States														
Ryan *et al.* (1985c)	NY State; adipose	(6)	83/84	CSOW	–	–	14.7 ± 2.5 (10.9–17.0)		28.7 ± 7.2 (15.1–52.8)	–	–	16.4 ± 4.0 (12.5 ± 23.8)	–	–
Ryan *et al.* (1986)	NY State		< 83	BSIW										
	Adipose (mean LC, 67%)	(3)			–	–	13.9 (6.5–17)		32.4 (ND–52)	–	–	12.1 (ND–24)	–	–
	Liver (mean LC, 24%)	(3)			–	–	4.1 (ND–6.9)		9.9 (4.2–17)	–	–	3.3 (ND–7.7)	–	–
	Adrenal (LC, 28 and 25%)	(2)			–	–	4.9–5.5		8.5–11	–	–	3.5–4.5	–	–
	Bone marrow (LC, 26%)	(1)			–	–	4.4		9.4	–	–	2.7	–	–
	Muscle (mean LC, 11%)	(3)			–	–	1.1 (ND–2.3)		2.4 (1.7–3.4)	–	–	ND	–	–
	Kidney (LC, 3.0 and 4.0%)	(2)			–	–	ND		ND	–	–	ND–1.7	–	–
Ryan (1986)	NY State, one man, 22 years old		85	BSIW										
	Adipose (LC, 83%)	(1)			–	–	4.2	–	–	–	–	–	–	–
	Liver (LC, 4.4%)	(1)			–	–	2.6	–	–	–	–	–	–	–
Schecter *et al.* (1986a)	Binghamton; adipose[b]	(1)	83–84	CRO	< 2	–	12.5	11.4	5.6	–	–	16.3	ND	< 20
		(1)			4.1	–	10.9	9.3	5.8	–	–	13.7	ND	< 20
		(1)			< 2	–	17.0	13	8.8	–	–	12.5	19.6	1.2
		(1)			< 2	–	16.5	22.9	15.4	–	–	23.8	20.6	1.5

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
United States (contd)														
Schecter *et al.* (1986a) (contd)	Adipose; LC, 70.6% (46%–88%)	(8)	< 85	BNW	–	–	14.3 (3.1–19.7)		31.3 (15.1–46.9)	–	–	16.5 (12.5–23.8)	–	–
Stanley *et al.* (1986)	US general population; adipose	(46)	82	BSO	9.1 ± 9.6 (< 2–32)	–	27 ± 16 (< 1.8–77)		18 ± 8.3 (2.9–55)	–	–	18 ± 12 (< 10–55)	–	60 ± 110 (< 2–360)
Nygren *et al.* (1988)	Era control; serum	(1)	< 88	BSIW	< 18	–	10	3.1	2.2	–	< 4	13.6	–	–
		(1)			< 0.1	–	16.4	17.6	12.6	–	< 3	23	–	–
		(1)			2.6	–	27	26	19	–	4.8	51	–	–
		(1)			10.4	–	51	10.4	3.6	–	< 1.5	12.6	–	–
		(1)			< 0.4	–	5.3	4.4	2.8	–	< 2	10	–	–
		(1)			0.6	–	10.9	8.5	5.4	–	1.4	10.7	–	–
		(1)			< 2.0	–	14.1	10.3	6.5	–	< 2.5	16.4	–	–
Schecter *et al.* (1989b)	One person		< 89	N										
	Fat[b]				–	–	17		52	–	–	15	–	–
	Abdomen	(1)												
	Subcutaneous	(1)			–	–	17		22	–	–	12	–	–
	Adrenal[b]	(1)			–	–	4.9		8.5	–	–	3.5	–	–
	Bone marrow[b]	(1)			–	–	4.4		9.4	–	–	2.7	–	–
	Liver[b]	(1)			–	–	ND		4.2	–	–	2.1	–	–
	Muscle[b]	(1)			–	–	1.1		2.1	–	–	ND		
	Kidney[b]	(1)			–	–	ND		2.1	–	–	ND		
	Lung[b]	(1)			–	–	ND		ND	–	–	ND		
Schecter *et al.* (1990b; 1991a)	Plasma	(20)	< 90		1.3	–	6.1	6.9	5.4	–	1.2	25.1	–	< 3
	Adipose	(20)	< 90	BSOW	1.6	–	6.8	5.6	3.7	–	1.5	16.4	–	< 1
	Whole blood	(4)	88/89		3.0	–	70.5	22.7	23.5	–	8.2	29	–	–
	Adipose	(4)	88/89		3.9	–	70.8	14.5	17.8	–	5.3	23.3	–	4.2
Kang *et al.* (1991)	Adipose		78	N										
	Viet Nam veterans	(36)			2.9	1.7	23.1	21.5	10.7	1.5	3.8	37.4	2.2	3.6
	Non-Viet Nam veterans	(79)			2.4	1.1	22.2	19.3	9.9	0.9	3.2	32.9	1.9	4.5
	Civilians	(80)			3.3	1.9	23.3	23.2	12.0	0.9	3.6	39.1	2.2	3.4

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
United States (contd)														
Piacitelli *et al.* (1992)	Referents; serum	(79)	87/88	BSIW	1.2	–	11 (3.3–28)	11 (4.2–28)	8.5 (3.7–18)	–	1.5	20 (2 pos.) (8.7–46)	0.8	1.1
Patterson *et al.* (1994)	General population; adipose	(4)	84/86	BSIW	1.1 (0.7–1.8)	–	3.7 (3.3–4.3)	3.7 (3.2–4.1)	5.8 4.0–8.3)	–	–	12.0 (8.9–15)	–	–
Schecter *et al.* (1994b)	Placenta; pool	(14)	< 94	BSOW	1.9	< 1.0	3.6	4.0	2.0	1.7	< 1.0	6.3	< 1	< 5
	Placenta	(1)	< 94		0.5	0.5	6.8	8.6	1.8	0.8	< 0.2	4.6	< 0.6	4
	Blood, pool	(50)	< 94		2.3	1.2	8.8	10.6	6.9	2.8	2.8	19.6	3.1	9.3
	Fetal tissue, 8–14 weeks, pool	(10)	94		1.3	< 0.2	1.1	2.2	1.0	–	1.5	3.1	< 0.9	< 3.2
Schecter *et al.* (1996c)	Adipose	(5)	96	BSNW	0.59	0.45	2.6	4.3	2.3	0.12	1.2	6.5	0.3	0.8
	Blood, before nursing	(5)	96	BSNW	0.87	0.52	3.0	5.9	3.4	ND	1.7	8.9	ND	1.9
	Placenta	(5)	96	BSNW	0.61	0.58	4.0	3.3	1.8	ND	0.53	2.7	0.52	2.2
	Cord blood	(5)	96	BSNW	< 1.2	< 0.7	0.87	1.5	1.5	ND	1.4	3.5	ND	< 5
	Mother's milk	(5)	96	BSNW	0.49	0.37	2.8	3.9	2.4	ND	1.4	5.4	0.53	< 2.9
Schecter *et al.* (1996d)	Blood pool	(100)	96	BSIW	< 2.0	< 1.4	11.1	14.1	7.9	3.5	< 3.7	12.0	< 4	< 5
	Serum pool	(100)	96		< 2.0	< 1.9	9.3	14.0	7.9	4.0	< 4.1	13.9	4.9	< 5
Viet Nam														
Schecter *et al.* (1986b)	N. Viet Nam; adipose (LC, 50%)	(7)	84	BSOW	–	–	9.7		9.3	–	–	4.2	–	–
	S. Viet Nam; adipose (LC, 60%)	(13)			–	–	13.0		31.7	–	–	17.0	–	–
Schecter *et al.* (1986c)	N. Viet Nam; adipose (LC, 56%)	(9)	84	BSOW	–	–	14.7 (ND–29.4)			13.3 (ND–20)		7 (ND–10.7)	–	–
	S. Viet Nam; adipose (LC, 62%)	(15)			–	–	21.0 (4.3–45.5)			58.3 (13.6–166.7)		28.9 (4.2–74.9)	–	–
Schecter *et al.* (1989c)	S. Viet Nam; adipose	(27)	84–88	ABN	7 (ND–17)	–	–	–	–	–	–	–	–	–

Table 21 (contd)

Reference	Origin; sample description (and no.)		Coll. period	Anal. meth.	PCDF concentration (ng/kg, lipid-based)									
					TCDF	PeCDF		HxCDF				HpCDF		OCDF
					2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Viet Nam (contd)														
Nguyen *et al.* (1989)	Ho Chi Minh City; adipose[b] (mean LC, 76%)	(9)	84/85	BSNW	–		13 (4.3–23)			49 (14–93)			29 (7.8–72)	–
Huteau *et al.* (1990b)	S. Viet Nam; Adipose	(27)	< 90	BSO	1.9 (20 pos.) (0.8–3.9)	4.1 (10 pos.) (1.0–16.8)	25 (21 pos.) (6.5–67.8)	26.2 (22 pos.) (1.4–121)	26.2 (22 pos.) (1.4–121)	8.9 (14 pos.) (2.0–38.9)	9.2 (2 pos.) (8.6–9.8)	47.3 (17 pos.) (9.5–238)	–	–
Schecter *et al.* (1990c)	Adipose		80s	BSO										
	N. Viet Nam	(10)			1.4	0.6	9.1	4.6	4.0	1.7	ND	8.0	0.3	2.2
	S. Viet Nam	(13)			0.8	0.7	7.4	6.4	5.1	0.8	–	13.2	0.2	1.6
Schecter *et al.* (1990d)	Liver, stillborn infants	(1)	< 89	BSOW	0.5	0.8	2.4	5.6	2.6	< 0.2	0.6	3.9	< 0.2	< 0.3
		(1)			1.2	2.3	2.6	5.7	3.8	< 0.4	0.8	6.6	< 0.5	< 0.7
		(1)			0.9	0.6	2.2	2.5	1.5	< 0.3	0.3	2.8	< 0.3	< 0.5
Schecter *et al.* (1992)	Blood		< 91	BSOW										
	N. Viet Nam; pool	(82)			4.6	1.7	7.6	20.6	11.1	0.5	2.2	46.7	1.9	4.2
	S. Viet Nam; pool	(383)			2.4	2.0	9.3	23.9	14.7	0.8	2.6	42.7	3.8	4.4
Schecter *et al.* (1995)	Blood		91/92	BSOW										
	S. Viet Nam; pool	(433)			2.1	1.8	8.3	21.1	13	0.7	2.3	37.6	3.4	3.9
	Centr. Viet Nam; pool	(183)			2.9	2.2	14.9	67.4	40.0	0.9	3.0	75.7	1.9	5.1

Data presented are means and, if available, ± standard deviation, with range in parentheses, unless otherwise indicated. Levels of congeners not detected at a known detection limit (for example, 4.2 ng/kg) are presented as < 4.2 when detection limit is given.

Explanation for analytical methods: All analyses use high-resolution gas chromatography: B, HRMS; C, LRMS; I, isomer-specific; O, others; N, no information; S, sophisticated clean-up; R, reduced clean-up; W, WHO-accepted laboratory; –, not reported; ND, not detected; LC, lipid content; pos., positive; S, south; N, north; Centr., central; [ ] Calculated by the Working Group

Summed TEQ values for PCDDs/PCDFs in these studies are given in Table 25 of the monograph on PCDDs in this volume.

[a] Overlap between these studies

[b] Concentrations on wet weight-basis

[c] Contained also 5.5 and 4.7 ng/kg 1,2,7,8-TCDF, respectively

[d] 150 fishermen and 150 controls between all groups

1.4.1 *Blood and tissue samples*

(*a*) *Austria*

Samples of milk from cows grazing in the vicinity of a metal reclamation plant showed significantly higher PCDD/PCDF levels than control samples. In the blood of two farmers, an increase in levels of certain PCDD and PCDF isomers was found. The highest PCDF value in one sample was 2,3,4,7,8-PeCDF at 839 ng/kg (Riss *et al.*, 1990).

(*b*) *Canada*

Ryan *et al.* (1985b) reported that some samples of adipose tissue from older subjects (> 60 years old) who had died in Ontario hospitals in 1979–81 contained small (mean, 3 ng/kg) amounts of 2,3,7,8-TCDF and larger amounts of 2,3,4,7,8-PeCDF (mean, 17 ng/kg).

(*c*) *China*

Human adipose tissue from seven patients (four men, three women; mean age, 54 years) undergoing general surgery in Shanghai was analysed by Ryan *et al.* (1987). Compared with data from other countries, the values for most congeners were low. [The presence of 1,2,7,8-TCDF suggests that sample contamination (from paper/pulp products) may explain, in part, the relatively high levels of 2,3,7,8-TCDF.]

(*d*) *Finland*

In conjunction with a study of possible effects of PCDDs and PCDFs on pulp and paper mill workers in Finland (Rosenberg *et al.*, 1995) (see also Section 1.3.1(*a*)(vii)), measurements were made in a comparison group with no known exposure (n = 14; mean age, 41 years). The mean I-TEQ level in blood plasma was 49 ng/kg (range, 20–99 ng/kg) (see monograph on PCDDs in this volume, Section 1.4.1). 2,3,4,7,8-PeCDF represented about one-third of the TEQ.

(*e*) *France*

Measurements of PCDDs and PCDFs in adipose tissue from eight persons living in Paris were reported by Huteau *et al.* (1990a). Most of the 2,3,7,8-substituted isomers were found, in some cases at unexpectedly high values (2,3,7,8-TCDF, 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF). Surprisingly, non-2,3,7,8-substituted isomers were also reported at relatively high values (TCDFs, TCDDs, HpCDFs). [Sample contamination cannot be excluded.]

(*f*) *Germany*

Age-related increases in blood levels of 2,3,4,7,8-PeCDF and the HxCDFs as well as I-TEQ have been reported (Schrey *et al.*, 1992; Sagunski *et al.*, 1993; Päpke *et al.*, 1996). No or very little age-dependence was observed for 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, HpCDF or OCDF.

The Kieselrotstudie (Wittsiepe *et al.*, 1993) was designed to assess the degree of exposure to PCDDs and PCDFs in 56 persons living in the vicinity of a former copper

smelter located in Marsberg (see Section 1.3.2(*c*)). The median I-TEQ values of the Marsberg subjects (43.2 ng/kg) and a reference group from Steinfurt (43.0 ng/kg) were similar, whereas the mean of the Marsberg group (52.7 ng/kg) was higher than that of the control group (44.4 ng/kg). The individuals of the Marsberg group had significantly higher levels of PeCDFs, HxCDFs and HpCDFs on average than the individuals of the reference group.

Near a metal reclamation plant in Rastatt, Baden-Württemberg, PCDD/PCDF contamination of soil, dust from homes, indoor air and vegetables was investigated in 1987. Blood samples from 22 volunteers living in the vicinity of the plant were analysed for PCDDs/PCDFs. Levels of certain Pe-, Hx- and HpCDF isomers were increased, in a similar pattern to the contamination throughout the area. The increase in PCDD/PCDF levels was attributed to occupational exposure in the case of workers and to food intake in the other cases. For children (four samples), soil and/or dust ingestion may be a pathway of special importance (Wuthe *et al.*, 1990).

No correlation was seen between adipose tissue or liver concentrations and age or sex in 28 subjects aged between 26 and 80 years (Thoma *et al.*, 1989, 1990). Large differences in the concentrations of PCDDs and PCDFs between adipose and liver were demonstrated for most of the isomers. Thoma *et al.* (1990) also reported concentrations of PCDDs and PCDFs in adipose tissue from eight infants (age, 2–12 months). The levels were lower than in adults for nearly all isomers (see **Table 22**).

Table 22. Concentrations of PCDF isomers in adipose and liver tissues from German adults and adipose tissues of infants

Compound	Adult; ratio liver : adipose	Adipose tissue; ratio infant : adult
TCDF	2.20	0.75
PeCDF	4.93	0.36
HxCDF	9.38	0.22
HpCDF	15.43	0.23
OCDF	7.43	1.02

From Thoma *et al.* (1989, 1990)

Background data on PCDDs and PCDFs in human blood from Germany published by Päpke *et al.* (1989b) have been updated since 1991 by various authors (see Table 27 of the monograph on PCDDs in this volume). The results suggest a decrease in PCDD/PCDF blood levels in Germany over the past decade.

(*g*) *Japan*

The first reports of PCDDs/PCDFs in human tissue from the general population were presented by Miyata *et al.* (1977) in connection with the *yusho* poisoning in Japan. Levels of PCDFs (isomers not separated) in the range of 17–45 ng/kg were reported in

four of six fat and in one of four liver biopsy/autopsy samples taken from the general Japanese population. At that time, no TCDFs or HxCDFs were detected.

Kashimoto *et al.* (1985) detected PCBs and PCQs in blood of *yusho* and *yucheng* patients. PCDFs were found only in *yucheng* patients. In 60 unexposed individuals, PCDFs were not detected at a detection limit of 10 ng/kg (in whole blood).

Thirteen samples of human adipose tissue from cancer patients were analysed for tetra- to octa-CDDs and -CDFs (Ono *et al.*, 1986). These compounds were identified in all of the analysed samples. Total PCDF concentrations were in the range of 7–120 ng/kg on a wet weight basis, and 2,3,4,7,8-PeCDF levels ranged from 4 to 71 ng/kg.

(*h*) *Taiwan*

In connection with the determination of blood serum levels of PCDFs (and PCBs) in *yucheng* children perinatally exposed to contaminated rice oil, Ryan *et al.* (1994) analysed a matched control population. The total PCDD/PCDF profile for the two pooled control sera from the matched children were very similar. The mean of two measurements was given, with an I-TEQ of 12.6 ng/kg for PCDFs. The characteristic '*yucheng* isomers', 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF, showed levels 10–15 times and 15–25 times, respectively, higher in the exposed children than in the matched controls.

(*i*) *United Kingdom*

PCDD/PCDF background data were measured in pooled human adipose tissue samples from five areas in Wales (Duarte-Davidson *et al.*, 1993). With the exception of OCDF, which was found at unexpectedly high values in all pooled samples (36–62 ng/kg), the concentrations were similar to those in other industrialized countries. 2,3,7,8-TCDD and 2,3,7,8-TCDF were not detected at detection limits of 10 ng/kg.

(*j*) *United States*

Six samples from both biopsy and autopsy fat taken in 1983–84 from New York State residents were analysed (Ryan *et al.*, 1985c). PCDDs and PCDFs were found in all samples with total (Cl_4–Cl_8) PCDD levels about an order of magnitude higher than total (Cl_5–Cl_7) PCDFs. Only the penta-, hexa- and hepta-PCDF congeners were detected, at levels that were of the same order of magnitude (15–29 ng/kg). TCDF and OCDF were absent.

The tissue distribution of PCDDs and PCDFs was studied in three autopsy subjects from the general population of New York State (Ryan, 1986; Ryan *et al.*, 1986). These were the first reports to show that several 2,3,7,8-chlorine substituted PCDDs/PCDFs are present not only in adipose tissues from the general population, but also in all other tissues assayed. The ratios of the PCDD/PCDF congeners to each other were similar in each tissue, with overall levels on a wet weight basis decreasing in the order fat, adrenal, bone marrow, liver, muscle, spleen, kidney and lung. If the levels are expressed on a lipid basis rather than on a wet weight basis, liver had the highest value and the variation between tissues showed only a two- to four-fold difference.

Analysis for Cl_4–Cl_8 PCDDs/PCDFs was performed for 46 adipose tissue samples prepared from the United States Environmental Protection Agency National Human

Adipose Tissue Survey (NHATS) as composites from over 900 specimens to represent the nine United States census divisions and three age groups (0–14, 15–44 and ≥ 45 years) (Stanley *et al.*, 1986). The results demonstrate that PCDDs/PCDFs are prevalent in the general United States population and that differences exist with age. Only means and ranges of all data were reported.

A comparison of PCDD/PCDF levels in whole blood, plasma and adipose tissue was performed by Schecter *et al.* (1994b). There were few differences in PCDD/PCDF levels between blood, plasma and adipose tissue and also between whole blood and adipose tissue when reported on lipid basis. Total PCDDs/PCDFs appeared higher in plasma than in adipose tissue, if reported by actual measurement. Comparing whole blood with adipose tissue, values were more similar.

PCDDs and PCDFs in adipose tissue of United States Viet Nam veterans and controls were determined by Kang *et al.* (1991). The samples were collected in 1978. The geometric mean (± SD) 2,3,7,8-TCDF levels in adipose tissue for Viet Nam veterans, non-Viet Nam veterans and civilian controls were 2.9, 2.4 and 3.3 ng/kg, respectively. The mean levels for all isomers for these groups were not significantly different from each other.

In a study by Schecter *et al.* (1994b), levels of PCDDs and PCDFs in placenta, blood and fetal tissue were measured. The highest I-TEQ values (lipid-based) were found in blood, followed by placenta. The fetal tissue contained approximately one third of the I-TEQ of the adult values.

In a further study of partitioning of PCDDs/PCDFs in human maternal tissues, including blood, milk, adipose tissue and placenta, Schecter *et al.* (1996c) collected samples from five American women (mean age, 21.6 years; range, 21–34 years) residing in upstate New York and undergoing caesarean section deliveries between September 1995 and January 1996. Blood, placenta and fat were collected at the time of delivery. The milk and second blood were collected about four to eight weeks later. The lowest concentrations were found in the cord blood, at about one half of the maternal adipose and blood levels. A reduction in PCDD/PCDF levels was observed in the 'second' blood samples after a breast-feeding period of between four and eight weeks.

PCDD/PCDF levels in two pools of whole blood and serum (n = 100) collected in 1996 were compared with older blood data; a decrease was not clearly shown. Mean age of the blood donors was not specified (Schecter *et al.*, 1996d).

(*k*) *Viet Nam*

Adipose tissue samples from south Viet Nam were compared with those from north Viet Nam (where there was no exposure to Agent Orange) (Schecter *et al.*, 1986b). 2,3,7,8-TCDF was not detectable. Most of the other chlorinated PCDFs were found at higher values in samples from south Viet Nam. A further 27 individual and 10 pooled human adipose tissue specimens, collected from persons in south and north Viet Nam, respectively, were analysed for 2,3,7,8-TCDD and 2,3,7,8-TCDF (Schecter *et al.*, 1989c). The mean values were 19 ng/kg 2,3,7,8-TCDD and 7 ng/kg 2,3,7,8-TCDF in the

samples from persons in the south; no 2,3,7,8-TCDD or 2,3,7,8-TCDF was detected in samples from persons in the north.

PCDD/PCDF levels in 27 adipose tissue samples from south Viet Nam were reported by Huteau *et al.* (1990b). Besides the usual 2,3,7,8-substituted isomers, they found non-2,3,7,8-substituted isomers in many samples. [Sample contamination cannot be excluded.]

In connection with analysis of blood samples from various geographical locations for PCDDs/PCDFs, Schecter *et al.* (1992) reported results for pooled samples from north Viet Nam (two analyses with a total of 82 persons) and south Viet Nam (nine analyses totalling 383 persons). The I-TEQ values for samples from north and south Viet Nam were 15 and 36 ng/kg, respectively.

1.4.2 *Human milk*

There have been a large number of studies of PCDD/PCDF concentrations in human milk. Many of the available results are shown in **Table 23** and summarized in **Table 24**. In terms of the I-TEQ concentrations, PCDFs account for between 17 and 78% of the total in human milk. The discussion in Section 1.4.2 of the monograph on PCDDs in this volume is equally applicable to PCDFs.

1.5 Regulations and guidelines

In Germany, an occupational technical exposure limit value of 50 pg I-TEQ/m^3 in air has been established for PCDDs and PCDFs (Deutsche Forschungsgemeinschaft, 1996).

At present, the regulatory requirements for incinerator emissions vary widely among the countries of the European Union. The European Union (1994) published a 'Council Directive on the incineration of hazardous waste' which would require that "the emission of PCDDs and PCDFs shall be minimized by the most progressive techniques" and which defines 0.1 ng/m^3 as a guide value which should not be exceeded by all average values measured over the sample period of 6–16 h.

Germany and the Netherlands have set daily average limit values of 0.1 ng I-TEQ/m^3 of exhaust gases for PCDDs/PCDFs from industrial waste incinerators, Sweden 0.1–0.5 ng TEQ/m^3, and the United Kingdom 1 ng I-TEQ/m^3 with a goal to reduce PCDD/-PCDF emissions from industrial and municipal waste incinerators to 0.1 ng/m^3 (ECETOC, 1992; Liem & van Zorge, 1995).

In Germany, sewage sludge used as a fertilizer for farmland is not allowed to contain more than 100 ng I-TEQ/kg dry matter (Ordinance on Sewage Sludge, 1992; Liem & van Zorge, 1995).

The Canadian Government has proposed a tolerable daily intake (TDI) value of 10 pg I-TEQ/kg bw per day for PCDDs and PCDFs (Government of Canada, 1993).

In Japan, a limit of 0.5 ng I-TEQ/m^3 2,3,7,8-PCDD/PCDF is recommended for municipal waste incinerators (Liem & van Zorge, 1995).

For milk and milk products, a maximal tolerable concentration for PCDDs/PCDFs of 17.5 ng I-TEQ/kg fat has been set in the United Kingdom. In Germany, PCDDs/PCDFs

Table 23. Concentrations of PCDFs in human milk

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Albania													
WHO (1996)	Librazhd; unpolluted area (WHO criteria)	10	92–93	0.3	0.2	3.7	1.4	1.2	< 0.1	0.8	2.7	0.1	0.3
	Tirana; polluted area (WHO criteria)	10	92–93	0.4	0.3	4.7	1.7	1.5	< 0.1	0.8	1.3	0.1	0.1
Austria													
WHO (1996)	Brixlegg; industrial area (WHO criteria)	13	92–93	0.9	0.3	13.5	3.5	2.6	< 0.1	1.3	4.6	0.1	2
Yrjänheikki (1989)	Tulln (WHO criteria)	51	86–88	3.9	1.3	16.9	5.3	4.8	ND	2.3	8.7	–	15.4
WHO (1996)	Tulln; rural area (WHO criteria)	21	92–93	0.6	0.2	8.5	3.4	2.3	< 0.1	1.2	2.6	0.1	2
Yrjänheikki (1989)	Vienna (WHO criteria)	54	86–88	4.4	1	16.2	4.8	3.6	ND	1.8	6.5	–	18.2
WHO (1996)	Vienna; urban area (WHO criteria)	13	92–93	0.7	0.2	9.2	3.3	2.1	< 0.1	1	4.9	0.1	5.9
Belgium													
Yrjänheikki (1989)	Industrial (WHO criteria)	–	86–88	6.2	2.9	32	14	6.5	1.4	6.6	7.3	–	0.3
	Rural (WHO criteria)	–	86–88	3.3	1.4	35	16	7.6	–	7	12	–	–
	Urban (WHO criteria)	–	86–88	4	1.3	32	13	6.1	3.3	–	2.2	–	5
WHO (1996)	Brabant Wallou (WHO criteria)	8	93	0.5	0.3	20.1	5.2	4.7	< 0.1	2.2	3.2	0.1	0.3
	Brussels (WHO criteria)	6	93	0.6	0.3	22	5.4	4.8	< 0.1	2.4	4.1	0.2	1.2
	Liege (WHO criteria)	20	93	0.7	0.3	26.7	5.8	5.3	0.1	2.1	3.8	0.1	0.3
Cambodia													
Schecter *et al.* (1991b)	Phnom Penh	8		0.52	0.32	1.6	0.74	0.79	< 0.5	0.41	2.2	< 0.5	2.4

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Canada													
WHO 1996	All provinces (WHO criteria)	200	81	4.2	< 1	13		17	< 1	4.3	15	< 1	< 2
	All provinces (WHO criteria)	100	92	1.4	< 1	6.2		8.1	< 1	2.3	9.2	< 1	< 2
Yrjänheikki 1989	British Columbia	23	86–88	2.4	< 1	10.3	5.2	4.3	< 1	2.2	7.6	–	< 2
	Maritimes	19	86–88	8	< 1	6.7	3.5	2.2	< 1	< 1	5.6	–	< 2
	Ontario N & E	32	86–88	2.9	< 1	7.4	3	2.7	< 1	1.5	3.8	–	< 2
	Ontario SW	44	86–88	1.8	< 1	9.1	3.6	2.8	< 1	1.5	5	–	< 2
	Prairies	31	86–88	5.7	< 1	5.6	4.8	4.2	< 1	2	6	–	< 2
	Québec	34	86–88	4	1.7	7.1	4.2	3.5	< 1	1.3	6.2	–	< 2
Dewailly *et al.* (1991)	Québec (rural area)	16	86–88	6.1	–	5.2	3.3	2.3	–	1.1	4.5	–	–
Croatia (Yugoslavia)													
Yrjänheikki (1989)	Krk (WHO criteria)	14	86–88	< 3.1	0.9	11.3	2.6	3	–	1.3	2.1	–	–
	Zagreb (WHO criteria)	41	86–88	< 2	< 0.9	9.7	3.2	2.9	–	1.6	1.9	–	–
WHO (1996)	Krk (WHO criteria)	10	93	0.4	0.2	7.9	2.5	2	< 0.1	0.8	1.7	0.1	0.3
	Zagreb (WHO criteria)	13	93	0.9	0.6	13.5	4	3.5	< 0.1	1.7	2.8	0.1	0.3
Czech Republic													
WHO (1996)	Kladno (WHO criteria)	11	93	0.9	0.4	16.3	5.7	3.8	< 0.1	1.1	3.4	0.1	0.2
	Uherske Hradiste (WHO criteria)	11	93	1.1	0.4	25.5	7.3	4.7	< 0.1	1.8	2.9	0.1	0.2

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Denmark													
Yrjänheikki (1989)	WHO criteria	10	86–88	1.2	–	12.8	7	5	–	1.5	8.5	–	–
	Pool	42	86~	1.2	–	12	5.6	4.4	–	1.5	8.8	–	–
WHO (1996)	7 cities (WHO criteria)	48	93	0.5	0.2	11.1	3.5	3	0.1	1.2	6.1	0.1	0.4
Abraham *et al.*	Faeroe Islands	1	94~	< 0.5	< 0.5	7	3	2.4	–	< 0.5	2.4	–	< 2
(1995b)		1	94~	1.6	< 0.5	6.2	5.4	3.5	–	2.2	5.3	–	< 2
		1	94~	1	< 0 .5	6	6	4.5	–	< 0.5	6.2	–	2.8
		1	94~	< 3	< 3	5.3	< 3	< 3	–	< 3	9.4	–	9.2
	pool	9	94~	0.7	< 0.2	4.2	2.5	1.9	–	0.9	1.6	–	< 0.5
Estonia													
Mussalo-Rauhamaa	Tallinn (primipara)	6	91	0.7	0.2	12.8	4.7	2.5	< 0.1	0.4	1.9	< 0.1	0.9
& Lindström (1995)	Tarto (primipara)	6	91	1.3	0.2	23.8	3.6	2.6	< 0.1	0.8	3.9	< 0.1	1.2
Finland													
Yrjänheikki (1989)	Helsinki (WHO criteria)	38	86–88	0.3	0.2	15	2.6	1	< 0.5	2	8.8	–	1.6
WHO (1996)	Helsinki (WHO criteria)	10	93	1.1	0.5	19	4.5	3.5	0.1	1.5	9.9	0.1	1.9
Yrjänheikki (1989)	Kuopio (WHO criteria)	31	86–88	0.3	0.3	14	2.9	1.3	< 0.5	2.3	12	–	1.9
WHO 1996	Kuopio (WHO criteria)	24	93	0.6	0.3	9.6	2.6	2.1	< 0.1	0.9	6.9	0.1	0.3
France													
González *et al.* (1996)	Paris	15	90	1.8	0.5	16.5			20.4			45	19

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Germany													
Beck *et al.* (1992a)	Mother having 1, 2 or 3 children	728	82–92	ND	ND	28.3	ND	ND	ND	ND	ND	ND	ND
	1 child	34	NR	2.1	1	13	5.1	5.7	–	2.7	5.9	–	0.3
	2 children	23	NR	2.9	1	24	8.6	8.9	–	3.6	9.9	–	1.8
	3 children	34	NR	2.9	1	18	7.4	7.2	–	2.9	7.6	–	0.9
Frommberger (1990)	Baden-Württemberg	490	88–89	4.2	0.3	38	7.9	5.9	–	2.9	6.8	–	1
Beck *et al.* (1987)	Berlin	30		2.5	< 1	20	8.7	7.8	–	3	8.5	–	< 3.1
Beck *et al.* (1989c)	Berlin	35		2.8	1	21	8.6	7.9	–	3.2	8.6	–	3
Yrjänheikki (1989)	Berlin (WHO criteria)	40	86–88	1.4	0.7	22	8.7	7.7	–	2.7	13	–	0.9
WHO (1996)	Berlin (WHO criteria)	10	93	< 0.4	< 0.4	11.9	5.5	4.4	< 0.4	1	3.3	< 0.1	< 0.1
Beck *et al.* (1989c)	Flensburg (Baltic coast)	6		1.6	0.6	25	8.7	8.4	–	2.6	9.3	–	0.3
Fürst *et al.* (1992b)	North-Rhine Westphalia	526	84–91	1.7	0.5	26.7	7.8	6.5	–	3.4	5.5	–	1.4
Yrjänheikki (1989)	North-Rhine Westphalia (WHO criteria)	79	86–88	2.3	0.6	30	8.2	6.7	< 0.5	3.8	5.3	–	7.2
Yrjänheikki (1989)	Oldenburg (WHO criteria)	35	86–88	2.4	0.9	23.7	15.2	15	ND	6.2	12.8	–	6.7
Beck *et al.* (1989c)	Recklinghausen; industrial area	10		1.4	0.7	22	7.7	9.2	–	3.1	13	–	4
Yrjänheikki (1989)	Recklinghausen (WHO criteria)	23	86–88	1.4	0.9	26	8.5	8	ND	3	8.4	–	1.3
Beck *et al.* (1989c)	Rheinfelden (rural area/PCP manuf.)	9		5.8	1.3	24	11	9.7	ND	3.9	12	ND	1.5
Beck *et al.* (1989c)	Weiden; rural area	14		3.3	1.1	22	7.4	7.5	–	3.3	8.7	–	0.7

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Hungary													
Yrjänheikki (1989)	Budapest (WHO criteria)	100	86–88	0.5	< 0.5	5.7	< 2	< 2	–	0.5	3.3	–	6.5
WHO (1996)	Budapest (WHO criteria)	20	93	0.3	0.2	5.9	2.6	2.1	< 0.1	0.8	2.8	0.1	0.2
Yrjänheikki (1989)	Szentes (WHO criteria)	50	86–88	0.7	< 0.5	7.6	< 2	< 2	–	0.4	< 2	ND	7.6
WHO (1996)	Szentes (WHO criteria)	10	93	0.4	0.3	5.6	2.5	2	< 0.1	1	2.7	0.1	0.3
Japan													
Schecter *et al.* (1989d)/Yrjanheikki (1989)	Fukuoka	6	86	3	1.3	26	4.5	3	< 1	2	4	–	< 2
Hirakawa *et al.* (1995)	Fukuoka (primipara)	7	94	2.3	0.6	11.4	4.3	4.5	1.9	2	2	0.2	2.7
Hirakawa *et al.* (1995)	Fukuoka (multipara)	8	94	2	0.6	7.8	3.3	3.2	1.6	1.5	2.1	0.7	3
Hashimoto *et al.* (1995b)	Various locations	26	93-94	1.7	1.6	38	6.5	6.8	1.2	4	4.2	5.9	3.6
Jordan													
Alawi *et al.* (1996b)	Amman; pool	4–6	94	< 3.2	< 3.2	< 3.2	<3.2	< 3.2	< 3.2	< 3.2	9.6	< 3.2	< 32
	Amman; pool		94	< 6.3	< 6.3	< 6.3	< 6.3	< 6.3	< 6.3	< 6.3	< 6.3	< 6.3	< 31
	Aqaba; pool		94	< 4.5	4.5	10.1	17.9	< 4.5	< 4.5	< 4.5	< 4.5	< 4.5	< 22
	Irbid; pool		94	8.3	11.1	75.9	161	104	7.4	54.6	391	106	189
	Madaba; pool		94	< 11	16.8	84.1	112	96.1	< 11	< 11	< 11	< 11	< 22
	Zarka; pool		94	< 2.6	2.6	4.4	5.2	4.4	< 2.6	<2.6	< 2.6	<2.6	<17
Kazakhstan													
Petreas *et al.* (1996)	WHO criteria	40	96	1.1	0.77	5.3	2.3	1.9	0.75	1.2	2.4	1	3

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Lithuania													
WHO (1996)	Anykshchiai; rural area (WHO criteria)	12	93	0.8	0.4	10.3	3.8	2.7	< 0.4	1.3	3.4	0.2	0.6
	Palanga; coastal area (WHO criteria)	12	93	1.1	0.4	16.4	4.1	3.2	< 0.2	1.6	1.8	0.1	0.2
	Vilnius; urban area (WHO criteria)	12	93	1.3	0.9	9.1	4	3	< 0.5	1.8	3.8	0.5	0.8
Netherlands													
Liem *et al.* (1995)	Primipara	103	93	0.4	0.2	18	5.2	4.4	–	2.4	6	0.1	0.3
Yrjänheikki (1989)	Rural area (WHO criteria)	13	86–88	3.1	0.8	24	7	6.3	ND	2.6	16	–	0.8
	Urban area (WHO criteria)	13	86–88	2.8	0.7	23	7.1	7.1	ND	ND	ND	–	2.4
WHO (1996)	WHO criteria	17	93	0.3	0.3	17.2	5.1	4.4	< 0.5	2.6	6	< 0.5	0.3
Norway													
Clench-Aas *et al.* (1992)	Hamar; rural area (WHO criteria)	10	85–86	4.1	0.8	11.4	4.6	2.7	0.7	1	5.5	–	1.2
WHO (1996)	Hamar; rural area (WHO criteria)	10	93	1.1	0.4	7.5	2	1.9	< 0.5	1.1	4.3	< 0.6	1.5
Clench-Aas *et al.* (1992)	Skien-Porsgrunn; Mg production (WHO criteria)	10	85–86	4.9	1.3	17.7	7.8	5.3	0.7	1.7	5.6	–	2.5
WHO (1996)	Skien-Porsgrunn; industrial area (WHO criteria)	10	93	1.2	0.5	10.9	4.5	3.7	< 0.5	1.4	5.2	< 0.6	1.3

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Norway (contd)													
Clench-Aas *et al.* (1992)	Tromsø; coastal area (WHO criteria)	11	85-86	4.3	0.8	12.9	3.6	2.6	0.7	0.9	6.2	–	1.1
WHO (1996)	Tromsø (WHO criteria)	10	93	1.8	0.3	7.6	1.9	1.7	< 0.3	1.4	18.7	< 0.5	3.3
New Zealand													
Buckland *et al.* (1990a)	Auckland (WHO criteria)	11	90~	0.8	0.35	4.9		5.9	< 0.6	0.71	6.2	< 0.5	< 6
	Christchurch (WHO criteria)	9	90~	0.74	0.23	5.8		7.7	< 0.9	0.84	7.4	< 0.8	< 6
	N. Canterbury (WHO criteria)	8	90~	0.78	0.2	6.6		8.8	< 0.6	0.91	7.8	< 0.7	< 6
	Northland (WHO criteria)	9	90~	1.1	0.22	4.7		8.6	< 0.7	1.1	7.5	< 0.7	< 8
Pakistan													
Schecter *et al.* (1990e)	Pool	7		1.2	< 4.3	6.5		5.8	< 3.9	1.5	4.3	< 3.5	< 6.6
WHO (1996)	Lahore (WHO criteria)	14	93	< 0.02	< 0.01	2.9	1.3	1.1	< 0.1	0.5	3.9	< 0.02	13.8
Poland													
Yrjänheikki (1989)	WHO criteria	5	86–88	1.7	4.3	15.4	18.6	10	–	5.9	35.1	–	–
Russian Federation													
WHO (1996)	Arkhangelsk	1	93	1.5	0.5	12.9	3.2	2.3	0.1	1	1.9	0.1	0.2
Schecter *et al.* (1990f)	Baikalsk; pool	5	88-89	2.7	1.3	9.6	8.2	3.2	< 0.5	0.6	1.4	< 0.5	0.4
	Irkutsk; pool	4	88-89	6.3	2.3	19	15	5	< 0.5	1.8	2.6	< 0.5	2
	Kachug; pool	4	88-89	2.8	1	7.4	5.7	2.2	< 0.5	0.7	0.6	< 0.5	0.5
WHO (1996)	Karhopol	1	93	0.7	0.2	5	1.4	0.9	< 0.1	0.3	0.8	0.1	0.1
Schecter *et al.* (1990f)	Moscow	1	88-89	1.9	0.4	11	4	2.5	< 0.5	1.1	1.5	< 0.5	0.8
	Novosibirsk; pool	10	88-89	1.7	0.8	8.4	5.4	2.4	< 0.5	0.8	0.7	< 0.5	1.5

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Slovakia													
WHO (1996)	Michalovce (WHO criteria)	10	93	1.1	0.4	21	5.8	3.5	< 0.1	1.1	5.5	0.1	0.2
	Nitra (WHO criteria)	10	93	0.8	0.5	14.5	5.4	4	0.1	1.4	2.7	0.1	0.3
South Africa													
Schecter *et al.* (1990e)	Pool												
	Black	6		0.8	0.3	2	2.4	1.8	0.6	0.6	5.2	0.6	6.1
	White	18		1.5	0.4	5.5	3.4	3.1	ND	1.3	4.7	0.4	2.8
Spain													
WHO (1996)	Bizkaia (WHO criteria)	19	93	0.9	0.4	16.9	5	4	0.1	1.5	3	0.2	0.5
	Gipuzkoa (WHO criteria)	10	93	0.7	0.4	20.9	6	4.7	0.1	2.2	3.1	0.1	0.2
González *et al.* (1996)	Madrid	13	90	1	0.7	0.9			30			7.2	18
Sweden													
Yrjänheikki (1989); Clench-Aas *et al.* (1992)	Borlänge; rural area	10	85–86	3.6	0.8	17	7	3.7	< 1.5	1.3	5.7	–	< 2.5
	Gothenburg; city (WHO criteria)	10	85–86	4.1	–	17.4	5.2	3.7	< 1.5	2.6	11.4	–	< 2.5
	Sundsvall; industrial (WHO criteria)	10	85–86	3.8	–	19.6	4	3.3	< 1.5	2	6.7	–	< 2.5
	Uppsala (MSWI) (WHO criteria)	10	85–86	3.7	–	17.1	5.3	4.4	< 1.5	2.4	12.1	–	< 2.5
Thailand													
Schecter *et al.* (1991b)	Bangkok	10		1.8	0.7	2.6	1.2	0.9	< 0.5	0.6	0.9	< 0.5	0.6

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
United Kingdom													
Wearne *et al.* (1996)	Cambridge (WHO criteria)	20	93–94	0.82	0.47	16	4.4	4	0.09	2.5	4	0.19	0.57
Startin *et al.* (1989)	Glasgow (WHO criteria)	50	87~	0.9	0.3	19	7.2	5	ND	2.3	7.1	–	6.9
Wearne *et al.* (1996)	Glasgow (WHO criteria)	20	93–94	0.78	0.3	15	4.2	3.6	< 0.1	2.2	4	0.15	0.81
Startin *et al.* (1989)	Sutton Coldfield (WHO criteria)	50	87~	1.4	0.5	25	8.3	7.8	ND	3.6	9.5	–	6.8
Wearne *et al.* (1996)	Birmingham (WHO criteria)	20	93–94	1	0.29	14	4.2	3.6	< 0.1	2	2.9	0.13	0.72
Ukraine													
WHO (1996)	Kiev (WHO criteria)												
	Area 1	5	93	0.8	0.6	9.5	7.1	4.4	0.2	1.3	5.7	0.8	1.9
	Area 2	5	93	0.8	0.5	9.9	7.1	4.6	0.2	1.3	4.6	0.7	1
United States													
Schecter *et al.* (1989d; 1994b; 1996a,b)	United States	43	88	2.85	0.45	7.3	5.6	3.2	< 0.75	1.9	4.1	< 1	4.1
Schecter *et al.* (1990e)	Tennessee; pool	9	–	1	< 1.5	4.1		7.8	< 1.4	1.2	8.1	< 2.7	< 5.8

Table 23 (contd)

Reference	Origin	No.	Coll. period	Mean PCDF concentration (ng/kg fat)									
				TCDF	PeCDF		HxCDF				HpCDF		OCDF
				2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Viet Nam													
Schecter *et al.* (1990e)	Binh Long; pool	4		1	1.3	7.1	8.8	6.7	< 1.3	2	13.2	< 3.5	< 7
Schecter *et al.* (1991b); Schecter (1994)	Da Nang	11	85–90	2.2	4.1	17	34	18	< 0.5	10	40	< 0.5	7.4
	Dong Nai	11	85–90	1.6	1	13	19	11	< 0.5	2.1	6.2	< 0.5	0.9
	Hanoi	30	85–90	2	1	6.1	4.2	3.1	< 0.5	1.4	3.4	< 0.5	2.1
	Ho Chi Minh	38	85–90	2.8	1.4	8.1	5.7	3.6	< 0.5	1.6	8	ND	2.6
	Song Be	12	85–90	2	2	8.7	12	7.8	< 0.5	2.7	10	ND	1.8
Schecter *et al.* (1990e)	Tay Ninh; pool	4		1.1	2	10.9		16.3	< 2.4	3.1	14.9	< 5.9	< 14
	Vung Tau	5		2	1.4	9.3	9.5	5.4	0.7	1.6	11.8	< 4.9	< 7

ND, not detected and detection limit not reported; –, not reported
WHO criteria are described in Section 1.4.2 of the monograph on PCDDs in this volume.
Summed TEQ values for PCDDs/PCDFs in these studies are given in Table 29 of the monograph on PCDDs in this volume.

Table 24. Summary of concentrations (ng/kg fat) of PCDFs in human milk (as reported in Table 23)

	TCDF	PeCDF		HxCDF				HpCDF		OCDF
	2378	12378	23478	123478	123678	123789	234678	1234678	1234789	
Mean	2.0	1.1	15	8.4	6.6	1.1	2.6	9.9	3.2	5.7
Minimum	0.3	0.2	0.9	0.74	0.79	0.09	0.3	0.6	0.1	0.1
5th percentile	0.4	0.2	4.2	1.6	1.3	0.1	0.58	1.5	0.1	0.2
25th percentile	0.8	0.3	7.3	3.5	2.7	0.1	1.1	3.3	0.1	0.4
Median	1.4	0.6	12	5.2	4.1	0.5	1.6	5.6	0.1	1.5
75th percentile	2.8	1	19	7.3	6.6	1.4	2.4	8.5	0.4	3.4
95th percentile	5.7	3.9	31	17	16	3.3	6.3	15	5.9	17
Maximum	8.3	17	84	161	104	7.4	55	391	106	189

must not exceed 5 ng I-TEQ/kg milk fat and, in the Netherlands, they must not exceed 6 ng I-TEQ/kg milk and milk product fat (Liem & van Zorge, 1995).

2. Studies of Cancer in Humans

Human beings have not been documented to have been exposed to toxicologically significant amounts of PCDFs alone. There have been two food poisonings in Asia in which PCBs contaminated by PCDFs were the etiological agent. The blood levels of PCBs of the victims in these incidents were higher than those of the general population but lower than are seen in highly exposed workers. [The Working Group noted that several cohorts with occupational exposure to PCBs have been followed; there is some evidence of increased incidence of liver and biliary cancer combined but not increased primary liver cancer (Brown, 1987).] The morbidity experienced by the poisoning victims was greater than is usually seen in PCB workers, and this difference in toxicity is usually attributed to the admixed PCDFs. Strictly, though, inferences about the toxicity of PCDFs, PCBs, or any component of the oil are not justified, since all the victims were exposed to all components. There has also been exposure to PCDFs in accidents, such as the Binghamton, NY, fire (see Section 1.2.1(*b*)(viii)), but they have been in situations in which there was also documented exposure to 2,3,7,8-TCDD, other PCDDs, PCBs, and other compounds.

The most toxic PCDFs are estimated to have a potency within one or two orders of magnitude of that of 2,3,7,8-TCDD. Thus, for some groups with environmental exposures, such as consumers of Baltic Sea fish, PCDFs may make up the major part of their potentially toxic exposures as estimated by total TEQs.

2.1 Rice oil contamination incidents

The poisoning incidents in Japan and Taiwan involving consumption of contaminated rice oil are described in Section 1.3.1(*b*)(i).

2.1.1 *Japan*

In 1968, in Fukuoka and Nagasaki, Japan, there was an outbreak of an illness consisting of severe cystic acne, hyperpigmentation and conjunctivitis. Clinical and epidemiological investigation showed a strong association with the consumption of specific lots of rice bran cooking oil (Kuratsune *et al.*, 1972). The illness was termed '*yusho*', Japanese for 'oil disease'. Initially, chemical analysis could show only that there was a large amount of chlorine in the oil; the contaminant was later shown to be PCBs and related compounds.

Eventually about 2000 cases were registered with Japanese health authorities. The reasons for registration included not only epidemiological surveillance but also clinical care and in some cases eligibility for compensation. [The Working Group noted that some people who were genuine cases may have avoided registration, and some with

minimal exposure may be included, but the combination of general publicity and the linking of registration to care probably means that most of those eligible were registered.]

The Japanese oil contained of the order of 1000 mg/kg PCBs and 5 mg/kg PCDFs. Estimates of intake are based on a study of 141 cases (Masuda, 1994). These patients consumed about 500 mL oil before becoming symptomatic, and about another 200 mL before the cause of the illness was determined and oil consumption ceased. Thus, they ingested about 500 mg PCBs and 2.5 mg PCDFs before becoming symptomatic, and about 600 mg PCBs and 3.5 mg PCDFs in total. This occurred over a period of weeks.

Ikeda and Yoshimura (1996) followed 1815 *yusho* patients identified from the registry from the Japanese Ministry of Health and Welfare to the end of March 1990. They then contacted the local health departments and obtained a copy of the death certificate for each of those who had died. The causes of death, standardized mortality ratios (SMRs) and confidence intervals (CIs) are presented in **Table 25**. The overall analysis used Japanese national data for its comparison group, but regional data were used for specific cancer sites in order to see whether regional variations explained observed excesses in mortality. The SMR for total mortality was 1.1 [95% CI, 0.9–1.2]; for total cancer in men, it was 1.6 [95% CI, 1.2–2.1]; and, for liver cancer in men, it was 3.4 [95% CI, 1.8–6.0]. Women had decreased total cancer mortality but a nonsignificant increase in liver cancer mortality (SMR, 2.3; [95% CI, 0.5–6.7]) based on three deaths. There was no excess mortality from cancer in women. Both sexes showed a non-significant excess mortality from non-malignant liver disease.

2.1.2 *Taiwan*

Although the rice oil processing machines were banned in Japan, at least one found its way to Taiwan. In 1979, an extraordinary replication of the Japanese incident occurred there (Hsu *et al.*, 1985), called '*yucheng*', meaning 'oil disease' in Chinese, again involving about 2000 persons.

The Taiwanese oil contained about 100 mg/kg PCBs and 0.4 mg/kg PCDFs. Estimates are based on a study of 99 cases. Patients consumed about 300 mg PCBs and 1.3 mg PCDFs during latency and about 1 g PCBs and 3.8 mg PCDFs in total (Hsu *et al.*, 1994). Some persons consumed the oil for six months before becoming symptomatic. The ratio of PCBs to PCDFs was similar in the *yusho* and *yucheng* episodes, and the dose of PCBs and PCDFs causing symptoms was roughly similar, although the Taiwanese consumed more oil that was less contaminated.

Yu *et al.* (1996) reported that a total of 2061 subjects were included in the *yucheng* registry by 1983; no cases were added nor active follow-up carried out after that year. They acquired the registry and traced cohort members through 31 December 1991. For the deceased cases, they acquired a copy of the death certificate from the local household registration offices and abstracted information on date, place and cause of death. The overall and cause-specific mortality of the exposed group was compared with that of the Taiwan general population using 1 January 1979 as the date of the incident and, as the end of follow-up, 31 December 1991, the date of death or the last date a subject was

known to be living. Of the 2061 subjects in the 1983 *yucheng* registry, 70 were actually offspring of the exposed subjects who were born after 30 June 1978 and were excluded. Of the remaining 1991 *yucheng* subjects, 154 did not have valid addresses and thus could not be traced; therefore, a total of 1837 *yucheng* subjects were included. Vital status was determined for 99.5%; 83 of the subjects had died during the follow-up period. The SMR for total mortality was 0.8 (95% CI, 0.7–1.0). There were 10 cancer deaths (SMR, 1.2; 95% CI, 0.6–2.3) including three from liver cancer (SMR, 0.8; 95% CI, 0.2–2.4). There was a 2.7-fold (1.3–4.9) excess of cirrhosis and non-malignant liver disease, based on 10 deaths. Hsieh *et al.* (1996) independently studied the Taiwanese cohort during the same time period and came to similar conclusions.

Table 25. Follow-up studies of mortality in the Asian PCB/PCDF poisonings

	Yusho (Japan)		*Yucheng* (Taiwan)			
	Ikeda & Yoshimura (1996)		Yu *et al.* (1996)		Hsieh *et al.* (1996)	
Number	1815		1837		1940	
Male	816		851		929	
Female	899		986		1011	
Years of follow-up	1968–90		1979–91		1979–91	
Median age at exposure	[~ 25 years]		[~ 22 years] (46% were < 20 years old)		[~ 22 years]	
Deaths	No.	SMR (95% CI)	No.	SMR (95% CI)	No.	SMR (95% CI)
Total deaths	200	1.1 [0.9–1.2]	83	0.8 (0.7–1.0)	102	1.1 (0.9–1.3)
Male	127	1.2 [1.0–1.4]	47	0.8 (0.6–1.1)	55	1.0 (0.8–1.3)
Female	73	0.9 [0.7–1.1]	36	0.9 (0.6–1.2)	47	1.3 (1.0–1.8)
Cancer deaths	58	1.2 [0.9–1.6]	10	1.2 (0.6–2.3)	11	0.6 (0.3–1.0)
Male	45	1.6 [1.2–2.1]	8	1.6 (0.7–3.2)	8	0.7 (0.3–1.4)
Female	13	0.7 [0.3–1.0]	2	0.6 (0.1–2.3)	3	0.4 (0.1–1.2)
Liver cancer deaths	15	3.1 [1.7–5.1]	3	0.8 (0.2–2.4)	2	0.7 (0.1–2.5)
Male	12	3.4 [1.8–6.0]	2	0.7 (0.1–2.5)	1	0.3 (0.0–1.6)
Female	3	2.3 [0.5–6.7]	1	1.3 (0.02–7.1)	1	1.1 (0.0–6.0)
Liver disease deaths	9	1.8 [0.8–3.5]	10	2.7 (1.3–4.9)	15	3.2 [1.8–5.3]
Male	6	1.7 [0.6–3.6]	7	2.5 (1.0–5.1)	9	2.5 [1.2–4.8]
Female	3	2.3 [0.5–6.7]	3	3.4 (0.7–9.8)	6	5.2 [1.9–11.4]

[ ] Calculated by the Working Group

2.1.3 *Comparison of Japan and Taiwan*

The cancer findings in the 12-year follow-up data from Taiwan are not consistent with the 22-year follow-up data from Japan. There was a clear excess of liver cancer mortality in males in Japan that was not seen in Taiwan. The excess of liver cancer was even greater in the Japanese data at 15 years of follow-up (Ikeda *et al.*, 1986) (SMR, 5.6) than it was at 22 years (SMR, 3.4). Both cohorts showed an excess of non-malignant

liver disease. The exposures to the heat-degraded PCBs appear to have been similar. Masuda (1994) showed that the differences in blood levels of PCBs and PCDFs reported between *yusho* and *yucheng* were a function of the time after the incident that the samples were drawn, rather than due to differences in exposure. The methods of cohort selection and follow-up do not appear to favour ascertainment of those with cancer in Japan compared with those in Taiwan. The belief among physicians that the status of being a *yusho* (or *yucheng*) case increases cancer risk, leading to a more frequent diagnosis, cannot be ruled out. However, such a diagnostic bias would have to be specific to Japan and to liver cancer to produce the observed effect. Liver disease and liver cancer are common in both countries, and the recognition and management of them is a regular part of clinical training. It is unlikely that liver cancer is being under-diagnosed among the Taiwanese.

Chronic hepatitis B infection confers a relative risk of as high as 100 for liver cancer. In the 1970s and 1980s, Japan as a whole probably had about a 2% seroprevalence for antibody to hepatitis B surface antigen, while Taiwan had about 15% (IARC, 1994a). It is therefore unlikely to be a confounder.

Hepatitis C virus is probably more prevalent in Japan than in Taiwan (IARC, 1994b). Ito *et al.* (1991), in a community-based survey of Japanese over the age of 40 years, showed a prevalence of 2.3% using a (relatively non-specific) first-generation ELISA assay. In Taiwan, Lin *et al.* (1991) showed a prevalence of 0.6% in pregnant women using a second-generation recombinant immunoblot assay. Thus, Japan has a four-fold higher rate, but the prevalences are low. Hepatitis C appears to be as carcinogenic as hepatitis B but, unless there is a different chemical interaction with the two viruses (for which there is no evidence), the difference in prevalence cannot account for the liver cancer excess in *yusho* patients in Japan.

Hepatitis B and possibly C infection increases dramatically at lower latitudes, and the prefectures of Japan involved, Nagasaki and Fukuoka, are southern ones. Relatively minor differences in the prevalence of hepatitis virus infection could readily produce a relative risk of 3 for liver cancer, since the national rates are dominated by the population centres further north. Ikeda and Yoshimura (1996), however, considered this possibility and found that, when the liver cancer rates among *yusho* patients were compared with the Nagasaki and Fukuoka rates, the relative risk declined from 3.4 to 2.3 in men but remained statistically significant. This may be too conservative, since only about half of the cases actually lived in Nagasaki and Fukuoka.

2.2 Fish consumption

Swedish investigators have studied mortality and cancer incidence in Swedish fishermen and their wives (Rylander & Hagmar, 1995) from the Baltic coast, who prefer salmon, herring and other fatty fish, and compared them both with the rates in the Swedish population (Hagmar *et al.*, 1992) and those of fishing families from the Atlantic coast, who prefer less fatty cod and flat fish (Svensson *et al.*, 1995a). Swedish fishermen were believed to eat about twice as much fish as the general population, and this was confirmed by dietary interviews in a sample of the wives. Baltic fish are contaminated by

organochlorine compounds, and the concentration of these substances in human body fat relates to the amount of fish consumed. The predominant exposure in terms of PCDDs and PCDFs from fatty fish from the Baltic Sea is to 2,3,4,7,8-PeCDF (Svensson *et al.*, 1991) [although even heavy fish consumers probably have body fat concentrations about three orders of magnitude lower than those of the victims of the Asian poisonings]. These fish also contain PCBs and other persistent chlorinated compounds.

The fishermen (> 99% of the cohort members were men) cohorts were formed from the records of the local fishermen's organizations. For the Atlantic coast, 8493 persons (16 women) had ever been members of the organization and, for the Baltic coast, 2907 persons (24 women). The cohorts consisted of 8477 Atlantic coast and 2896 Baltic coast fishermen observed from 1965 for the Atlantic and from 1968 for the Baltic. After the fishermen were identified, the wives were sought through linkage to the national Swedish population registry and also records in local parishes. For the Atlantic coast, 7166 women were identified who either were or had been married to one of the fishermen. For the Baltic coast, there were 2175 women. Information was updated for everyone to 31 December 1988, including a subset of the Baltic coast men who had been reported on previously (Hagmar *et al.*, 1992). Data on death came from Statistics Sweden and those on cancer occurrence from the Swedish Cancer Registry (Svensson *et al.*, 1995b).

Stomach cancer occurred more frequently in the Baltic coast fishermen. Compared with the regional population, the standardized incidence ratio (SIR) was 1.6 (95% CI, 1.0–2.4) and, compared with Atlantic coast fishermen, the incidence rate ratio (IRR) was 2.2 (1.3–3.5). Squamous-cell cancer of the skin was diagnosed more frequently in the Baltic coast fishermen (SIR, 2.3; 1.5–3.5) compared with the regional population and (IRR, 1.9; 1.2–3.1) compared with the Atlantic coast fishermen. Both cohorts of fishermen had higher mortality from multiple myeloma compared with the general population, with SMRs of 3.1 on the Baltic coast and 1.3 on the Atlantic coast. Ischaemic heart disease was decreased among the Baltic coast fishermen but not among those from the Atlantic coast, consistent with their reported differences in diet and the possible protective role of *n*-3 polyunsaturated fatty acids found in the fatty fish preferred by the former population (Svensson *et al.*, 1995b). Compared to the Swedish rates, the Baltic coast wives had a slightly higher and the Atlantic coast wives a slightly lower incidence of breast cancer, but comparisons with neither the population nor the other group were significant (Rylander & Hagmar, 1995).

2.3 Industrial cohorts

[The Working Group noted that exposure to PCDFs may have occurred among workers in the phenoxy herbicides/chlorophenols industrial production cohorts which have been reviewed in the monograph on PCDDs. Exposure to PCDFs, however, is inadequately characterized in these cohorts. Furthermore, the Working Group considered that confounding by concomitant exposure to PCDDs seriously complicates any interpretation of these data regarding cancer risk in relation to PCDF exposure.]

3. Studies of Cancer in Experimental Animals

3.1 Administration with known carcinogens

Studies on PCDFs in combination with known carcinogens are summarized in **Table 26**.

3.1.1 *Mouse skin*

2,3,7,8-Tetrachlorodibenzofuran

Groups of 20 female HRS/J hairless (*hr/hr*) mice, eight weeks of age, were given skin applications of 0 or 5 μmol/animal *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in 50 μL acetone followed by 1 μg/animal 2,3,7,8-TCDF in 50 μL acetone twice weekly for 20 weeks. Skin papillomas developed in 19/19 mice (4.9 tumours/mouse) in mice treated with MNNG plus 2,3,7,8-TCDF compared with 1/20 (0.05 tumours/mouse) in mice treated with 2,3,7,8-TCDF alone and 0/23 with MNNG alone (Poland *et al.*, 1982).

2,3,4,7,8-Pentachlorodibenzofuran

Three groups of 20 female HRS/J hairless (*hr/hr*) mice, five to eight weeks of age, were treated with single skin applications of 5 μmol/animal MNNG in 50 μL acetone. Starting seven days later, the mice were treated with 25, 50 or 100 ng/animal 2,3,4,7,8-PeCDF in 25 μL acetone twice weekly for 20 weeks. A control group of 20 mice received acetone followed by 100 ng/animal 2,3,4,7,8-PeCDF. The numbers of surviving mice with papillomas of the skin were 9/19, 11/18 and 8/18 in mice treated with MNNG and 25, 50 or 100 ng/animal 2,3,4,7,8-PeCDF compared with 0/20 in mice treated with 2,3,4,7,8-PeCDF alone and 1/19 in mice treated with MNNG alone. Skin carcinomas were found in 1/19 mice treated with MNNG + 25 ng 2,3,4,7,8-PeCDF, 1/19 mice treated with MNNG + 100 ng 2,3,4,7,8-PeCDF and in 1/19 mice treated with MNNG alone (Hébert *et al.*, 1990a).

1,2,3,4,7,8-Hexachlorodibenzofuran

Three groups of 20 female HRS/J hairless (*hr/hr*) mice, five to eight weeks of age, were treated with single skin applications of 5 μmol/animal MNNG in 50 μL acetone. Starting seven days later, the mice were treated with 250, 500 or 1000 ng/animal 1,2,3,4,7,8-HxCDF in 25 μL acetone twice weekly for 20 weeks. A control group of 20 mice received acetone followed by 1000 ng/animal 1,2,3,4,7,8-HxCDF. The numbers of surviving mice with papillomas of the skin were 15/19, 7/14 and 3/17 in mice treated with MNNG and 250, 500 or 1000 ng/animal 1,2,3,4,7,8-HxCDF compared with 1/17 in mice treated with 1,2,3,4,7,8-HxCDF alone. Skin carcinomas occurred in 1/19 mice treated with MNNG + 250 ng 1,2,3,4,7,8-HxCDF, 2/17 mice treated with MNNG + 1000 ng 1,2,3,4,7,8-HxCDF and 1/19 mice treated with MNNG alone (Hébert *et al.*, 1990a).

Table 26. Enhancement of tumorigenesis in animals by administration of PCDFs in combination with known carcinogens

Strain/species (sex)	Known carcinogen	Route of administration	Interval	Dose and frequency	Route of administration	Enhancement	Reference
Skin							
HRS/J hairless mice (*hr/hr*) (F)	5 µmol MNNG	Skin		1 µg 2,3,7,8-TCDF/2 per wk/20 wk	Skin	+	Poland *et al.* (1982)
HRS/J hairless mice (*hr/hr*) (F)	5 µmol MNNG	Skin	7 days	25 ng 2,3,4,7,8-PeCDF/2 per wk/20 wk	Skin	+	Hébert *et al.* (1990a)
		Skin	7 days	50 ng 2,3,4,7,8-PeCDF/2 per wk/20 wk	Skin	+	
		Skin	7 days	100 ng 2,3,4,7,8-PeCDF/2 per wk/20 wk	Skin	+	
		Skin	7 days	250 ng 1,2,3,4,7,8-HxCDF/2 per wk/20 wk	Skin	+	
		Skin	7 days	500 ng 1,2,3,4,7,8-HxCDF/2 per wk/20 wk	Skin	+	
		Skin	7 days	1000 ng 1,2,3,4,7,8-HxCDF/2 per wk/20 wk	Skin	+	
Liver							
Wistar rats (M)	50 mg/L NDEA in drinking-water for 4 weeks	Oral	None	10 µg/kg bw 2,3,4,7,8-PeCDF per wk/16, 20 wk	s.c.	–	Nishizumi & Masuda (1986)
		Oral	None	10 µg/kg bw 2,3,4,7,8-PeCDF per wk/24 wk	s.c.	+	
		Oral	None	100 µg/kg bw 2,3,4,7,8-PeCDF per wk/16, 20, 24 wk	s.c.	+	
		Oral	None	10 µg/kg bw 1,2,3,4,7,8-HxCDF per wk/ 24 wk	s.c.	–	
		Oral	None	100 µg/kg bw 1,2,3,4,7,8-HxCDF per wk/ 24 wk	s.c.	+	
SD rat (F)	PH/30 mg/kg bw NDEA	i.p.	35 days	0.8 then 0.16 µg/kg bw 2,3,4,7,8-PeCDF per wk/20 wk	s.c.	–	Waern *et al.* (1991)
		i.p.	35 days	3.2 then 0.64 µg/kg bw 2,3,4,7,8-PeCDF per wk/20 wk	s.c.	+	
		i.p.	35 days	13 then 2.6 µg/kg bw 2,3,4,7,8-PeCDF per wk/20 wk	s.c.	+	

MNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine; NDEA, *N*-nitrosodiethylnitrosamine; i.p., intraperitoneal injection; PH, partial hepatectomy; F; female; M, male

3.1.2 *Rat liver*

2,3,4,7,8-Pentachlorodibenzofuran

Groups of 12 male Wistar rats, five weeks of age, were given 50 mg/L (ppm) *N*-nitrosodiethylamine (NDEA) in the drinking-water for four weeks. The rats were then given weekly subcutaneous injections of olive oil or 10 or 100 μg/kg bw 2,3,4,7,8-PeCDF for 16, 20 or 24 weeks. At the end of treatment, the animals were killed (four per treatment per time point) and the number and size of liver tumours (hepatocellular carcinomas and hyperplastic nodules) were assessed. The numbers of liver tumours per rat were significantly greater in the 2,3,4,7,8-PeCDF-NDEA animals (at 24 weeks, 10 μg 2,3,4,7,8-PeCDF + NDEA, 17/rat; 100 μg 2,3,4,7,8-PeCDF + NDEA, 24.3/rat) than in the rats treated with NDEA alone (at 24 weeks, 3/rat). The number of hepatocellular neoplasms was increased at the 16-week observation period in the 100 μg/kg 2,3,4,7,8-PeCDF/NDEA rats (3.3/rat) compared with those treated with NDEA alone (0.3/rat). The lesions were also larger in animals receiving the 2,3,4,7,8-PeCDF/NDEA combination treatment than in those treated with NDEA alone (Nishizumi & Masuda, 1986). [The Working Group noted that the number of animals with tumours was not given.]

Groups of 10 female Sprague-Dawley rats [age unspecified] were subjected to a 70% partial hepatectomy followed by administration of 30 mg/kg bw NDEA by intraperitoneal injection and treatment with corn oil vehicle or 2,3,4,7,8-PeCDF by subcutaneous injection starting five weeks later for 14 or 20 weeks. The 2,3,4,7,8-PeCDF was given as an initial loading dose (5 × maintenance dose) followed by weekly maintenance doses of 0.16, 0.64 and 2.6 μg/kg bw 2,3,4,7,8-PeCDF for 19 weeks. The rats were killed after 20 weeks of treatment with vehicle or 2,3,4,7,8-PeCDF and analysed for the presence of γ-glutamyltransferase-positive focal hepatic lesions. A significant increase in the percentage of liver occupied by these lesions was observed for all doses (approximately: low-dose, 0.25%; mid-dose, 0.5%; high-dose, 0.5%) compared with NDEA alone (0.15%). A significant increase in the number of foci per liver was also seen at the two highest doses (approximately: low-dose, 2500; mid-dose, 3500; high-dose, 4500) as compared to NDEA alone (2000) (Waern *et al.*, 1991).

1,2,3,4,7,8-Hexachlorodibenzofuran

Groups of 12 male Wistar rats, five weeks of age, were given 50 mg/L (ppm) NDEA in the drinking-water for four weeks. The rats were then given weekly subcutaneous injections of olive oil or 10 or 100 μg/kg bw 1,2,3,4,7,8-HxCDF for 16, 20 or 24 weeks. At the end of treatment, the animals were killed (four per treatment per time point) and the number and size of hepatocellular carcinomas and hyperplastic nodules were assessed. At 24 weeks, the highest dose of 1,2,3,4,7,8-HxCDF increased the number of liver tumours per rat (12/rat) as compared to NDEA alone (3/rat). No effect was seen at the low dose (2.3 tumours/rat) (Nishizumi & Masuda, 1986). [The Working Group noted that the number of animals with tumours was not given.]

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Kinetic data on PCDFs have been reviewed (Olson, 1994).

In an individual exposed accidentally to PCDFs during a fire in Binghamton, NY, United States (see page 364), elimination half-lives of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF and 1,2,3,4,6,7,8-HpCDF were found to be 4–7 years (Schecter *et al.*, 1990a). Flesch-Janys *et al.* (1996a) investigated 48 workers who had been exposed to PCDDs and PCDFs in a herbicide-producing plant and calculated median half-lives that ranged from 3.0 years for 1,2,3,4,5,6,7,8-HpCDF to 19.6 years for 2,3,4,7,8-PCDF. In *yucheng* patients who had ingested PCB-contaminated rice oil in 1979 (see pages 362–363), half-lives of 2–3 years were found for 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,4,6,7,8-HpCDF during the period 1–12 years after the incident. *Yusho* patients were contaminated in 1968 and were examined 15–25 years after the incident showed considerably longer half-lives of 8–13 years (Ryan *et al.*, 1993; Masuda, 1996). These data suggest an increase in half-lives at lower dose levels. This behaviour is reflected in the kinetic model of Carrier *et al.* (1995b).

Half-lives of 1.3 years for 2,3,7,8-TCDF and 6.3 years for 2,3,4,7,8-PeCDF were calculated (Schlatter, 1991) using a method that compares daily intakes and body burdens of PCDFs of the normal population with those of 2,3,7,8-TCDD.

Concentrations of 2,3,4,7,8-PeCDF and 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs were 3–5-fold higher in adipose tissue than in liver (wet weight basis) in deceased *yusho* patients but considerably lower in adipose tissue than in liver in *yucheng* patients (Olafsson *et al.*, 1988). In the normal population, the concentration ratios of liver : fat (on a wet weight basis) were 0.2 for 2,3,4,7,8-PeCDF, 0.5 for OCDF and 1.1 for 1,2,3,4,6,7,8-HpCDF (Thoma *et al.*, 1990; Wacker *et al.*, 1990).

During one year of breast-feeding, PCDD and PCDF levels in human milk fell by 50–70% and those in the milk of mothers nursing their second child were 20–30% lower than those in the milk of mothers nursing their first child (Fürst *et al.*, 1989). These results are concordant with predictions of kinetic models (Carrier *et al.*, 1995b; Van der Molen *et al.*, 1996).

4.1.2 *Experimental systems*

(*a*) *Absorption*

The efficiency of absorption of 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF has been studied in rats, hamsters and guinea-pigs after oral uptake using oily vehicles. For both compounds, 70–90% absorption from the gastrointestinal tract was observed (Birnbaum *et al.*, 1980; Yoshimura *et al.*, 1986; Brewster & Birnbaum, 1987; Kamimura *et al.*,

1988). In the guinea-pig, gastrointestinal uptake of 2,3,7,8-TCDF was more efficient than that of 2,3,7,8-TCDD and this was attributed to higher solubility of the former compound (Nolan *et al.*, 1979; Decad *et al.*, 1981a). As with PCDDs, gastrointestinal absorption of PCDFs depends on the vehicle, molecular size and solubility of the congener. The latter two properties appear to be the more significant in decreasing absorption of the hepta- and octa-CDFs (McLachlan *et al.*, 1990). As for 2,3,7,8-TCDD, it was shown that enterohepatic circulation was not significant for 1,2,3,7,8-PeCDF or its metabolites in rats (Brewster & Birnbaum, 1988).

Percutaneous absorption of 2,3,4,7,8-PeCDF in rats was age-dependent, with much more effective uptake in younger animals (Banks *et al.*, 1990). The dermal absorption of 2,3,7,8-TCDF and 1,2,3,7,8- and 2,3,4,7,8-PeCDFs in rats was also found to be dose- and structure-dependent, with 2,3,7,8-TCDF absorbed most efficiently (Brewster *et al.*, 1989). Compared with oral uptake, skin permeation is much slower. After dermal application of 1,2,3,7,8-PeCDF to the skin of a rhesus monkey, 99% of the dose was still present at the application site after 6 h (Brewster *et al.*, 1988). The uptake of seven compounds from a dermal application site showed a good inverse correlation with the octanol–water partition coefficients (Jackson *et al.*, 1993).

As with PCDDs, the adsorption of PCDFs on environmental matrices such as soil and combustion particles can strongly reduce the bioavailability of these compounds. The oral bioavailability factor which has been suggested for PCDDs (25–50% for Cl_4- and Cl_6-congeners) can also be considered applicable to PCDFs (Van den Berg *et al.*, 1994).

(*b*) *Distribution*

The PCDFs have a similar tissue distribution to that of the PCDDs in both rodents and non-human primates, the liver, adipose tissue and skin being the major storage sites. The 2,3,7,8-substituted PCDFs are the major congeners retained in most mammalian tissues and fluids. In this respect, the guinea-pig forms a distinct exception, as it also retains in the liver PCDFs with a 2,3,(4),6,7-chlorine substitution pattern, which apparently cannot be effectively metabolized by the cytochrome P450 system of the guinea-pig (Van den Berg *et al.*, 1986c; Ahlborg *et al.*, 1990). In other rodent species, the retention of these 'pseudolateral' PCDFs (for example, 2,3,4,6,7-PeCDF) is rarely observed (Van den Berg *et al.*, 1994). Some tissue retention of non-2,3,7,8-substituted PCDFs has been found in rats and marmosets (Abraham *et al.*, 1989; Neubert *et al.*, 1990a), but the concentrations observed are not considered to be toxicologically relevant when compared with the predominance of 2,3,7,8-substituted congeners. An increasing binding affinity to plasma proteins is found for the higher-chlorinated PCDFs and binding to plasma proteins and lipoproteins appears to be the major mode of transport in the blood (Patterson *et al.*, 1989; Schecter *et al.*, 1990e).

Studies with 2,3,7,8-TCDF and -TCDD have shown these compounds to have similar tissue distribution in the rat (Birnbaum *et al.*, 1980). A number of higher-chlorinated PCDFs, especially 2,3,4,7,8-PeCDF, have a much higher liver affinity in rodents than 2,3,7,8-TCDD. For these PCDFs, liver retention of 75–90% of the administered dose has been reported (Van den Berg *et al.*, 1994). Studies with mixtures of both PCDDs and PCDFs showed that tissue distribution in rats and hamsters was not significantly different

between the hepta- and octa-CDFs and -CDDs (Van den Berg *et al.*, 1986c, 1987). In rhesus monkeys, the liver retention of 2,3,4,7,8-PeCDF, which is unusually high in rodents, is lower and not much different from that of 2,3,7,8-TCDD in rhesus monkeys (Kuroki *et al.*, 1980; Brewster *et al.*, 1988). In contrast, marmosets more closely resemble rats in tissue distribution of PCDFs as well as PCDDs (Abraham *et al.*, 1989). As with 2,3,7,8-TCDD, dose-dependent hepatic retention of PCDFs has been observed in a number of rodent studies, but some other studies have not found this dose-dependence (Van den Berg *et al.*, 1994). With respect to the occurrence of inducible hepatic binding sites in rodent liver (Poland *et al.*, 1989a), it should be noted that 2,3,4,7,8-PeCDF is a strongly binding substrate as well as an inducer of CYP1A2 (Yoshimura *et al.*, 1984; Kuroki *et al.*, 1986; Yoshimura *et al.*, 1987).

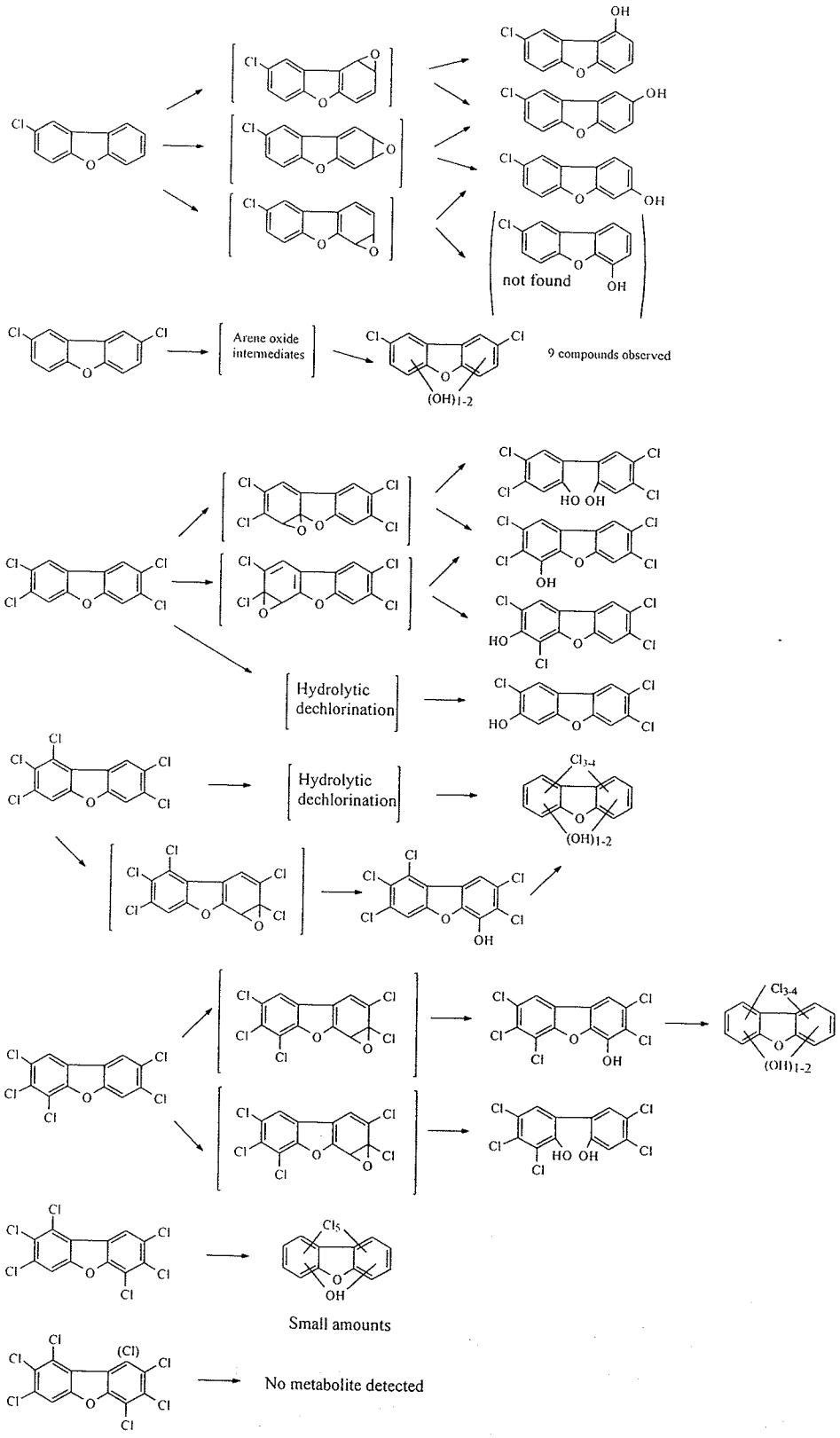
(*c*) *Metabolism*

As with the PCDDs, the oxidation of PCDFs occurs preferentially on the 2, 3, 7 or 8 positions, yielding a higher number of hydroxylated metabolites than with the PCDDs due to the asymmetric structure of the dibenzofuran molecule (Veerkamp *et al.*, 1981; Poiger *et al.*, 1989). Based on studies with rats and 2,3,7,8-TCDF, it appears that the preferred site of metabolism of 2,3,7,8-TCDF is near the furan oxygen, with oxygenation at C4 predominating over oxygenation at C3 (Burka *et al.*, 1990). In rats, the CYP1A1 protein is directly involved in phase I metabolism of 2,3,7,8-TCDF (Olson *et al.*, 1994) and not the CYP1A2 protein (Tai *et al.*, 1993). Sulfur-containing metabolites have also been observed as minor metabolites, with S substitution preferentially at the 4 position (Kuroki *et al.*, 1989, 1990). In contrast to the PCDDs, the 4-4a positions in the dibenzofuran molecule are more susceptible to metabolic mixed function oxidase attack (Plüss *et al.*, 1987; Burka *et al.*, 1990). As a result, the biotransformation of 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF is much more rapid than that of their dioxin analogues. If chlorine atoms on the 4 or 6 position are present in a 2,3,7,8-substituted PCDF, metabolism is strongly decreased, leading to an extremely low rate of elimination from the body (Brewster & Birnbaum, 1987, 1988; Van den Berg *et al.*, 1989a,b). Further chlorination of 2,3,7,8-substituted PCDFs results in a decrease in the number of metabolites and elimination rate (Veerkamp *et al.*, 1981; Poiger *et al.*, 1989). Virtually no information is available on differences between species in PCDF metabolism. In **Figure 1**, a generalized scheme for metabolic pathways of PCDFs is given, which is based on mammalian studies *in vivo* (Van den Berg *et al.*, 1994).

(*d*) *Excretion*

The elimination of PCDFs, like that of the PCDDs, depends strongly on the position of the chlorine atoms. Those congeners with a 2,3,7,8-chlorine substitution pattern exhibit the slowest elimination rates in all laboratory species studied. As PCDFs are stored primarily in the liver and adipose tissue, the whole-body half-life of these compounds is governed mainly by the elimination from these two body compartments. Although kinetic information for PCDFs is more limited, elimination rates and half-lives

Figure 1. A generalized scheme of pathways for the biotransformation of PCDFs based on the information from in-vivo mammalian studies



From Van den Berg *et al.* (1994)

appear to be similar to those of the PCDDs (Van den Berg *et al.*, 1994). Exceptions are seen with 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF, for which elimination in rodents is much faster than for the other 2,3,7,8-substituted PCDFs. This rapid elimination can be directly attributed to the higher susceptibility of the C-4 position to metabolic attack in the dibenzofuran molecule. The presence of a chlorine atom on the C-4 position dramatically decreases the rate of elimination (Birnbaum *et al.*, 1981; Brewster & Birnbaum, 1988; Brewster *et al.*, 1988; Van den Berg *et al.*, 1989a,b; Ahlborg *et al.*, 1990). As a result, the half-life in the liver of the rat increases from several days for 1,2,3,7,8-PeCDF to more than 100 days for 2,3,4,7,8-PeCDF (Brewster & Birnbaum, 1988; Van den Berg *et al.*, 1989b). This importance of chlorine substitution on the 4/6 position is also seen in the short half-life of 1,2,3,7,8,9-HxCDF of less than 10 days in rats, compared with those of 2,3,4,6,7,8-HxCDF, 1,2,3,6,7,8-HxCDF and 1,2,3,4,7,8-HxCDF (Ahlborg *et al.*, 1990). Guinea-pigs eliminate 2,3,7,8-TCDF less efficiently than mice, the half-life in guinea-pigs being 20 days, compared with 4 days in DBA/2J mice and just 2 days in C57BL/6J mice (Decad *et al.*, 1981a,b; Ioannou *et al.*, 1983). The fact that the acute toxicities of 2,3,7,8-TCDD and -TCDF in the guinea-pig are in the same range has been attributed to the limited ability of this species to metabolize and eliminate the latter congener (Van den Berg *et al.*, 1994).

As in rodents, the elimination rates of 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF in primates are faster than those of the other 2,3,7,8-substituted congeners. The half-lives for both compounds in rhesus monkeys and marmosets have been estimated to be approximately one week or less (Birnbaum *et al.*, 1981; Neubert *et al.*, 1990a,b). As for PCDDs, the elimination of PCDFs from most body compartments can be described as a one-compartment open model, but models with two- or three-phase eliminations for 2,3,7,8-TCDF in rodents and monkeys have been reported. In view of the non-linear distribution of PCDDs in many experimental systems, the use of physiologically based pharmacokinetic models has been successfully applied (Carrier *et al.*, 1995a,b).

4.2 Toxic effects

4.2.1 *Humans*

The results in this section are not lipid-based.

[The Working Group noted that in the *yusho* and *yucheng* incidents, exposures were to PCDFs and planar and non-planar PCBs and that one cannot unequivocally attribute the effects to one class of chemicals or the other.]

(*a*) *Non-cancer effects of ingestion of rice oil contaminated with polychlorinated dibenzofurans, quaterphenyls and biphenyls in Japan* (yusho) *and Taiwan* (yucheng)

In both groups, the most notable acute effects were dermatological and neurological signs and symptoms of fatigue, headaches and gastrointestinal distress (nausea, vomiting, abdominal pain) (Kuratsune, 1989; Rogan, 1989).

Yusho

The initial recognition of *yusho* occurred in 1968. About 2000 individuals were identified as part of the *yusho* population (Masuda *et al.*, 1985). Tissue concentrations of PCDFs in these people are given in **Table 18**.

Effects observed shortly after exposure included elevated triglyceride levels and effects on female reproductive hormones manifest as changes in menstrual and basal body temperature patterns and lowered excretion of oestrogens and pregnanediol in exposed women (Kuratsune, 1989). However, fertility and other measures of reproductive function were not evaluated. Evidence of chronic bronchitis and respiratory infections still remained 14 years after exposure ended (Nakanishi *et al.*, 1985). However, more than 10 years after exposure, PCB levels were not related to serum levels of triiodothyronine, thyroxine and thyroxine-binding globulin (Murai *et al.*, 1987). Although the liver is the suspected target organ for halogenated hydrocarbons and marked proliferation of the endoplasmic reticulum was observed in that organ, clinical evidence of liver damage, such as alterations in liver enzymes or liver disease, was not observed (Kuratsune, 1989).

Dermatological effects were the most evident signs, characterized by hyperpigmentation of the nails, gingivae and face and by nail deformities, horny plugs, comedones, acneform eruptions, cysts and other abnormal keratotic changes. Acneform eruptions were observed on the face, cheeks, auricles, retroauricular areas, inguinal regions and external genitalia (Urabe & Asahi, 1985). More than 80% of *yusho* cases experienced one or more dermatological effects (Kuratsune, 1989), which diminished in severity over time (Urabe & Asahi, 1985).

Ophthalmological effects were characterized by swelling and hypersecretion of the meibomian glands and pigmentary changes of the conjunctiva (Kuratsune *et al.*, 1972). More than 80% of *yusho* cases exhibited ocular changes, which, in some cases, appeared to persist 15 years after exposure ended (Kuratsune, 1989).

Thirty per cent of the cases reported having at least one symptom consistent with neurological involvement, such as limb paraesthesia and spasms, weakness, headaches and fatigue (Kuratsune, 1972). As summarized by Kuratsune (1989), Kuriowa *et al.* (1969) found mostly sensory deficits, identified through slowed nerve conduction velocities in 23 cases. Follow-up of these cases indicated that the neurological symptoms disappeared over time; however, conduction velocity measurements were not repeated.

A number of studies examined the immune status of *yusho* cases (Kuratsune, 1989). Significant decreases in mean IgA and IgM and increases in IgG were noted in 28 cases tested in 1970 ($p < 0.05$). Within two years, means levels of all three immunoglobulins returned to normal. Small increases in the percentage of $CD4^+$ cells, small decreases in the percentage of $CD8^+$ cells and enhanced lymphocyte stimulation were also noted in *yusho* cases (Nakanishi *et al.*, 1985).

Mortality in the *yusho* population was assessed among 1761 patients registered by the end of 1983. Among 887 men and 874 women, there were 79 and 41 deaths, respectively (Masuda, 1994). Mortality from chronic liver disease and cirrhosis was elevated in men only (6 deaths; SMR, 2.7).

Studies of offspring of *yusho* cases have been limited to descriptions of effects on newborns exposed *in utero*. An early description of 13 children born to exposed mothers noted two stillborn infants, one of whom was diffusely and deeply hyperpigmented (Rogan, 1982). Neonates described in other reports were darkly pigmented and had marked secretions of the conjunctival palpebra, gingival hyperplasia, hyperkeratosis, calcification of the skull, low birth weight and natal teeth (Yamashita & Hayashi, 1985). The abnormal pigmentation disappeared after 2–5 months. No other physical abnormalities (neurological, cardiovascular or malformations) were identified.

Yucheng

The initial recognition of *yucheng* occurred in 1979. As of 1983, approximately 2000 individuals were found to have been exposed to the contaminated rice oil. Serum concentrations of PCDFs in these people are given in **Table 19**.

The ophthalmological and dermatological changes observed in *yucheng* cases were very similar in character and anatomical distribution to those noted in *yusho* cases (Lü & Wu, 1985). In 89 cases followed for up to 17 months, dermatological conditions of 38% of the cases improved, 54% remained the same and 7% showed deterioration of their condition (Lü & Wong, 1984).

Like *yusho* cases, *yucheng* cases examined within two years of exposure for nerve function exhibited slowing of sensory nerve conduction. They also exhibited motor nerve slowing and mixed deficits (Chen *et al.*, 1981, 1983; Chia & Chu, 1984; Chen *et al.*, 1985a). Of a population of 27 individuals, 20% also had abnormal electroencephalograms (EEGs) (Chia & Chu, 1984). However, the authors suggested that any correlation between PCB exposure and the abnormal EEGs might be spurious due to low PCB levels in the cerebrospinal fluid (0.5–2.3 μg/kg, measured in four subjects), despite much higher blood PCB levels of 48–64 μg/kg. A sample of 28 individuals with peripheral neuropathy in 1980 was re-examined in 1982 and was found to have normal EEGs and some recovery of sensory and motor nerve conduction velocity (Chia & Chu, 1985).

In 1981, immunological function was assessed on several subsets of *yucheng* cases and summarized by Lü and Wong (1984). In 30 cases compared with unexposed controls, both IgA and IgM were significantly decreased, while IgG did not differ from controls. In this same group, percentages of active T cells and T cells (E-rosette lymphocytes) were significantly decreased ($p < 0.05$), while total lymphocyte count and percentage of B cells were unchanged. Significant decreases in helper T cells (T4) but not suppressor T cells (T8) were also observed. In another group of cases, response to lymphocyte-stimulating mitogens was mixed and the findings were unclear. In 143 cases, reaction to streptococci antigen appeared to be significantly ($p < 0.05$) depressed relative to controls.

Alterations in porphyrin levels and liver enzymes have been identified as acute reactions to exposure to halogenated polycyclic hydrocarbons, including PCBs. Porphyrin levels were measured in two exposed groups (Chang *et al.*, 1980; Gladen *et al.*, 1988). In 1980, statistically significant elevations in 24-h urinary excretion of uroporphyrin (exposed, 41.23 μg ± 24.56; unexposed, 13.57 μg ± 11.76; $p < 0.01$) and

α-aminolaevulinic acid (exposed, 1.002 mg ± 0.600; unexposed, 0.715 mg ± 0.337; $p < 0.05$) were noted among 69 poisoned and 20 normal subjects (Chang *et al.*, 1980). Coproporphyrin and porphobilinogen levels were increased (but not significantly) in the exposed group. The second study group was composed of 75 children born between June 1978 and March 1985 to mothers who ingested contaminated rice oil (Gladen *et al.*, 1988). Spot urines were collected in 1985. Mean total porphyrin (exposed, 95.2 µg/L; unexposed, 80.7 µg/L) and coproporphyrin (exposed, 72.4 µg/L; unexposed, 59.8 µg/L) excretion was elevated in the exposed, possibly due to extremely high levels (> 200 µg/L) in eight exposed children and two controls (Rogan *et al.*, 1988). However, no porphyria cutanea tarda, a severe form of porphyria, was observed in either group of children. Moderate, but statistically significant, increases were observed in aspartate transaminase and alanine transaminase levels in 23 cases tested one year after exposure (Lü & Wong, 1984). Lactate dehydrogenase and bilirubin levels were not significantly elevated. As in *yusho* cases, triglyceride levels were significantly increased to approximately twice the level in unexposed controls.

Effects observed in offspring of *yucheng* cases are described in Section 4.4.1.

4.2.2 *Experimental studies*

(*a*) *Species comparisons of toxic effects*

(i) *General effects*

Thirteen-week dietary studies of Sprague-Dawley rats given 1,2,3,4,8-PeCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF or 1,2,3,6,7,8-HxCDF revealed that both toxicity, including body weight loss and thymic atrophy, and depletion of hepatic vitamin A followed the rank order of the compounds to bind to the Ah receptor and to induce CYP1A activity (Plüss *et al.*, 1988a,b; Håkansson *et al.*, 1990). When these PCDFs were administered as a mixture, it was observed that the individual PCDF toxicity was additive (Plüss *et al.*, 1988b). Toxicity of 1,2,3,7,8-PeCDF was significantly lower than that of 2,3,4,7,8-PeCDF and this was attributed to rapid detoxification by biotransformation (see Section 4.1.2(*c*)) (Brewster & Birnbaum, 1988; Plüss *et al.*, 1988a).

In male Sprague-Dawley rats fed 10 mg 2,3,7,8-TCDF per kg of diet, thymus, ventral prostate and seminal vesicle weights were significantly decreased (Oishi *et al.*, 1978), and haemoglobin and haematocrit values were reduced.

Guinea-pigs given a single oral dose of 1–15 µg/kg 2,3,7,8-TCDF or 2,3,4,7,8-PeCDF showed a reduction in body weight gain. All animals that received 10 µg/kg or 15 µg/kg 2,3,7,8-TCDF or 2,3,4,7,8-PeCDF died 9–20 days after dosing. In mice, 22 daily oral doses of 30–300 µg/kg bw/day 2,3,7,8-TCDF did not induce clinical signs of toxicity (Moore *et al.*, 1979). In contrast with other rodents, 2,3,7,8-TCDF was highly toxic to guinea-pigs, the acute toxicity being similar to that of 2,3,7,8-TCDD in this species (Ioannou *et al.*, 1983; Moore *et al.*, 1979). The high sensitivity of the guinea-pig was attributed to the low biotransformation rate in this species (see Section 4.1.2(*b*)) (Van den Berg *et al.*, 1994).

A single dose of 1500 µg/kg 2,3,7,8-TCDF was lethal to 2/2 rhesus monkeys (Moore *et al.*, 1979). Those animals which survived a dose of 1000 µg/kg (2/4) developed facial

oedema and loss of eyelashes, fingernails and toenails. Most animals accumulated a white, wax-like exudate in the ear canal and showed a dry, leathery texture of the skin. Blood analysis 28 days after dosing revealed mild anaemia, relative lymphopenia and marked relative and absolute neutrophilia. Serum cholesterol was decreased by 33–50%. Major microscopic lesions were hyperkeratosis of the epidermis, squamous metaplasia of the meibomian and ceruminous glands (eyelid and ear canal, respectively) and a dilatation of hair follicles filled with keratinaceous debris in the facial area. The thymus showed extensive reduction of the cortex and necrotic debris in the medulla. Furthermore, the bile duct mucosa was found to be extremely hyperplastic with cystic dilatation and inflammation. Mild skin lesions were also found in the two rhesus monkeys that had received 500 μg/kg.

Packed blood cell volume and serum triglyceride and bile acid concentrations were significantly increased in rhesus monkeys after a single intravenous dose of 34 μg/kg 2,3,4,7,8-PeCDF (Brewster *et al.*, 1988). Serum cholesterol, protein, albumin, triiodothyronine and thyroxine concentrations were decreased. After 28–58 days, the animals exhibited alopecia, hyperkeratinization of the toe- and finger-nails, facial chloracne-like lesions and loss of body weight. Two out of three animals subsequently died. Pathological findings indicated hyperplastic and metaplastic changes in the gastric mucosa, the meibomian glands of the eyelid and the ceruminous glands of the ear.

In cynomolgus monkeys (*Macaca fascicularis*), PCB mixtures similar to those ingested by *yusho* patients but without PCDFs caused immunosuppression and enlargement and histopathological changes of the liver (interstitial inflammation, proliferation of bile-duct epithelial cells). Treatment with a PCDF-containing PCB mixture, however, led to more pronounced decreases in body weight, immunosuppression, fatty liver and histopathological changes. In addition, the PCDF-containing mixture caused hair loss, acneform skin eruptions, oedema of the eyelid, congestions and abscesses of the meibomian gland and cornification of the skin (Hori *et al.*, 1982).

(ii) *Skin*

In haired and hairless newborn and adult mice, dermal application of 2,3,4,7,8-PeCDF or 1,2,3,4,7,8-HxCDF caused involution of sebaceous glands (Puhvel & Sakamoto, 1988). Epidermal hyperplasia and hyperkeratinization, however, were induced in the hairless mice only. The density of inflammatory cell infiltrates in the dermis was not reduced by topical treatment with anti-inflammatory agents. The distinct pattern of chloracne observable in hairless mice (Puhvel *et al.*, 1982) did not include hyperkeratinization of the sebaceous follicles typical of human chloracne. Histopathological changes observed with all acnegenic compounds were epidermal hyperkeratosis and hyperplasia, loss of sebaceous glands, keratinization of intradermal pilar cysts and diffuse lymphohistiocytic infiltration of the dermis. Atrophy or complete absence of the hair follicles were evident in severe lesions (Hébert *et al.*, 1990a). In these cases, the epidermis was hypoplastic with increased keratin on the surface. The data for dermal toxicity and changes in body weight and organ weights indicated that 2,3,4,7,8-PeCDF was 0.2–0.4 times, and 1,2,3,4,7,8- HxCDF 0.08–0.16 times, as toxic as 2,3,7,8-TCDD following repeated dermal exposure.

The ability of several PCDFs to induce a flat, cobblestone-like morphology in cell cultures was studied in a nonkeratinizing derivative (XBF) of the keratinizing XB mouse epithelial cell line cocultured with irradiated 3T3 feeder cells. The minimum concentrations required to produce these changes from the normal spindle-shape cells, over a 14-day exposure period, were > 2.38 μg/kg for 2,6-DCDF, 0.032 μg/kg for 2,3,7,8-TCDF, 0.378 μg/kg for 2,3,4,6,7,8-HxCDF and 4.48 μg/kg for OCDF (Gierthy & Crane, 1985).

Osborne and Greenlee (1985) reported that 2,3,7,8-TCDF decreased DNA synthesis, proliferation and epidermal growth factor (EGF) binding, and induced differentiation in several lines of human keratinocytes.

(iii) *Liver*

While no histopathological signs of liver damage were observed in guinea-pigs treated with 15 μg/kg 2,3,7,8-TCDF or 20 μg/kg 2,3,4,7,8-PeCDF, Sprague-Dawley rats showed liver cell vacuolization, necrosis of single hepatocytes and Kupffer cell hypoplasia after treatment with 1,2,3,6,7,8-HxCDF (200 μg/kg in the diet). These alterations were less pronounced with 1,2,3,7,8-PeCDF (200 μg/kg in the diet) and 1,2,3,6,7,8-HxCDF (20 μg/kg in the diet). No liver lesions were observed after administration of 1,2,3,4,8-PeCDF (6000 μg/kg in diet) (Plüss *et al.*, 1988a).

C57BL/6fh(J67) mice receiving 22 daily oral doses of 300 μg/kg 2,3,7,8-TCDF showed a 17% increase in liver weight and a 25% increase in liver/body weight ratio; fluorescence indicative of porphyria was not observed. Guinea-pigs receiving single oral doses of up to 15 μg/kg 2,3,7,8-TCDF did not develop liver pathology. In rhesus monkeys, single oral doses of 2,3,7,8-TCDF up to 1500 μg/kg resulted in inconsistently increased liver weight but no histopathological liver lesion (Moore *et al.*, 1979). Brewster *et al.* (1988) did not report histopathological liver changes except for deposits of haemosiderin in Kupffer cells after administration of a single intravenous dose of 34 μg/kg 2,3,4,7,8-PeCDF to rhesus monkeys.

(*b*) *Immunological responses*

Only five out of 135 PCDF congeners have been studied for their effects on the mammalian immune system (Holsapple, 1995).

Kerkvliet *et al.* (1985) studied the humoral immunosuppressive effect of a single oral dose of 1,2,3,4,6,7,8-HpCDF in C57BL/6 mice, two days before sheep red blood cell (SRBC) challenge. Splenic IgM antibody response was measured five days later ('HAIR-assay'). The 50% immunosuppressive dose (ID_{50}) was calculated as 208 μg/kg, while the ID_{50} for 1,2,3,4,5,6,7,8-HpCDD was 85 μg/kg. [For comparison, the ID_{50} for 2,3,7,8-TCDD was 0.74 μg/kg (Kerkvliet & Brauner, 1990)].

Davis and Safe (1991) compared the effects of a series of congeners with respect to their suppression of the in-vitro plaque-forming anti-SRBC response using cells from either C57BL/6 or DBA/2 mice. The immunosuppressive potencies of 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF, 1,2,3,7,9-PeCDF and 1,3,6,8-TCDF in this in-vitro assay were similar to each other and to that of 2,3,7,8-TCDD, using spleen cell cultures from both mouse

strains, although *in vivo* their immunotoxic potentials differ by up to 14 900-fold in C57BL/6 mice (Davis & Safe, 1988).

Harper *et al.* (1993) studied the effects of a single intraperitoneal injection of 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, 1,2,3,7,9-PeCDF or 1,3,6,8-TCDF on the splenic plaque-forming cell (PFC) response to the T-cell-independent antigen TNP-LPS in C57BL/6 and DBA/2 mice. The effective doses (μg/kg) required to decrease by 50% (ED_{50}) the end-point 'PFCs/10^6 viable cells' were:

Congener	C57BL/6 mice	DBA/2 mice
2,3,7,8-TCDD	1.5	9.7
2,3,4,7,8-PeCDF	2.0	2.6
1,2,3,7,9-PeCDF	391	4 690
1,3,6,8-TCDF	1 484	17 167

Similarly designed experiments were performed with B6C3F1 mice. The effects induced by the same four congeners after intraperitoneal injection were compared with those observed after in-vitro exposure of mouse splenocytes. The ED_{50} of the PFC response to 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF and 1,2,3,7,8-PeCDF and 1,3,6,8-TCDF was 14.1, 5.5, 1695 and 34 800 nmol/kg, respectively. Corresponding values derived from in-vitro studies were 7.0, 10.6, 149 and 2325 nM, respectively (Harper *et al.*, 1995).

Vecchi *et al.* (1983) studied the suppressive effects of a single intraperitoneal injection of 180 μg/kg bw 2,3,7,8-TCDF on antibody production in C57BL/6 mice and in DBA/2 mice. A pronounced decrease in the number of PFC as a response to the injection of SRBCs was observed in C57BL/6 mice only.

A single dose of 20 ng/kg 2,3,4,7,8-PeCDF had no effect on the proportions of sub-populations of lymphocytes in peripheral blood of marmosets, studied by flow cytometry. In contrast, 10 μg/kg bw 2,3,7,8-TCDD induced a decrease in the number of $CD20^+$ cells and the number of $CD4^+$ $CDW29^+$ cells (Neubert *et al.*, 1993b).

(c) *Biochemical responses*

There appear to have been few studies of the biochemical responses attributable to PCDF exposure, other than those on induction of CYP1A1 and CYP1A2 expression (see Section 4.3).

EGF receptor autophosphorylation was decreased in placenta after in-utero exposure to PCBs and PCDFs ingested from contaminated rice oil in the *yucheng* incident (Sunahara *et al.*, 1987). In contrast, EGF receptor expression was increased in mouse embryonic palatal medial epithelial cells (Abbott & Birnbaum, 1989b). Support for the role of the Ah receptor in mediating downregulation of the EGF receptor was supported by structure–activity studies in mice (Ryan *et al.*, 1989b) and the differential responsiveness of congenic mice differing only at the Ah locus (Lin *et al.*, 1991a).

4.3 Interaction with Ah receptor and its early molecular consequences and other biochemical responses

Laterally substituted PCDF congeners bind to the Ah receptor and produce the same biological and toxic effects as the PCDDs. Among these PCDFs, the congeners with the 2,3,7,8-chlorine substitution pattern are the most potent ones (Poland & Knutson, 1982; Safe, 1990). The binding affinities of 2,3,7,8-TCDF, 1,2,3,7,8- and 2,3,4,7,8-PeCDFs to the Ah receptor are of the same order of magnitude as that of 2,3,7,8-TCDD (see Section 4.3 in the monograph on PCCDs in this volume). The Ah receptor binding affinity for the class of congeners is dependent upon the extent and pattern of chlorination (Whitlock, 1986; Okey, 1990; Safe, 1990).

In general, induction of *CYP1A1* gene expression by PCDFs tends to follow the same rank order of potency as receptor binding *in vitro*. Like many planar aromatic substances, including 2,3,7,8-TCDD, the 2,3,7,8-substituted PCDFs also induce CYP1A2 and bind strongly to this protein (Yoshimura *et al.*, 1984; Kuroki *et al.*, 1986; Poland *et al.*, 1989b). Ah receptor-regulated genes encoding phase-two metabolizing enzymes (e.g., UDP-glucuronosyl transferase and DT diaphorase) are also induced following PCDF exposure, but information is limited (Safe, 1990; Van den Berg *et al.*, 1994).

Although the binding of some 2,3,7,8-substituted PCDFs to the Ah receptor and associated *CYP1A1* induction *in vitro* is similar to that of 2,3,7,8-TCDD, the general toxicity of some of these congeners is significantly lower due to faster biotransformation in several rodent species. This is especially the case for 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF (Van den Berg *et al.*, 1994).

Enzyme induction has been observed in both pre- and postnatally exposed rats; the endocrine implications of these effects are unclear (Waalkens-Berendsen *et al.*, 1996).

Numerous PCDF congeners have been shown to produce Ah receptor-mediated responses such as thymic atrophy, immunotoxicity and teratogenicity in many mammalian species (reviewed by Safe, 1990).

Like the 2,3,7,8-substituted PCDDs (see Section 4.3 in the monograph on PCDDs), PCDFs negatively modulate some 17β-oestradiol-induced biological responses in certain target tissues. The above effects can be of the same order of magnitude as those produced by 2,3,7,8-TCDD (Safe *et al.*, 1991).

The binding of these compounds to the Ah receptor and associated biological responses depend on the cell type, species, sex, age and assay used (Poland & Knutson, 1982; Safe, 1986; Whitlock, 1986; Okey, 1990; Safe, 1990).

Four PCDFs have been shown to increase levels of both hepatic and urinary porphyrins following subchronic exposure in mice, as observed with 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD (van Birgelen *et al.*, 1996b).

4.4 Reproductive and developmental effects

4.4.1 *Humans*

Fetal PCB syndrome, as described among babies in Japan born to mothers who consumed contaminated oil, is characterized at birth by brown pigmentation ('cola-coloured babies') on the skin and the mucous membrane, gingival hyperplasia, very early postnatal eruption of the teeth or natal teeth, calcification of the skull and low birth weight (Yamashita & Hayashi, 1985). In addition, among *yucheng* babies born between 1979 and 1983, a high perinatal mortality rate was observed (eight of 39) (Hsu *et al.*, 1985). Retrospective ascertainment of neonatal dermatological findings among 128 children exposed transplacentally and born in Taiwan between 1979 and 1985, indicated increased rates of hyperpigmentation, eyelid swelling and discharge, deformed nails, acne, natal teeth and swollen gums, compared with 115 control children (Rogan *et al.*, 1988; Gladen *et al.*, 1990). In neither Japan nor Taiwan was there a clear relationship between symptoms or fetopathy and PCB dose (Yu *et al.*, 1991).

Many follow-up studies were initiated among *yucheng* children to assess metabolic impairment or anomalies in physical or cognitive development. In 1985, a cohort was constructed to include all children born between June 1978 and March 1985 who had been exposed prenatally. The exposed cohort consisted of 132 children, living in 1985, from 159 pregnancies occurring among 74 women (Rogan *et al.*, 1988). In April 1985, 117 exposed children aged one month to six years (average, 32 months) and 108 control children (average age, 31 months) were examined. Exposed children were smaller (93% of control weight and 97% of control height) than controls of the same age and sex. Medical histories since birth indicated a higher rate of bronchitis among exposed children. Clinical examination showed a higher frequency of hyperpigmentation and nail deformities, differences in eyebrow flare, hypertelorism and clinodactyly, and an increased prevalence of clinically detectable developmental delay (10% exposed versus 3% controls).

One hundred and fifteen exposed children from the original cohort and 115 highly matched controls were tested for cognitive development annually from 1985 through 1990. The exposed children scored approximately five points lower on age-appropriate tests of intelligence from the age of two to the age of seven. Children born later were as affected as children born shortly after the outbreak (Yu *et al.*, 1991; Chen *et al.*, 1992; Lai *et al.*, 1994).

A behavioural survey was performed on the same groups (Chen *et al.*, 1994). At each year of follow-up and at each age, exposed children scored higher on tests for hyperactivity and conduct disorders.

At school-age, there was evidence of higher prevalence of congenital lack of permanent teeth among some exposed *yucheng* children (five of 18) compared with controls (one of 44) matched for sex, age, father's occupation, family economic status and area of residence (Lan *et al.*, 1989). [Selection of exposed children is not clearly described, and control children had a low participation rate of 61%.]

In a series of 55 *yucheng* children (out of 132 identified during the same period of 1978–85) and 55 controls matched for age and sex, there was evidence in 1991 of decreased height and decreased muscular development (as indicated by total lean mass) among exposed children (Guo *et al.*, 1994).

Seven to nine years after the poisoning, there was no difference in any immunological or haematological parameters investigated between 19 exposed children and 32 matched controls (Lan *et al.*, 1990).

In an examination conducted in 1993 of 104 exposed children, *yucheng* girls were significantly shorter (2.5 cm) than controls, and the penile length of *yucheng* boys, aged 11–14 years, was shorter than that of controls. Neither effect was related to sexual development by the Tanner scale (Guo *et al.*, 1993). In a separate examination, 22% of tympanic membranes in 110 *yucheng* children were abnormal versus 17% of controls ($p < 0.01$) (Chao & Hsu, 1994).

Analysis of physical and cognitive development began in October 1991 of 104 children whose mothers were exposed and 109 children whose fathers but not mothers were exposed and of three matched controls born after 1985 (Guo *et al.*, 1993; Chen *et al.*, 1992). Like children born before 1985, the later-born children were shorter in stature and lower in weight than controls, although the differences were no longer statistically significant. *Yucheng* children were reported to have higher activity levels but no physical temperament, habit or other behavioural problems. Overall, scores on all tests among paternally exposed children were similar to those of the controls. However, maternally exposed children scored lower on the Stanford-Binet IQ test Wechsler and on all subscales of the Wechsler Intelligence Scale for Children. In a follow-up study based on a random sample of the above children, the exposed children had significantly lower verbal and full-scale IQs and auditory event related potential. No neurophysiological changes were observed, including pattern visual evoked potentials and short-latency somatosensory evoked potentials.

In summary, there is evidence that babies born after the *yusho* incident or after the *yucheng* incident (for which more data are available) present signs of intra-uterine growth retardation and congenital anomalies at birth. Some authors have proposed that these findings were consistent with a generalized disorder of ectodermal tissue (Rogan *et al.*, 1988). Sunahara *et al.* (1987) showed that *yucheng* babies with low birth-weight had depressed autophosphorylation capacity of the EGF receptor in the placenta, induced by exposure to PCBs and PCDFs during gestation. There is evidence of deficits on cognitive development scores among *yucheng* children up to seven years of age.

4.4.2 *Experimental systems*

PCDFs are teratogenic in mice, causing the same spectrum of birth defects and developmental toxicity as 2,3,7,8-TCDD (Birnbaum, 1991). Whether administered orally to the dam as a single dose during the middle of organogenesis or in divided doses on gestation days 10–13, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF cause cleft palate and hydronephrosis at doses which are not maternally or fetally toxic (Weber & Birnbaum, 1985; Birnbaum *et al.*, 1987a,b). The dose–response

curves for these four PCDFs are parallel to each other and to that of 2,3,7,8-TCDD. The ED_{50} values and the relative potency values for induction of cleft palate are as follows: 2,3,7,8-TCDD 3.4 μg/kg, 1.0; 2,3,7,8-TCDF 70.1 μg/kg, 0.05; 1,2,3,7,8-PeCDF 132.9 μg/kg, 0.025; 2,3,4,7,8-PeCDF 35.9 μg/kg, 0.1; and 1,2,3,4,7,8-HxCDF 344.8 μg/kg, 0.01. The ED_{50} for hydronephrosis was about five times lower than that for cleft palate. Mixtures of these chemicals demonstrate strict additivity for induction of cleft palate.

Prenatal exposure of mice to 2,3,4,7,8-PeCDF results in haemorrhage of embryonic blood into the maternal circulation because of rupture of the embryo–maternal vascular barrier (Khera, 1992). Exposure of pregnant rats on gestation day 1 to 43 nmol/kg (15 μg/kg) 2,3,4,7,8-PeCDF resulted in a decrease in sperm count in the male offspring and a delay or lack of vaginal opening in the females (Waalkens-Berensen *et al.*, 1996).

Oral treatment of adult mice with 100 μg/kg 2,3,4,7,8-PeCDF five times over a 16-week period led to an increase in the growth of surgically induced endometriosis (Johnson *et al.*, 1996).

4.5 Genetic and related effects (see also Appendix 3 and **Table 27**)

4.5.1 *Humans*

Peripheral lymphocytes from 35 Taiwanese women exposed in the *yucheng* incident (Lundgren *et al.*, 1988) that occurred in 1979 and those from 24 matched controls were assessed for the levels of sister chromatid exchange in the presence or absence of α-naphthoflavone and for chromosomal aberrations in 1985. Serum levels of PCBs were measured for 32 individuals and those of PCDFs were measured for only 12 exposed women. Blood concentrations of total PCBs in the exposed population and in controls averaged approximately 15 and 0.34 μg/kg, respectively. PCDFs detected were primarily 1,2,3,4,7,8-HxCDF (10.8 ng/kg) and 2,3,4,7,8-PeCDF (2.7 ng/kg). Sister chromatid exchange frequencies in the absence of α-naphthoflavone and chromosomal aberrations were similar in control and exposed populations. Differences in the level of α-naphthoflavone-induced sister chromatid exchange between the two groups were highly significant. These findings indicate that exposure to PCBs or PCDFs *in vivo* results in an enhanced sensitivity of lymphocytes to the sister chromatid exchange-inducing effects of α-naphthoflavone.

Placentas from nonsmoking Taiwanese women (38–35 years of age) from the *yucheng* cohort were obtained in 1983 and 1984. The formation of DNA adducts in placental DNA was investigated using ^{32}P-postlabelling, but none was detected (Gallagher *et al.*, 1994).

4.5.2 *Experimental systems* (see **Table 27**)

3-Chlorodibenzofuran induced reverse mutation in *Salmonella typhimurium*. Elevated frequencies of sister chromatid exchange and micronucleus formation were induced by 2,3,4,7,8-PeCDF in human lymphocytes *in vitro* in the presence or absence of α-naphthoflavone.

Table 27. Genetic and related effects of PCDFs

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
3-Chlorodibenzofuran				
SAO, *Salmonella typhimurium* TA100, reverse mutation	+	+	100	Matsumoto & Ando (1991)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	40	Matsumoto & Ando (1991)
2,3,4,7,8-Pentachlorodibenzofuran				
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	NT	0.0008	Nagayama *et al.* (1995a)
MIH, Micronucleus test, human lymphocytes *in vitro*	+	NT	0.005	Nagayama *et al.* (1993)
BVD, Binding (covalent) to DNA, rat liver *in vivo* (^{32}P-postlabelling)	–		0.1 p.o. × 4	Randerath *et al.* (1993)
1,2,3,7,8-Pentachlorodibenzofuran				
BVD, Binding (covalent) to DNA, rat liver *in vivo* (^{32}P-postlabelling)	–		0.1 p.o. × 4	Randerath *et al.* (1993)
1,2,4,7,8-Pentachlorodibenzofuran				
BVD, Binding (covalent) to DNA, rat liver *in vivo* (^{32}P-postlabelling)	–		0.1 p.o. × 4	Randerath *et al.* (1993)
2,3,4,6,7,8-Hexachlorodibenzofuran				
BVD, Binding (covalent) to DNA, rat liver *in vivo* (^{32}P-postlabelling)	–		0.1 p.o. × 4	Randerath *et al.* (1993)
Mixed PCDFs and PCBs				
BVD, Binding (covalent) to DNA, human placenta *in vivo* (^{32}P-postlabelling)	–		NG	Gallagher *et al.* (1994)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; p.o., oral; NG, not given

Changes in DNA I (indigenous)-compound formation were studied in female Sprague-Dawley rats treated by gastric instillation with 1,2,3,7,8-PeCDF, 1,2,4,7,8-PeCDF, 2,3,4,7,8-PeCDF or 2,3,4,6,7,8-HxCDF (100 μg/kg bw in corn oil per week for four weeks). No test compound–DNA adducts were detected, but there were significant, structure-dependent reductions in hepatic I-compound formation. Potencies increased in the order: control (100%, 122 modifications in 10^9 DNA nucleotides) = 1,2,4,7,8-PeCDF (104%) < 1,2,3,7,8-PeCDF (80%) < 2,3,4,7,8-PeCDF (61%) = 2,3,4,6,7,8-HxCDF. These activities parallel the reported Ah receptor-binding activities (Randerath *et al.*, 1993).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Polychlorinated dibenzofurans (PCDFs) are formed as inadvertent by-products in the production and use of polychlorinated biphenyls (PCBs) and, in combination with polychlorinated dibenzo-*para*-dioxins (PCDDs), in the production of chlorophenols and have been detected as contaminants in these products. PCDFs and PCDDs also may be produced in thermal processes such as incineration and metal processing and in the bleaching of paper pulp with free chlorine. PCDFs are also found in residual waste from the production of vinyl chloride and the chloralkali process for chlorine production. The relative amounts of PCDF and PCDD congeners produced depend on the production or incineration process and vary widely.

Like PCDDs, PCDFs are ubiquitous in soil, sediments and air. Excluding occupational or accidental exposures, most background human exposure to PCDFs occurs as a result of eating meat, milk, eggs, fish and related products, as PCDFs are persistent in the environment and accumulate in animal fat. High exposures have occurred in relation to incidents in Japan (*yusho*) and Taiwan (*yucheng*) involving contamination of rice oil and in accidents involving electrical equipment containing PCBs. Occupational exposures also may occur in metal production and recycling, and in the production and use of chlorophenols and PCBs.

Based on limited data, the sum of the mean background levels of the penta- and hexachlorinated PCDF congeners commonly found in human tissues is generally in the range of 10–100 ng/kg fat, and the PCDF contribution to tissue international toxic equivalent (I-TEQ) values is typically of the same order of magnitude as that of the PCDDs. Since the mid-1980s, mean tissue levels of total PCDFs and PCDDs (measured as I-TEQ) in the general population have decreased by two- to three-fold. Five-fold higher tissue levels have been found in subpopulations consuming large amounts of PCDF-contaminated fish. Accidental exposures to PCDFs have led to tissue levels one or more orders of magnitude higher than background levels.

5.2 Human carcinogenicity data

In the *yusho* and *yucheng* incidents, each involving about 2000 cases, people were exposed to sufficient PCBs and PCDFs to produce symptoms. Fatal liver disease is 2–3 times more frequent than national rates in both cohorts. In Japan, at 22 years of follow-up, there is a three-fold excess of liver cancer mortality in men, which was already detectable and even higher at 15 years of follow-up. In Taiwan, at 12 years of follow-up, there is no excess of liver cancer mortality. This difference does not appear to be the result of study design, differences in diagnostic habits, exposure or age at exposure, but may be related to differences in the time of follow-up.

5.3 Animal carcinogenicity data

There are no long-term carcinogenicity studies on PCDFs.

2,3,7,8-Tetrachlorodibenzofuran (2,3,7,8-TCDF) treatment following a single dose of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) resulted in an increased incidence of mouse skin papillomas.

2,3,4,7,8-Pentachlorodibenzofuran (2,3,4,7,8-PeCDF) treatment following a single dose of MNNG resulted in an increased incidence of mouse skin papillomas. 2,3,4,7,8-PeCDF treatment following four weeks' treatment with *N*-nitrosodiethylamine (NDEA) resulted in an increased incidence of hepatocellular carcinomas and hyperplastic nodules in male rats. Treatment with the same compound after a single dose of NDEA increased the incidence of focal hepatic lesions in female rats.

1,2,3,4,7,8-Hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF) treatment following a single dose of MNNG resulted in an increased incidence of mouse skin papillomas. 1,2,3,4,7,8-HxCDF treatment following four weeks' treatment with NDEA resulted in an increased incidence of hepatocellular carcinomas and hyperplastic nodules in male rats. Treatment with the same compound after a single dose of NDEA increased the incidence of focal hepatic lesions in female rats.

5.4 Other relevant data

Kinetics

The half-lives of PCDFs in humans are much longer than those in experimental animals.

In most vertebrate species, the 2,3,7,8-substituted PCDFs are the congeners which are preferentially retained in tissues. Oxidation by cytochrome P450 primarily occurs at the 4 and 6 positions in the molecule and the presence of chlorine atoms at these positions reduces metabolism more than substitution at the 1 and 9 positions. Consequently, chlorine substitution on these positions strongly hinders elimination. In rodents, some PCDFs, e.g. 2,3,4,7,8-PeCDF, show an extremely high affinity for liver tissue, which has been attributed to binding to the CYP1A2 protein. As Ah-receptor-mediated effects are primarily caused by the parent compound, biotransformation should be considered as a detoxification process.

Toxic effects

In animal experiments, 2,3,7,8-substituted PCDFs exhibit the same pattern of toxicity as those documented for PCDDs.

Studies of adults in Japan (*yusho*) and Taiwan (*yucheng*) who ingested rice oil contaminated with PCBs, PCDFs and other by-products of PCB thermal degradation have observed effects in multiple systems. In both situations the poisonings were characterized by chloracne, elevated triglyceride levels, abnormal neurological symptoms, ophthalmic changes and alterations in immune parameters. In *yucheng*, porphyrin levels were also elevated.

Biochemical responses and mechanism of action

2,3,7,8-Substituted PCDFs bind to the Ah receptor and, as documented for PCDDs, induce *CYP1A1* and *CYP1A2* gene expression. Ah-receptor-binding affinities of 2,3,7,8-TCDF, 1,2,3,7,8- and 2,3,4,7,8-PeCDF are of the same order of magnitude as that observed for 2,3,7,8-TCDD. With increasing chlorination, receptor binding affinity decreases. The enzyme induction follows the same structure–activity relationship.

Reproductive and developmental effects

In the *yucheng* population, eight of 39 children exposed *in utero* died before birth. Surviving children showed signs of intra-uterine growth retardation and congenital anomalies at birth, a deficit of cognitive development up to seven years of age, and defects in musculoskeletal development and pigmentation.

Several PCDFs have been shown to be teratogenic in mice, causing cleft palate and hydronephrosis. 2,3,4,7,8-PeCDF leads to persistent reproductive effects (reduced sperm count, structural alterations of the female genital tract) following prenatal exposure. It also promotes the growth of surgically induced endometriosis in mice. All of these effects are also observed with 2,3,7,8-TCDD.

Genetic and related effects

2,3,4,7,8-PeCDF increased the frequencies of sister chromatid exchange and micronucleus formation in human lymphocytes *in vitro*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of polychlorinated dibenzofurans.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,3,7,8-tetrachlorodibenzofuran.

There is *limited evidence* in experimental animals for the carcinogenicity of 2,3,4,7,8-pentachlorodibenzofuran.

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[1] For definition of the italicized terms, see Preamble, pp. 26–27.

There is *limited evidence* in experimental animals for the carcinogenicity of 1,2,3,4,7,8-hexachlorodibenzofuran.

Overall evaluation

Polychlorinated dibenzofurans *are not classifiable as to their carcinogenicity to humans (Group 3).*