

## Dioxins and Dibenzofurans

### Physico-chemical Properties

Polychlorinated compounds discussed in this section include polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and some coplanar polychlorinated biphenyls (PCBs). PCDDs and PCDFs consist of two benzene rings connected by a third oxygenated ring. The middle ring of PCDDs contains two oxygen atoms, while PCDFs contain one such atom. PCBs are created by chlorination of biphenyls. There are 75 possible different positional congeners of PCDDs and 135 different congeners of PCDFs. In general, these compounds are very poorly soluble in water, essentially non-volatile under normal environmental conditions and very stable.

Table 1. Physical and Chemical Properties of selected chlorinated dibenzodioxins, dibenzofurans and some PCBs. (Adapted from US EPA, 1994a)

Property	Substance	Congener Average	Substance	Congener average	Substance	Congener average
Substance	2,3,7,8-TCDD		1,2,3,7,8-PeCDD		1,2,3,4,6,7,8-HpCDD	
CAS No.	1746-01-6		40321-76-4		35822-46-9	
Molecular weight	321.98	321.98	356.42	356.42	425.31	425.31
Melting point °C	305-306		240-241		264-265	
Water Solubility at 20°C (mg/L):	1.93 E-5 @ 22°C	3.5 E-4 @ 25°C		1.2 E-4	2.4 E-6	2.4 E-6
Log K <sub>ow</sub>	6.64	6.4	6.64	6.6	8.0	20
Log K <sub>oc</sub>	6.4	6.2		5.7		
Vapour pressure at 25°C (mm Hg)	7.4 E-10	8.1 E-7	9.48 E-10	7.3 E-10	3.21E-11	3.2 E-11
Henry's law constants (atm·m <sup>3</sup> /mol):	1.6 E-5	3.2 E-5		2.6 E-6	7.5 E-6	7.5 E-6

Property	Substance	Substance	Substance	Congener average	Substance	Congener average
Substance	1,2,3,4,7,8-HxCDD	1,2,3,6,7,8-HxCDD	1,2,3,7,8,9-HxCDD		2,3,7,8-TCDF	
CAS No.	39227-28-6	57653-85-7	19408-74-3		51207-31-9	
Molecular weight	390.87	390.87	390.87	390.87	305.98	305.98
Melting point °C	273-275	285-286	243-244		227-228	
Water Solubility at 20°C (mg/L):	4.40 E-6			4.4 E-6	4.19 E-4	4.2 E-4
Log K <sub>ow</sub>	7.79			7.3	6.53	6.2
Log K <sub>oc</sub>	5.92			5.9		
Vapour pressure at 25°C (mm Hg)	1.01E-10	3.6 E-11	4.9 E-11	5.9 E-11	8.96 E-9	2.5 E-8
Henry's law constants (atm·m <sup>3</sup> /mol):	1.2 E-5			1.2 E-5	8.6 E-6	8.6 E-6

Property	Substance	Substance	Substance	Substance	Substance	Congener average
<b>Substance</b>	<b>1,2,3,4,6,7,8,9-OCDD</b>	<b>1,2,3,4,7,8-HxCDF</b>	<b>1,2,3,6,7,8-HxCDF</b>	<b>1,2,3,7,8,9-HxCDF</b>	<b>2,3,4,6,7,8-HxCDF</b>	
CAS No.	3268-87-9	70648-26-9	57117-44-9	72918-21-9	60851-34-5	
Molecular weight	460.76	374.87	374.87	374.87	374.87	374.87
Melting point °C	325-326	225.5-226.5	232-234	246-249	239-240	
Water Solubility at 22.7°C (mg/L):	7.4 E-8 @ 25°C	8.25 E-6	1.77 E-5			1.3 E-5
Log K <sub>ow</sub>	7.59					
Log K <sub>oc</sub>						
Vapour pressure at 25°C (mm Hg)	8.25 E-13	2.4 E-10	2.2 E-10		2.0 E-10	2.8 E-10
Henry's law constants (atm·m <sup>3</sup> /mol):	7.0 E-9	1.4 E-5	6.1 E-6			1.0 E-5

Property	Substance	Substance	Congener average	Substance	Substance	Congener average
<b>Substance</b>	<b>1,2,3,7,8-PeCDF</b>	<b>2,3,4,7,8-PeCDF</b>		<b>1,2,3,4,6,7,8-HpCDF</b>	<b>1,2,3,4,7,8,9-HpCDF</b>	
CAS No.	57117-41-6	57117-31-4		67562-39-4	55673-89-7	
Molecular weight	340.42	340.42	340.42	409.31	409.31	409.31
Melting point °C				236-237	221-223	
Water Solubility at 22.7°C (mg/L):		2.36 E-4	2.4 E-4	1.35 E-6		1.4 E-6
Log K <sub>ow</sub>	6.79	6.92	6.4	7.92		7.9
Log K <sub>oc</sub>						
Vapour pressure at 25°C (mm Hg)	2.72 E-9	3.29 E-9	2.7 E-9	1.33 E-10	1.07 E-10	9.9 E-11
Henry's law constants (atm·m <sup>3</sup> /mol):		6.2 E-6	6.2 E-6	5.3 E-5		5.3 E-5

Property	Substance	Substance	Substance	Substance	Substance	Substance
<b>Substance</b>	<b>3,3',4,4'-TCB</b>	<b>3,4,4',5'-TCB</b>	<b>2,3,3',4,4'-PeCB</b>	<b>2,3,4,4',5'-PeCB</b>	<b>2,3',4,4',5'-PeCB</b>	<b>3,3',4,4',5'-PeCB</b>
CAS No.	32598-13-3	70362-50-4	32598-14-4	74472-37-0	31508-00-6	57465-28-8
Molecular weight	291.99	291.99	326.44	326.44	326.44	326.44
Melting point °C	453	410	398	392	378	398
Water Solubility at 25°C (mg/L):	5.49 E-10	8.43 E-6	1.98 E-3	3.68 E-6	4.27 E-6	1.0 E-3
Log K <sub>ow</sub>	6.21	6.4	6.6	6.6	7.12	6.9
Log K <sub>oc</sub>					5.7	
Vapour pressure at 25°C (mm Hg)	1.37 E-7	2.8 E-10	5.9 E-6	5.96 E-10	8.45 E-10	2.9 E-6
Henry's law constants (atm·m <sup>3</sup> /mol):	9.4 E-5	1.28 E-4	9.9 E-5	6.9 E-5	8.5 E-5	5.4 E-5

Property	Substance	Substance	Substance	Substance	Substance	Substance
Substance	1,2,3,4,6,7,8,9-OCDF	2,3,3',4,4',5,5'-HpCB	2,3,3',4,4',5-HxCB	2,3,3',4,4',5-HxCB	2,3',4,4',5,5'-HxCB	3,3',4,4',5,5'-HxCB
CAS No.	39001-02-0	39635-31-9	38380-08-4	69782-90-7	52663-72-6	32774-16-6
Molecular weight	444.76	396.33	360.88	360.88	360.88	360.88
Melting point (°C)	258-260	431	414	414	408	485
Water Solubility at 25° C (mg/L):	1.2 E-6	4.5 E-5	7.44 E-7	3.6 E-4	3.6 E-4	4.2 E-5
Log K <sub>ow</sub>	8.78	7.7	7.14	7.16	7.17	7.47
Log K <sub>oc</sub>						
Vapour pressure at 25° C (mm Hg)	3.75 E-12	3.0 E-7	1.4 E-6	1.2 E-6	2.0 E-6	1.5 E-6
Henry's law constants (atm·m <sup>3</sup> /mol):	1.9 E-6	6.6 E-5	8.7 E-4	5.8 E-4	1.1 E-4	6.5 E-5

TCDD	Tetrachlorodibenzo-p-dioxins
PeCDD	Pentachlorodibenzo-p-dioxins
HxCDD	Hexachlorodibenzo-p-dioxins
HpCDD	Heptachlorodibenzo-p-dioxins
OCDD	Octachlorodibenzo-p-dioxins
TCDF	Tetrachlorodibenzofurans
PeCDF	Pentachlorodibenzofurans
HxCDF	Hexachlorodibenzofurans
HpCDF	Heptachlorodibenzofurans
OCDF	Octachlorodibenzofurans
TCB	Tetrachloro polychlorinated biphenyls
PeCB	Pentachloro polychlorinated biphenyls
HxCB	Hexachloro polychlorinated biphenyls
HpCB	Heptachloro polychlorinated biphenyls

## 2. Environmental Fate

### PCDDs and PCDFs

The environmental fate of PCDDs and PCDFs have been reviewed extensively (CEPA, 1993; US EPA, 1994a). Only a brief summary will be presented in this section.

PCDDs and PCDFs are highly fat soluble and poorly soluble in water. As a result they are typically found in the environment bound to particulate matter. Once sorbed on to the particles, PCDDs and PCDFs do not leach or volatilize to a significant degree. In this form they are highly stable. This applies in particular to tetra-chlorinated congeners and compounds with greater chlorination. PCDDs and PCDFs are removed from the atmosphere primarily by photodegradation or by dry or wet deposition. Photodegradation applies primarily to those chlorinated hydrocarbons not bound on particulate matter.

Once deposited, these compounds tend to get buried in place or to erode and end up in water bodies. Some photodegradation on the soil-air interface may take place. The half-life of PCDDs/PCDFs at the soil surface has been estimated as years, while the subsurface half-life is estimated in tens of years. These compounds show little upward or downward movement in the soil, unless a carrier such as waste oil is present.

PCDDs/PCDFs entering the water column tend to undergo sedimentation and burial – the ultimate sink for these compounds. The half-lives for removal of these compounds from the water column is estimated in days. Some photodegradation may take place on the water-air interface. Near the surface, the half-life for photodegradation is estimated to be days. Estimated volatilization half-lives are in weeks.

Levels of PCDDs/PCDFs in fish and invertebrates have been found to be higher than those in the water column, suggesting bioaccumulation. It is not clear, however, whether these high levels might arise directly or indirectly from ingestion of contaminated benthic organisms, which in turn are contaminated by filtering or ingestion of contaminated sediment.

### **Coplanar PCBs**

The fate of PCB in the environment has been reviewed in detail by Agency for Toxic Substances and Disease Registry (ATSDR, 1997), International Agency for Research on Cancer (IARC, 1978), US EPA (1994a). Only a brief summary will be provided.

Based on their physicochemical properties, these compounds are likely to be associated mostly with particulate matter and to be chemically and thermally stable. The main means of transport are soil erosion and sediment transport in water bodies, as well as volatilisation from water or soil surfaces followed by atmospheric transport and deposition. Photodegradation to less chlorinated congeners followed by slow anaerobic or aerobic biodegradation are the principal means of destruction of these compounds.

The major means of removal of PCBs from surface water is volatilisation and sedimentation. Adsorption of PCBs is enhanced by high content of organic matter or by the presence of clay and microparticle content. PCB concentrations are higher in sediment and suspended matter than in the associated water column. Less chlorinated PCBs will sorb less strongly than the highly chlorinated components. Sediment acts as a reservoir from which PCBs are slowly released. Redissolved PCBs are then available for volatilisation. In water, PCBs are primarily broken down by photolysis. PCBs with up to six chlorines are broken down slowly (half-life in months). PCBs with greater chlorine substitution are broken down faster with half-life less than a day. The process is strongly dependent on the presence of sunlight and the breakdown is therefore slower in winter. Biodegradation is also possible under both aerobic and anaerobic conditions, but it is slow. Lightly chlorinated biphenyls are more readily biodegraded than the heavily chlorinated congeners.

PCBs are strongly adsorbed to soil and leaching should not occur under most conditions. Sorption is strongest among the most chlorinated congeners. Sorption is also proportional to soil organic carbon content and, therefore, leaching is expected to be greatest from soils with low organic carbon. Leaching will be enhanced by the presence of organic solvents. PCBs may volatilise from soil to air. The

volatilisation rate will be greater from soil with low organic carbon, due to the weaker sorption of PCBs to this type of soil. Volatilisation is also enhanced by soil moisture.

In the air, PCBs exist primarily in the gaseous phase, but some, particularly the more chlorinated congeners, will be particle-bound. PCBs are removed from the atmosphere by both dry and wet aerial deposition. In the atmosphere, PCBs react with hydroxyl radicals (which are photochemically formed by sunlight). The estimated half-lives for different PCBs are in days to weeks. Photodegradation is an important process for PCBs, particularly the highly chlorinated ones. The main products of photolysis are mostly lower chlorinated PCBs.

High levels of PCBs have been found in the tissues of aquatic organisms and their predators. Several factors seem to determine the PCBs levels in these organisms. In general, the levels of PCBs in the organism relative to the levels in the water column rise with an increase in the octanol water partition coefficient ( $K_{ow}$ ). There is a tendency for chlorinated compounds to bioaccumulate more readily, but this is not always the case. Metabolism may result in PCBs tissue levels lower than predicted from the compounds  $K_{ow}$  values.

There is evidence for biomagnification within the food chain and higher PCB levels in higher trophic levels of organisms. Certain benthic organisms accumulate PCBs from water in the sediment zone, where the concentration of PCBs is generally higher than in the general body of water. They may also accumulate higher levels by intake of phytoplankton and zooplankton, which contain higher concentrations of PCBs than the overlying water. As a result, levels in these organisms could be higher than predicted from the water concentration using  $K_{ow}$  values.

The surface microlayer of water bodies may become enriched with PCBs from aerial deposition. Species, which reside in this layer tend to have higher levels of PCBs in their tissues than species which reside lower in the water column.

Uptake of PCBs in plants through their roots is minimal but gaseous PCBs may be absorbed and particulate-bound PCBs may become adsorbed on plant surfaces.

### **3. Toxicokinetics**

The toxicokinetics of PCDDs and PCDFs have been reviewed extensively elsewhere (US EPA, 1994b; CEPA, 1993; IARC, 1997). Only a brief summary will be presented here.

The weight of evidence suggests that PCDDs/PCDFs are bioavailable by oral route from most soils, although the absorption from soils may be less than the absorption from experimental vehicles such as corn oil. Results depended on the soil used and the experimental conditions. Bioavailability from soils ranges from being comparable to bioavailability from corn oil to more than an order of magnitude less available than from soils. The bioavailability from experimental vehicles also varies, but it has been generally reported to be higher than 50% and in a single study on a single human subject, the absorption was marginally below 90%. Based on the limited database it appears that there are no major interspecies differences in the gastrointestinal absorption of these compounds among mammals.

Dermal absorption of PCDDs/PCDFs is very slow and dose-dependent. Most of the administered dose is trapped in the stratum corneum layer of the skin. Three days after exposing rats to these compounds, approximately 10 to 40% of the administered dose was absorbed, while the rest was retained in the stratum corneum. Percentage of the total dose absorbed tends to decrease with increasing dose, although the absolute amount absorbed increases with increasing dose. Lipophilic vehicles reduce the absorption of PCDDs/PCDFs. Administering these compounds in a soil matrix reduces the bioavailability of PCDDs/PCDFs by more than an order of magnitude.

Rodent intratracheal instillation studies suggest that for PCDDs/PCDFs transpulmonary absorption is almost complete. The effect of the particulate matrix on bioavailability by this route is not known.

It is known the developing fetus can be exposed through placental transfer of dioxin-like compounds in maternal blood. In addition, exposure is likely to increase in the early postnatal period through intake of mother's milk containing dioxin-like compounds.

Following gastrointestinal absorption, PCDDs/PCDFs are primarily distributed by the lymphatic system. Once absorbed into blood, these compounds are initially found in the well-perfused tissues, but within hours, the highest levels are eventually found in the liver and adipose tissue. The distribution of coplanar PCBs is similar to that of PCDDs/PCDFs. The elimination half-life from various tissues is in hours to weeks for rodents, but in the one rhesus monkey study, the elimination half-life from adipose tissues was about a year. In humans, the elimination half-life from adipose tissue and/or blood is in years.

Most of the PCDDs/PCDFs are eliminated in urine, rather than feces. Regardless of whether the elimination is via urine or feces, most of the eliminated PCDDs/PCDFs are the metabolites of the administered compounds. The half-life for elimination is in days to weeks. Most of the identified metabolites are the product of hydroxylation or glutathione conjugation. Tested metabolites were substantially less biologically active than the parent compounds.

PCDDs/PCDFs and coplanar PCBs are thought to produce their effect by binding to the Ah intracellular receptor. The binding of the Ah receptor-dioxin complex to DNA elicits alteration of gene expressions giving rise to the wide spectrum of biological effects typical of TCDD, including induced transcription of the corresponding cytochrome P-4501A1 (CYP1A1) gene and other additional TCDD-responsive genes, such as glutathione-S-transferase, quinone reductase, and aldehyde dehydrogenase. Although the mechanism(s) of dioxin action is not fully understood, the majority of investigators believe that most, if not all, biological and toxic responses to dioxin and related compounds are Ah-receptor mediated.

As Ah-receptor mediated effects are caused primarily by the parent compounds, biotransformation to more water-soluble metabolites should be considered a detoxification process. In most mammals, the 2,3,7,8-substituted PCDDs are the congeners that are predominantly retained. If chlorine atoms are present in all the 2, 3, 7, 8 positions, the biotransformation of the molecule becomes greatly reduced, resulting in significant bioaccumulation. Likewise, coplanar PCBs are not readily metabolized.

## 4. Human Health Effects

Evaluation of the extensive toxicological database for dioxin and its related compounds (i.e. PCDD, PCDF, and coplanar PCBs) indicate that these compounds have the ability to produce a wide spectrum of response in animals and humans, if the dose is high enough. Though epidemiological data for chronic effects are limited, evidence suggests that animal models are appropriate for evaluating the hazard and risk due to dioxin and related compounds. In particular, humans have a fully functional Ah receptor and both *in vivo* and *in vitro* studies have illustrated comparability of biochemical responses in humans and animals. A weight-of-the-evidence approach in which all available data (both human and animal) are examined is therefore utilized (US EPA, 1994b, 2000; CEPA, 1993; IARC, 1997; WHO, 1998). Only a brief summary of the health effects will be provided in this section.

### Chloracne

Chloracne and associated skin changes are widely recognized responses to chlorinated compounds in humans. Chloracne is a severe acne-like condition that develops within months of first exposure to high levels of dioxin. For many individuals, the condition disappears after discontinuation of exposure, despite serum levels of dioxin in the thousands of parts per trillion; for others, it may remain for many years.

### Cancer

There is sufficient evidence from animal studies that TCDD and perhaps other PCDDs/PCDFs are carcinogenic. Several epidemiological studies are suggestive of PCDDs/PCDFs being carcinogenic to humans, but there is not yet a full consensus on this topic. US EPA (1994b) outlines its position as follows.

*“...publication of additional studies of human populations exposed to dioxin and related compounds since the last EPA assessment ...has strengthened the inference, based on all the evidence from mechanistic, animal, and epidemiological studies, that these compounds are appropriately characterized as probable human carcinogens. While the data for 2,3,7,8-TCDD are particularly comprehensive, the data on other congeners remain limited. This puts added emphasis on the assumptions and inferences regarding toxicity equivalence in evaluating complex exposures to dioxin and related compounds with regard to carcinogenicity. The evolving understanding of the complex interplay between dioxin-like compounds and hormones and other modulators of cell growth and differentiation continues to complicate more precise determinations of cancer hazard and risk.”*

In the draft reassessment of dioxin published in 2000, US EPA has classified dioxin and related compounds as likely human carcinogens in accordance to the 1996 US EPA draft carcinogenicity guideline. This evaluation is currently under review by the US EPA Science Advisory Board.

In contrast, IARC (1997) has upgraded its assessment of TCDD from Group 2A (*The agent (mixture) is probably carcinogenic to humans*) to Group 1 (*The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans*). In making the overall evaluation, IARC has taken into consideration a number of supporting evidence. 1. TCDD is a multi-site

carcinogen in animal studies, which has been shown via independent lines of evidence to be Ah receptor-mediated. 2. The Ah receptor functions the same way in humans as in experimental animals. 3. Tissue concentrations in exposed human populations showing an increased incidence in cancer occurrence are similar as in rats exposed to carcinogenic dosage regimens in bioassays.

TCDD acts mainly as a cancer promoter rather than as a cancer initiator in animal studies. This evaluation is borne out by short-term studies showing a lack of direct DNA-damaging effects including covalent binding to DNA by TCDD, mouse skin and rat liver tumour promotion studies. Both the mouse skin and rat liver tumour studies support a non-genotoxic mechanism for the induction of neoplasms by TCDD. A number of dioxin-like PCDDs and PCDFs, as well as several PCBs, have also been demonstrated to be tumor promoters in two-stage initiation-promotion) protocols in rodent liver and skin. Both empirical data and the results of modeling efforts suggest that they may be functioning indirectly to produce irreversible genetic changes in exposed cells. The genotoxicity, initiation and promotion have considerable effect in estimating potencies of these compounds as cancer-causing substances. These issues will be discussed in the *Potency* section.

Overall, the strongest evidence for the carcinogenicity of TCDD in humans is for all cancers combined. Of the different human cancer types associated with dioxin exposure, the best evidence continues to be for lung cancer and soft tissue sarcoma. Although they were criticized for a variety of reasons, several recent studies found elevated incidence of soft tissue sarcoma, supporting findings from previous studies. The fact that similar results were obtained in independent studies of differing design evaluating populations exposed to dioxin-like compounds under varying conditions, along with the rarity of this tumor type, weighs in favor of a consistent and real association.

### **Reproductive and Developmental Effects**

Altered development may be among the most sensitive TCDD end points in laboratory animal systems although the likelihood and level of response in humans are much less clear. A wide variety of developmental effects in several species and vertebrate classes were reported, suggesting that dioxin has the potential to disrupt a large number of critical developmental events at specific developmental stages. TCDD appears to increase embryo/fetal mortality as well as disrupt organ system structure and irreversibly impair organ function.

It is not possible to quantify human sensitivity to the developmental effect of dioxins at present. In mammals, postnatal functional alterations involving learning behaviour and the developing reproductive system appear to be the developmental events most sensitive to prenatal dioxin exposure. Developing immune systems may also be highly sensitive. Reproductive effects in male and female animals have been demonstrated, but they generally occur at body burdens that are higher than those required to generate developmental effects.

These observations indicate that there is variability among species in the profile of developmental responses elicited by TCDD. However, essentially all dioxin-like PCB, PCDD, and PCDF congeners that have Ah receptor affinity and intrinsic activity produce the same pattern of developmental effects within a given vertebrate species if a sufficiently high dose of the congener is given.

### **Immunotoxicity**

Extensive evidence has accumulated over the past 20 years to demonstrate that the immune system is a target for toxicity of TCDD and structurally related compounds, including PCDDs, PCDFs, PCBs, and PBBs.

Alterations in specific immune functions and increased susceptibility to infectious disease have been identified at doses of TCDD well below those that cause lymphoid tissue depletion. Both cell-mediated and humoral immune responses are suppressed following TCDD exposure, suggesting that there are multiple cellular targets within the immune system that are altered by TCDD. Epidemiological studies also provide conflicting evidence for the immunotoxicity of these compounds in humans. The developing immune system may be particularly sensitive to the effects of exposure to dioxin and related compounds.

### **Other Effects**

There is epidemiological and some experimental evidence in support of association between reduced testosterone level and increased luteinizing hormone in males. Increased risk of diabetes and changes of glucose levels have also been ascribed to TCDD. Induction of a number of enzymes involved in biotransformation reactions was referred to earlier. Increased activity of some of these enzymes has been implicated in the toxic responses seen in animals in response to dioxin-like compounds.

## **5. Potency Estimates**

Assessment of the toxicity of PCDD/PCDF/coplanar PCB mixtures is usually conducted using toxic equivalency factors (TEFs). The concept of toxic equivalence is based on a common mechanism of action within this class of compounds. TEFs are assigned to individual dioxins, furans and coplanar PCBs on the basis of how toxic they are in comparison with the toxicity of 2,3,7,8-TCDD, the most potent dioxin. This approach first estimates the potency of TCDD and then expresses the environmental levels of other dioxin-like compounds as “TCDD equivalents” (TEQs). In order to estimate the toxicity of a mixture of dioxin-like compounds, the total number of TCDD equivalents in the mixture is multiplied by the potency for TCDD. The result is numerically equivalent to summing up risks attributable to individual dioxin-like compounds in the mixture.

### **Cancer Effects**

Although dioxin-like compounds induce a wide range of effects, the dose-response assessments conducted by a number of major regulatory agencies focus on cancer as an endpoint. However, there are major differences in the way these organisations established the dose-response relationship and this difference has a major effect on the estimates of toxicity.

#### Threshold versus non-threshold dose-response effects

Some chemicals are believed to induce adverse effects even at very minute doses although the likelihood of the adverse effect at low doses is low. There is no safe dose level, at which the risk is zero and the

level or risk rises as the exposure increases. Many cancer-inducing compounds and some other toxicants fall into this category and they are referred to as non-threshold toxicants.

In contrast, most non-cancer inducing chemicals and some carcinogens are thought not to induce an adverse effect, until a certain minimal exposure (threshold exposure) is reached. Above the threshold, the severity of the effect would increase as the exposure level increases. For example, atropine will cause widening of the pupil at a certain concentration. Below that concentration, atropine is thought to have no effect on the pupil. These toxicants are referred to as threshold toxicants.

The distinction between threshold and non-threshold effects is needed, because the approach to assessing the risk for the two groups of chemicals is different. For chemicals with a threshold, the purpose of the dose-response assessment is to identify this threshold at which no adverse effect is expected. No observable adverse effect level (NOAEL) or a benchmark dose is determined either experimentally or in a human epidemiological study. For threshold toxicants, NOAEL is a measure of toxic potency. The more potent the threshold toxicant is, the lower the dose at which no adverse effect is detected. By applying an appropriate safety factor that accounts for the uncertainties in the estimation of the threshold, the reference dose (RfD), which is also called tolerable daily intake (TDI) is determined.

Since there is no “safe” level for non-threshold chemicals, it is necessary to establish a level of exposure for each chemical that is deemed operationally as “tolerable”. Such a level is called risk-specific dose (RsD).

“Tolerable” risk levels differ not only from chemical to chemical but also from organisation to organisation, circumstance to circumstance and they are often controversial. What is tolerable depends usually on an individual’s perspective. Generally for environmental exposures, a tolerable risk has been operationally defined as the probability of an adverse event ranging from one in 10,000 to one in a million. Most organisations use RsDs at one in a million risk for human health. This is the risk level that will be used in this report.

RsD is affected not only by the level of risk deemed tolerable, but also by the potency of the non-threshold effect of the toxicant. Potency is generally expressed as the initial slope of the dose-response curve. This slope estimates the increase in risk as exposure is incrementally increased. The higher the potency, the greater the increment of risk resulting from a given increment of exposure and the steeper the slope of the dose-response curve is. The RsD is derived from this slope.

The decision as to whether to treat an agent as a threshold or non-threshold toxicant often has a large impact on its potency estimate. Non-threshold estimates tend to be far more conservative in many circumstances. In the case of dioxin-like compounds, there is no consensus on whether to treat this family of compounds as threshold or non-threshold carcinogens. However, the arguments are complex and beyond the scope of this report. It should be noted that while US EPA (1994) assessed the potency of TCDD and thus of all the other compounds for which TEFs are developed as non-threshold carcinogens, WHO (1995) and CEPA (1993) treated these compounds as threshold carcinogens. This is probably the main reason for the large discrepancy among the exposure limits derived by the three agencies (see below for further details).

### US EPA (2000)

US EPA (2000) assumed a non-threshold dose-effect relationship for dioxin-like substances. It conducted its dose-response assessment using three occupational studies (Fingerhut *et al.* 1991; Manz *et al.* 1991; Zober *et al.* 1990). The human data suggests an ED<sub>.01</sub> based on the average lifetime body burden in the range of 6-80 ng/kg for all cancers combined and 36-250 ng/kg for lung cancer. These estimates correspond to upper bound slope factors of 8.6 E-3 to 2.5 E-4 risk per pg TCDD/kg/day. Since there is no a priori reason to choose one specific study over the other, US EPA performed a meta-analysis by combining all data sets into a single large data set yielding a slope factor of approximately 1 E-3 per pg TCDD/kg/day. This value represents US EPA's most current upper bound cancer slope factor for estimating human cancer risk based on human data. The slope factor derived from animal data supports this estimate.

### WHO (1995)

WHO implicitly assumed threshold for the effects of TCDD-like substances and developed a tolerable daily intake (TDI) of 10 pg/kg/day based on TCDD-induced liver cancer in rats, for which the No Adverse Effect Level (NOAEL) was 1000 pg/kg/day. This dose corresponds to 540 ng of TCDD/ kg of liver wet weight. In humans, such TCDD content in the liver is estimated to require an intake of 100 pg/kg/day of TCDD. The TDI is derived from this value by applying an uncertainty factor of 10. This factor is intended to account for differences among individuals in sensitivity to TCDD.

### CEPA (1993)

CEPA has estimated the TDI to be 10 pg/kg/day. Their estimate is based on the assumption that dioxin-like substances are non-genotoxic and that a threshold (NOAEL) exists for their action at approximately 1000 pg of TCDD/kg/day. An uncertainty factor was applied in order to account for differences among individuals and severity of the observed effect.

### **Comparison of TEF values used by WHO, CEPA and US EPA**

The different TEF values currently used by WHO (1997), US EPA (1994) and CEPA (1994) are listed in table 2. In essence, both schemes assume that mono-, di- and tri-substituted dioxins and dibenzofurans and higher substituted congeners without substitution in the position 2,3,7,8 are either without effect (US EPA, 1994) or have possibly low effect (CEPA, 1993). The schemes used by CEPA and US EPA follow the one developed by NATO (1988). WHO's scheme is an update of that of NATO. Variations in TEF values for various PCDDs and PCDFs in the WHO updated scheme and the original NATO scheme (used by CEPA and US EPA) are minor, especially considering the large differences in the potency estimates for TCDD by the different agencies. WHO's scheme also includes selected PCBs. US EPA (1996) has adopted the WHO ranking of PCBs in the context of US EPA's PCB assessment.

**Comparison of the assessments and recommendations**

There are very large differences in the estimates of potency for TCDD between US EPA (2000) on one hand and WHO (1995) and CEPA (1993) on the other hand. Since the potencies of other PCDDs, PCDFs and some PCBs are expressed in terms of the potency of TCDD, these differences have a large impact on health evaluation outcome for these compounds. Estimates of average intake for adults in Canada are about 0.6 to 2.1 pg TEQ/kg/day (CEPA, 1993) and 1 to 3 pg TEQ/kg/day in the USA and Europe. The daily intake associated with one in a million risk from all cancers according to the US EPA estimate would be 0.001 pg TEQ/kg/day. If US EPA (2000) is correct, an average North American or European faces cancer risk from exposure to dioxins and dibenzofurans in the range of one in a thousand to one in a hundred, without considering the additional risk from exposure to dioxin-like PCBs.

According to the National Cancer Institute (1998) data, the lifetime risk of lung cancer in the Canadian population is about 7% and the risk for all cancers about 40%. The incidence attributable to PCDDs/PCDFs can be calculated as a product of TEQ daily intake and TCDD slope factor. Based on the Canadian intake estimates and US EPA slope factors provided above, it could be calculated that PCDDs/PCDFs would account for about 1% of lung cancers and about 1% of all cancers observed in the Canadian population. In contrast to the US EPA's assessment, CEPA's estimate and WHO's estimate would suggest little or no cancer risk from PCDDs/PCDFs for an average North American or European, although there is only about an order of magnitude difference between the current typical exposure and tolerated daily intake.

The approach used by US EPA is controversial but cannot be ruled out. The use of the TDI developed by WHO is recommended until a consensus emerges regarding the existence of threshold for the dioxin-like effects. Use of the updated TEFs prepared by WHO (1997) is also recommended, although the differences between these TEF values and the TEF values developed by NATO (1988) and used by US EPA and CEPA are unlikely to have profound effect on the outcome of the risk assessment.

Table 2. TEFs for humans. Comparison of the TEFs used by WHO (1997), CEPA (1993) and US EPA (1994b)

Compound	WHO (1997)	CEPA (1993) and US EPA (1993)
2,3,7,8-TCDD	1	1
1,2,3,7,8-PeCDD	1*	0.5
1,2,3,4,7,8-HxCDD	0.1 a	0.1
1,2,3,6,7,8-HxCDD	0.1 a	0.1
1,2,3,7,8,9-HxCDD	0.1 a	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001 a*	0.001
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PeCDF	0.05	0.05
2,3,4,7,8-PeCDF	0.5	0.5
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1

Compound	WHO (1997)	CEPA (1993) and US EPA (1993)
1,2,3,7,8,9-HxCDF	0.1 a	0.1
2,3,4,6,7,8-HxCDF	0.1 a	0.1
1,2,3,4,6,7,8-HpCDF	0.01 a	0.01
1,2,3,4,7,8,9-HpCDF	0.01 a	0.01
OCDF	0.0001 a*	0.01
3,4,4',5'-TCB (81)	0.0001 a,b,c,e	
3,3',4,4'-TCB (77)	0.0001	
3,3',4,4',5'-PeCB (126)	0.1	
3,3',4,4',5,5'-HxCB(169)	0.01	
2,3,3',4,4'-PeCB (105)	0.0001	
2,3,4,4',5'-PeCB (114)	0.0005 a,b,c,d	
2,3',4,4',5'-PeCB (118)	0.0001	
2',3,4,4',5'-PeCB (123)	0.0001 a,c,d	
2,3,3',4,4',5'-HxCB(156)	0.0005 b,c	
2,3,3',4,4',5'-HxCB(157)	0.0005 b,c,d	
2,3',4,4',5,5'-HxCB(167)	0.00001 a,d	
2,3,3',4,4',5,5'-HpCB(189)	0.0001 a,c	

"\*" Indicates an updated value from those developed by NATO (1998) and used by US EPA (1994) and CEPA (1993)

- a) limited data set
- b) structural similarity
- c) QSAR modelling prediction from CYP1A induction
- d) no new data from 1993 review
- e) in vitro CYP1A induction

### Non-cancer effects

#### WHO (1998)

In light of emerging new toxicological, epidemiological and mechanistic data since a TDI of 10 pg/kg was established for TCDD, WHO organized a consultation in 1998 to re-evaluate the TDI for dioxins. Critical studies for the assessment of low dose effects of dioxins and furans were assembled. Among these are developmental and reproductive effects in rats and monkeys. Endometriosis in the mother, decreased sperm count, immune suppression, increased genital malformations and neurobehavioural effects (learning) in the off springs occur at maternal body burdens in the range of 28-73 ng/kg (see table 3). These body burdens were transformed into estimated daily human intakes that on a chronic basis would be expected to lead to similar body burdens in humans using equation 1. f is the fraction of dose absorbed and is assumed to be 50%

$$\text{Intake (ng/kg/day)} = \text{Body burden (ng/kg)} * (\ln(2)/\text{half-life})/f \quad \text{equation 1}$$

for absorption from food for humans. The half-life for TCDD was estimated to be 7.5 years for humans.

Table 3 Animal body burdens TCDD and related human estimated daily intakes (WHO, 1998)

Study	Response (LOAELs)	Maternal Body Burden (ng/kg)	Related Human Daily Intakes (pg/kg/day)
Gray <i>et al.</i> 1997a	Rats: sperm count in offspring	28	14
Gehrs <i>et al.</i> 1997; Gehrs & Smailowicz, 1998	Rats: Immune suppression in offspring	50	25
Gray <i>et al.</i> 1997b	Rats: Increased genital malformation in offspring	73	37
Schantz and Boman, 1989	Monkeys: neurobehavioural (object learning) effects in offspring	42	21
Rier <i>et al.</i> 1993	Monkeys: endometriosis	42	21

By applying an uncertainty factor of 10 to the range of LOAELs (Lowest Adverse Effect Levels) of 14 - 37 pg TCDD/kg/day, a TDI of 1 - 4 TEQ pg/kg/day was established for dioxins and dioxin-like compounds. The uncertainty factor addresses the use of a range of LOAELs instead of a NOAEL (No Adverse Effect Level), the possible differences in susceptibility to these compounds between humans and experimental animals, the potential differences in sensitivity within the human population and differences in half-lives of elimination for the compounds of a complex TEQ mixture. The uncertainty factor is relatively small because of the following reasons. 1. For some endpoints, humans might be as sensitive as experimental animals to the adverse health effects of dioxin and related compounds. 2. The LOAELs were considered to be within a factor of 2-3 to the NOAELs. 3. The differences in half-lives between the dioxin and dioxin-like PCBs were small and partly accounted for in the establishment of the TEF values.

The TDI represents a tolerable daily intake for lifetime exposure and that occasional short-term excursions above the TDI would have no health consequences provided that the averaged intake over long periods is not exceeded. WHO (1998) advised that the upper range of the TDI of 4 pg/kg TEQ/kg should be considered the maximal tolerable intake on a provisional basis and that the ultimate goal is to reduce human intake levels below 1 pg TEQ/kg/day.

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