Chapter 5.11 Polychlorinated dibenzodioxins and dibenzofurans

General description

Physical and chemical properties

The polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are two series of almost planar tricyclic aromatic compounds with very similar chemical properties. The general structures are given in Fig. 1. The number of chlorine atoms can vary between 1 and 8. The number of positional congeners is quite large; in all there are 75 PCDDs and 135 PCDFs.

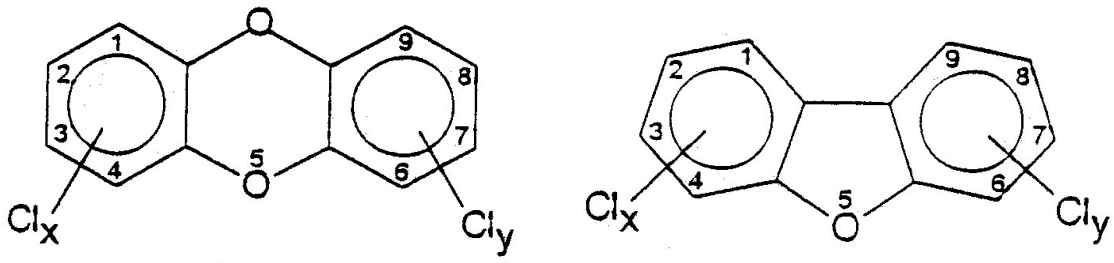

Fig. 1. General structures of PCDDs (left) and PCDFs (right)

PCDDs and PCDFs are solids at room temperature and have a rather low volatility. Dispersion in the atmosphere is thus likely to occur mainly in particulate aerosols.

The most toxic and most extensively studied representative of the chlorinated dioxins (PCDDs) is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Its structural formula is shown in Fig. 2.

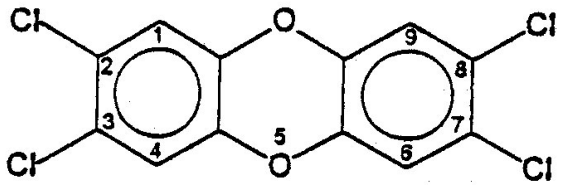

Fig. 2. Structural formula for TCDD

Sources

PCDDs and PCDFs are not commercially produced but are formed as trace amounts of undesired impurities in the manufacture of other chemicals, such as chlorinated phenols and their derivatives, chlorinated diphenyl ethers and polychlorinated biphenyls (PCBs). Ongoing or earlier use of pentachlorophenol is considered to be a major source of PCDDs and PCDFs in many industrialized countries *(1)*. PCDDs and PCDFs are also formed in combustion

processes such as waste incineration and in the production of iron and steel *(2)*. Chlorine bleaching of pulp and paper has also been an important source and low concentrations of PCDDs and PCDFs have been found in earlier paper products *(3,4)*. Chlorine-alkali plants using graphite electrodes have been identified as a point source *(5)*, and car exhausts, mainly exhausts from leaded petrol in which chlorinated solvents have been used as so-called "scavengers", also produce these compounds *(6–8)*. Although a variety of sources of PCDDs and PCDFs have been identified, including sewage sludge *(9)* and garden composts *(10)*, in which they are formed naturally, there may well be a substantial fraction that originates from unidentified sources *(5)*. There is no known technical use for PCDDs and PCDFs.

Table 1. Examples of PCDDs and PCDFs in air reported for various locations[a]

Country	Sum of toxic equivalents (pg/m^3)	Reference
Belgium		
Ambient air, 6 sites	0.02 –0.59	*(11)*
Netherlands		
Air from the North Sea	0.005	
Local background	0.010–0.015	
Downwind of municipal waste incinerator	0.140	*(12)*
Germany		
Rural	<0.07	
Urban	0.07–0.35	
Close to major sources	0.35–1.6	*(13)*
Rural, 1 site	0.05	
Industrial/rural with industries, 5 sites	0.08–0.15	*(14)*
Sweden		
Urban/suburban	0.013 – 0.024	
Remote/coastal	0.003–0.004	*(15)*
Long-range transport:		
– from the United Kingdom	0.055	
– from Germany	0.0056	
– from Iceland	0.0033	*(16)*
United Kingdom		
Urban, 4 sites:		
– median (range)	0.10 (ND–1.8)[b]	
– mean	0.17	*(17)*
United States		
Mean value, coastal environment (winter)	0.10	*(18)*
Japan		
Mean (range):		
– urban (summer)	0.79 (0.4–1.3)	
– urban (winter)	1.46 (0.3–2.9)	*(19)*
Australia		
Sydney, 4 sites	0.02–0.06	*(20)*

[a] Owing to differences in sampling, analytical methods, detection limits and handling of not detected congeners, data from individual studies must be compared with caution (see also the section on analytical methods).
[b] ND = not detected.

Occurrence in air

Few studies have been conducted to measure ambient air levels of PCDDs and PCDFs owing to the low detection limits required to quantify the expected low concentrations of specific congeners of PCDDs and PCDFs. Some examples of the available data are summarized in Table 1 *(11–20)*. In general, these indicate fairly comparable levels in Europe, Japan and the United States of America. Higher concentrations have been found close to known sources and in urban areas.

Tysklind et al. studied the content of PCDDs and PCDFs in 72-hour air trajectories *(16)*. At one sampling site on the Swedish west coast, a variation in content of 15–20 times was found, depending on the trajectories. The lowest value was found when the air was coming from the north (i.e. from Iceland).

A study comparing the distribution of PCDDs and PCDFs between the particulate and vapour phase in air indicated that most of these compounds occurred in the particulate phase *(17)*. Owing to their higher vapour pressure, a higher proportion of the lower chlorinated congeners are found in the vapour phase.

Specific measurements

Several studies have indicated high concentrations in vehicle tunnel air as a result of emissions from cars *(21–23)*. In one *(23),* concentrations inside a Belgian tunnel were found to be twice as high as in ambient air. Balfanz et al. *(24)* found high indoor air concentrations of PCDDs and PCDFs in houses using particle board that had been coated with PCBs (Clophen A 60). In two such measurements, toxic equivalent concentrations of 1.67 and 2.62 pg/m^3 were found.

The concept of toxic equivalency factors

Owing to the fact that dioxin-like compounds normally exist in environmental and biological samples as complex mixtures of congeners, the concept of toxic equivalents (TEQs) has been introduced for risk assessment and regulation. In applying this concept, relative toxicities of dioxin-like compounds in relation to TCDD (i.e. toxic equivalency factors, TEFs) are determined from *in vitro* and *in vivo* studies. This approach is based on the evidence that there is a common, receptor-mediated mechanism of action for these compounds. However, it has limitations owing to a number of simplifications, the most important being that the combined toxic effects of the components of a given mixture are assumed to be additive, neglecting possible synergism, antagonism or differences in toxicokinetics.

The criteria for including a compound in a TEF scheme have been discussed *(25–27)*; the following criteria should be met.

- It should show structural relationship to the PCDDs and PCDFs.
- It should bind to the aryl hydrocarbon (Ah) receptor.
- It should elicit dioxin-specific biochemical and toxic responses.
- It should be persistent and accumulate in the food-chain.

An international scheme of toxic equivalency factors (I-TEF) recommended by the North Atlantic Treaty Organisation Committee on the Challenges of Modern Society and covering the 2,3,7,8-substituted PCDDs and PCDFs normally occurring in various compartments of the

environment has been widely used *(28)*. An international expert group, convened by WHO in 1997, revisited the existing TEFs for human risk assessment and recommended TEFs for wildlife *(29)*. In the TEF scheme, the toxicity of TCDD is set at 1 and the toxicity of the other PCDDs and PCDFs is expressed as fraction (TEF) of the TCDD toxicity. The analytical data from a given sample can thus be converted to provide a TCDD toxic equivalency (TEQ) which can be used for risk assessment and management purposes. The current WHO TEFs are summarized in Table 2.

Table 2. Toxic equivalency factor (TEFs) for PCDDs and PCDFs recommended by the World Health Organization *(29)*

Congener	TEF
TCDD	1
1,2,3,7,8-PeCDD	1
2,3,7,8-substituted HxCDDs	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0001
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.05
2,3,4,7,8-PeCDF	0.5
2,3,7,8-substituted HxCDFs	0.1
2,3,7,8-substituted HpCDF	0.01
OCDF	0.0001

The TEF concept will be used in the following discussions on ambient air concentrations and their assessment.

Analytical methods in air

Ambient air levels of PCDDs and PCDFs are generally very low. For their detection and analysis, high-volume sampling is necessary with the use of filters and absorbants such as polyurethane foam plugs. This approach measures the total amount of PCDDs and PCDFs, but does not allow the separation of concentrations in the vapour and particulate phase. Spiking with $^{13}C_{12}$-labelled PCDD and PCDF surrogate is usually done before sampling. After extraction and sample cleaning, analysis is performed with electron-impact, high-resolution mass spectrometry.

A few comparative interlaboratory studies on the determination of PCDDs and PCDFs in ambient air have been performed *(30,31)*. However, the variable handling of not detected values in calculating concentrations and TEQs, makes it difficult to perform direct comparisons between the different studies.

Indirect measurements
Soil deposition is an important parameter; some direct and indirect methods of analysis have been used but they need to be validated under various climatic conditions.

Routes of exposure

Air

On the basis of ambient air levels reported from Germany, it was concluded that the intake of PCDDs and PCDFs via air is low, amounting in TEQs to 4 pg/person per day *(32)*. This figure assumed an average ambient air concentration of 0.2 pg/m^3 and a respiration volume of 20 m^3 per day in adults. More recent data seem to indicate that the average ambient air concentrations in Europe in TEQs are about 0.1 pg/m^3 *(11,14,17,33,34)*. Similar average figures have also been reported from the United States *(35),* while higher figures have been reported from Japan *(19)*. It was also noted that exposure could occur in specific situations, e.g. contaminated indoor air in houses where pentachlorophenol had been used as a wood preservative *(32)*. Even higher intakes may occur under specific situations where PCB-treated coated particle boards have been used indoors. On the basis of the analysis by Balfanz et al. *(24)*, TEQ intakes of up to 50 pg/day can be estimated. Smoking 20 cigarettes/day could result in an additional TEQ intake of up to 3 pg/day *(36)*.

Drinking-water

Using data from Rappe et al. 1990 *(37)*, WHO concluded that intake of PCDDs and PCDFs through drinking water is negligible *(32)*. The limited data available indicated TEQ levels of 0.003 pg/litre, which could result in a daily TEQ intake of less than 0.005 pg/person, assuming an average daily water intake of 1.5 litres/day.

Food

It is generally agreed that the general population currently receives its major exposure to PCDDs and PCDFs through the intake of food. Since PCDDs and PCDFs are lipophilic and accumulate in the food-chain, food of animal origin is the most important source. In general, plants contain only low levels of PCDDs and PCDFs, commonly close to the detection levels for these chemicals.

Several studies have analysed concentrations of PCDDs and PCDFs in a variety of food commodities and calculated the dietary intake. In Germany, independent studies indicated a daily TEQ intake of slightly less than 1.5 pg/kg body weight (bw), with food of animal origin being the most important source *(38,39)*. Figures in the same range were found for the United Kingdom (1.8 pg/kg bw per day) *(40)* and the Netherlands (1.6 pg/kg bw per day) *(41)*. The calculated dietary TEQ intake in the United States has been estimated to be in the range 1–3 pg/kg bw per day *(35)*.

Calculations based on data from Norway and Sweden *(42,43)* indicated a current daily TEQ intake of about 0.7 pg/kg bw based on very recent Norwegian data on levels in food and food consumption *(43*). Higher daily TEQ intakes of up to 1.6 pg/kg bw were estimated from calculations based on levels of PCDDs and PCDFs in the blood *(44,45)* and breast milk *(46–48)* from background-exposed individuals in Norway and Sweden. The discrepancy is most probably due to the fact that the calculations based on human levels represent the accumulated intake over many years whereas the food data are very recent and probably

mirror a decrease in environmental levels following extensive control of known sources in the Nordic countries.

Local eating habits, e.g. intake of fatty fish from contaminated waters, may significantly increase the daily intake of PCDDs and PCDFs. Thus, Swedish fishermen in the Baltic Sea with a much higher than average intake of herring and salmon were found to have blood levels of PCDDs and PCDFs about three times higher than those in the general population *(42)*. Similarly, extensive consumers of crabs from a contaminated Norwegian fjord system had an intake (calculated as TEQs in pg/kg bw per day), which was 5.4 times that of background-exposed people *(44)*. There may be other population groups with enhanced exposure due to dietary habits.

Population groups at higher exposures

PCDDs and PCDFs are found in human breast milk at comparatively high concentrations. The infant receiving breast milk as the only or dominating food source will consequently have a much higher intake than adults. Measurements of the concentrations of 2,3,7,8-substituted congeners in human milk samples in the WHO-coordinated second round of exposure studies on human milk, in which 19 countries participated, showed that the lowest TEQ levels were found in Albania, Hungary, Pakistan and the less industrialized regions in Croatia, Norway and the Russian Federation (4–10 ng/kg of milk fat) *(49)*. The highest TEQ levels, around 20–30 ng/kg of milk fat, were found in samples from Belgium, Canada, Finland, the Netherlands and Spain. This would correspond to a daily TEQ intake ranging from about 20 up to about 130 pg/kg bw. These figures are on average about 35% lower than those that were found in the first WHO exposure study *(50),* although such a decrease could not be observed in all countries. When the contribution from dioxin-like PCBs is taken into account, the intake for the breastfed infant is about 50–100% higher. However this increase is highly variable from country to country. The factors determining the levels found in humans include both lifestyle and the degree of industrialization. Monitoring programmes have indicated a declining trend in PCDD/PCDF concentrations in human breast milk during the last 5–15 years, probably reflecting the relatively recent emission control measures *(51,52).*

Toxicokinetics

The literature on the toxicokinetics of PCDDs and PCDFs is quite extensive and recent reviews on the subject are available *(53,54)*. A brief summary is given below.

Absorption

Exposure to PCDDs and PCDFs may result from inhalation of contaminated fly ash, dust and soil. Only a few studies have been devoted to the question of bioavailability of PCDDs and PCDFs in connection with the inhalation of contaminated particles. Nevertheless, Nessel et al. were able to demonstrate effects on several biomarkers in rats indicating systemic absorption following intratracheal installation or inhalation exposure of TCDD dissolved in corn oil or bound to gallium oxide particles or soil *(55,56)*.

Uptake following oral exposure of the most toxic PCDDs and PCDFs in experimental animals is generally in the range 50–90% depending on the vehicle *(54).* Uptake of higher chlorinated congeners is much lower because of lower solubility and larger molecular size *(57,58)*. Absorption of more than 90% has been demonstrated in breastfed infants *(59,60).*

In general, PCDDs and PCDFs adsorbed on combustion or soil particles are less available following oral uptake; a figure of 5–20% has been suggested for PCDDs and PCDFs adsorbed on combustion particles *(54)*.

Distribution

Liver and adipose tissues are the predominant storage sites of absorbed PCDDs and PCDFs *(54)*. However, the distribution is highly dose-dependent because of induction of specific binding proteins in the liver, and there are large differences in the distribution pattern between various PCDDs and PCDFs. PCDDs and PCDFs have been shown to cross the placenta.

Metabolism and excretion

The toxicity of PCDDs and PCDFs is primarily caused by the parent compounds, since metabolites are several order of magnitude less potent with respect to effects mediated by the Ah receptor (see below) *(61)*. There are clear differences in the kinetic behaviour of PCDDs and PCDFs in different species. The whole-body half-life of TCDD in the rat ranges from 17 to 31 days, depending on dose and strain *(62–67)*. For humans it is much longer; the plasma half-life has been estimated to be approximately 7 years *(68)*. PCDDs and PCDFs are also excreted in human milk.

Biomarkers of exposure

Induction of the monooxygenases, e.g. CYP1A1 and CYP1A2, can be used as a biomarker of exposure by measuring the increased activity of, for example, ethoxyresorufin-O-deethylase (EROD), a marker for CYP1A1 induction, or by using the (3-methyl-^{14}C)-caffeine CO_2 breath test as a marker for CYP1A2 induction *(69,70)*. In humans a similar method can be applied to determine CYP1A2 induction by measuring ^{13}C-caffeine in urine. However, both enzyme activities (CYP1A1 and CYP1A2) are also influenced by other contaminants in the environment (e.g. dioxin-like PCBs or natural compounds). The EROD induction test is quite extensively used as a biomarker in animal experiments but there are also many other bioassays currently being developed and evaluated.

Physiologically based pharmacokinetic modelling (interspecies and interindividual differences)

Physiologically based pharmacokinetic (PBPK) modelling of TCDD has been reviewed *(35)*. However, owing to the complex nature of the mixture of PCDDs and PCDFs occurring in environmental samples, very few data are available that can be applied to total TEQ exposure *(71,72)*.

Health effects

PCDDs and PCDFs are among the most extensively studied organic chemicals and there are a large number of publications on the toxicological effects of these compounds. Many recent reviews and evaluations are available. WHO has carried out a number of consultations on the subject, and has published several reports on the subject. The most important ones are: an environmental criteria document on PCDDs and PCDFs *(53)*, reports on levels of PCBs, PCDDs and PCDFs in breast milk *(49,50)*, a report on the prevention and control of accidental and environmental exposure to PCBs, PCDDs and PCDFs *(73)* and an assessment of the tolerable daily intake of PCDDs and PCDFs *(32,74,75)*. In addition, several national and regional reviews and health risk evaluations have become available during recent years, e.g. from the Nordic countries *(76)*, the United Kingdom *(77)*, the Netherlands *(78)*, Germany *(79)*, the United States *(35),* France *(80)* and Japan *(81)*.

The available data are briefly summarized below.

Effects on experimental animals and *in vitro* test systems

Toxicological effects
Most of the toxic and biochemical effects caused by PCDDs and PCDFs are probably mediated by the Ah receptor. TCDD is the prototype compound for structurally similar polychlorinated aromatic hydrocarbons that act through the Ah receptor mechanism *(82–84)*. The initial step by which TCDD causes biological effects is through binding stereospecifically and with high affinity to the cytosolic receptor. Endogenous ligands for the receptor have not been identified. After initial binding, the TCDD-receptor complex dimerizes with the Ah-receptor nuclear translocator protein (Arnt). The TCDD-receptor-Arnt complex binds to dioxin response elements (DREs) on DNA resulting in induction of target gene (e.g. CYP1A1) transcription. The Ah receptor binding is thought to be necessary but not sufficient to produce toxicity. The genes whose expression is increased or decreased as a result of TCDD action, which are required for the tissue and species specific toxic responses have not been identified. Biological responses to TCDD and related compounds are observed in animal species expressing Ah receptor. The signs of toxicity caused by TCDD and related compounds that bind to the Ah receptor can include lethality, body weight loss, immunosuppression, oedema, dermal, developmental, reproductive, neurobehavioural, liver and endocrine toxicity, alterations in lipid metabolism and gluconeogenesis, modulation of responsiveness to hormones and growth factors, alterations in circulating levels of hormones, thymic atrophy, cancer, tumour promotion and induction of various enzyme activities including aryl hydrocarbon hydroxylase (AHH) and EROD activities that are associated with the induction of cytochrome P-4501A1 *(35,82,85,86).*

Carcinogenic effects
Many studies have been conducted to evaluate the carcinogenicity of TCDD in rodents. This information has been reviewed *(53,87)*. TCDD has been shown to be carcinogenic in rats, mice and hamsters. Tumours have been demonstrated in several organs but predominantly in the liver. WHO *(32)* concluded that the NOAEL in these studies was 1 ng/kg bw per day for the induction of hepatic adenomas *(88)* and that, at this dose, the level of TCDD in the rat liver was 540 ng/kg on a wet weight basis. A mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDDs has also been demonstrated to cause liver tumours in rodents, albeit at higher dosages *(89)*. Oral administration of 2,7-dichloro-dibenzo-*p*-dioxin to rats (110 weeks) and mice (90 weeks) did not lead to increases in tumour incidence *(90)*.

Several studies have demonstrated that TCDD is a very potent tumour promoter in two-stage promoter models *(91–95)*. Several other PCDDs and PCDFs, e.g. 1,2,3,7,8-PeCDD, 2,3,4,7,8-PeCDF and 1,2,3,4,6,7,8-HpCDD have also been shown to be potent tumour promoters *(96,97)*. WHO concluded that the tumour-promoting action of TCDD showed a clear-cut threshold and also that, at lower doses, "protective" effects against tumour induction were observed *(32)*. It should be noted that at these doses, other noncarcinogenic effects may occur.

Mutagenic effects and effects identified by other in vitro *assays*
Numerous *in vitro* and some *in vivo* studies have failed to demonstrate a genotoxic activity of TCDD *(98)* and it does not bind covalently to DNA *(99,100)*. WHO concluded in 1992 that TCDD was not genotoxic *(32)*, an opinion confirmed by the International Agency for Research on Cancer that evaluated the carcinogenicity of PCDDs and PCDFs in 1997 *(101)*.

Since that time, there have been a number of publications in which TCDD is reported to produce significant effects. These include sister chromatid exchanges (SCEs) and micronucleus induction in cultured human lymphocytes *(102)*, cell transformation in immortalized but not primary human keratinocytes *(103)*, inhibition of gap-junctional intercellular communication (GJIC) in mouse hepatoma cells *(104)* and rat hepatocyte cultures *(105)* and, *in vivo*, DNA strand breaks in rat peritoneal lavage cells *(106)*, and mutations in the mouse spot test *(107)*. The doses producing these significant effects were higher than those required for tumour induction in experimental animals, except for the demonstration of GJIC inhibition in primary cultures of rat hepatocytes.

Critical organs, tissues and effects

The toxic potency of PCDDs and PCDFs is a function of the number and positions of chlorine substituents. PCDDs and PCDFs with a decreased number of lateral chlorine atoms (positions 2, 3, 7 and 8) or increased non-lateral chlorine atoms are less toxic than TCDD *(25)*. However, most of these 2,3,7,8-substituted congeners are toxic and the pattern of the responses within animals of the same species, strain, sex and age will be similar to that of TCDD *(82,108)*.

TCDD exposure mainly affects epithelial tissues *(82)*. Lesions vary between tissues and include proliferative as well as metaplastic and atrophic changes.

PCDDs, PCDFs and related compounds cause a number of immune responses and are clearly immunotoxic in experimental animals including non-human primates. The information on effects on the immune system in humans is limited, and a definite immunotoxic effect of these compounds in humans has not been shown. Animal data show that, in susceptible species, the fetus and young animal are especially sensitive to the immunotoxic effect. PCDDs and PCDFs may be immunotoxic at some levels in humans, the impact on the immune system and implications for characterizing risks are largely unknown at present.

Exposure to TCDD during pregnancy causes prenatal mortality in primates and rodents. Gestational TCDD exposure has been shown to cause subcutaneous oedema, gastrointestinal haemorrhage and decreased fetal growth *(109–114)*. PCDDs and PCDFs can produce developmental effects in the offspring of experimental animals following *in utero* and lactational exposure, and these effects, which may persist into adulthood, include neurobehavioural effects, developmental reproductive effects and neurochemical effects *(115–122)*. Although the dose–response data available to date are limited, the LOAELs, based on TEQ body burden in monkeys and rodents are close to the background human body burden. WHO estimated human daily intakes corresponding with body burdens similar to those associated with LOAELs for the most sensitive responses in animals. These intakes ranged from 14–37 pg/kg bw/day *(74,75)*.

Interactions with other chemicals

The most important interactions are probably those related to simultaneous exposure to PCBs. These environmental contaminants are also widely distributed in the environment and human exposure occurs through the same routes as described for PCDDs and PCDFs. Some of the PCB congeners bind to the Ah receptor and elicit the same type of toxicity as PCDDs and PCDFs. WHO has recommended TEFs for some of these dioxin-like PCBs *(123)*.

There are examples where antagonism has been observed when simultaneously exposing animals to both dioxin-like and non-dioxin-like PCBs (e.g. on enzyme induction, immunotoxicity, teratogenicity). There are other examples where such exposures have been demonstrated to cause both additive and synergistic responses (e.g. tumour promotion *(124)* and porphyria *(125)*). The consequences of such combined exposure are highly dependent on the toxic endpoint studied. As a result, there are examples where the application of the TEF-concept, limited to dioxin-like PCBs, may not precisely predict the possible risk of mixed exposure to PCDDs, PCDFs and PCBs.

Certain non-chlorinated environmental pollutants such as polycyclic aromatic hydrocarbons, bind to the Ah receptor and elicit the prototypical, nontoxic, dioxin-like response – induction of cytochrome P-4501A1 *(126)*. Naturally occurring compounds, such as the indolecarbinols, have similar transient Ah-receptor-mediated effects typified by induction of monooxygenase activity *(127)*. In general, both the polycyclic aromatic hydrocarbons and the indolecarbinols have lower binding affinity than TCDD for the Ah receptor and may fail to produce a sustained effect on gene expression because they are rapidly biotransformed to metabolites that do not bind the Ah receptor. Consequently, these non-chlorinated classes of chemicals may fail to elicit the entire spectrum of dioxin-like toxic effects. However, many of the natural Ah-receptor-binding compounds occur in high concentrations, e.g. in certain foods, so that humans may have a high intake of such compounds.

Effects in humans

Toxicological effects

Information on effects in humans predominantly comes from high exposure in industrial settings or accidents and intoxication incidents, e.g. the contamination of rice oil with PCBs that contained comparatively high concentrations of PCDFs in Japan and Taiwan in 1968 and 1979, respectively. The effects observed are generally in agreement with what could be expected from animal experimentation, although the most typical human effect of high exposure to PCDDs and PCDFs seems to be the dermatological response chloracne. Subtle endocrinological effects, e.g. modulation of thyroid hormone and testosterone levels in plasma, and decreased glucose tolerance and subtle neurological effects have been observed in humans, but their clinical significance is currently unknown *(128–132)*.

Carcinogenic effects

Numerous epidemiological studies have been performed on occupationally or accidentally highly exposed groups. WHO concluded that there is consistent evidence that workers, who were involved in high-level exposure, demonstrated an increased risk of cancer, although the statistical power of these studies is low *(32)*. Data on high-dose exposure (exhibiting chloracne) were found to demonstrate that for those workers who were observed for a period of 20 years after exposure and beyond, there was a small increased risk (standardized mortality ratio (SMR) 2.01) for the category of "all cancers combined". Several recent epidemiological studies support the association between high levels of dioxin exposure and cancer *(133–135)*. The International Agency for Research on Cancer evaluated all available evidence in 1997 and classified 2,3,7,8-TCDD as a human carcinogen (Group 1). Other polychlorinated dibenzo-*p*-dioxins were not classifiable as to their carcinogenicity for humans *(101)*.

Evaluation of human health risks

Exposure evaluation

Food is the main source of human intake of PCDDs and PCDFs; intake through drinking-water is negligible. Calculated as TEQs, average intakes in European countries have been estimated to be in the range 1.5–2 pg/kg bw per day. Very recent data from the Nordic countries indicate that this figure today may be slightly less than 1 pg/kg bw per day. For the United States, intake estimates are in the range 1–3 pg/kg bw per day.

If the contributions of dioxin-like PCBs are taken into account (using the WHO TEFs for PCBs), the TEQ intake would be in the range 2–6 pg/kg bw per day. For certain risk groups, e.g. fishermen from the Baltic sea and Inuits in the Arctic, intakes may be considerably higher.

Inhalation exposure to PCDDs and PCDFs is generally low. Assuming an ambient air TEQ level of 0.1 pg/m^3 and an inhaled volume of air of 20 m^3/day for adults, inhalation intake would amount to about 0.03 pg/kg bw per day. However, certain industrial and urban areas as well as areas close to major sources, may have up to 20 times higher air concentrations. The contribution to the total TEQs of dioxin-like PCBs from ambient air cannot be calculated owing to lack of congener-specific data. Under special circumstances, i.e. indoor air highly contaminated from coated particle boards containing PCBs, inhalation exposure may reach 1 pg/kg bw per day.

Although present concentrations of PCDDs and PCDFs in ambient air do not present a health hazard through direct human exposure, these concentrations will lead to deposition of PCDDs and PCDFs followed by uptake through the food-chain.

Health risk evaluation

In 1990 WHO has established a TDI for TCDD at 10 pg/kg bw *(32)*. This was based on TCDD-induced liver cancer in rats *(88)* for which the NOAEL was 1 ng/kg bw. Owing to toxicokinetic differences between humans and rats, this corresponded to a daily intake in humans of 100 pg/kg bw, to which value an uncertainty factor of 10 to cover interindividual variation was applied.

Since then, new data on hormonal, reproductive and developmental effects at low doses in animal studies (rats and monkeys) have been published. Therefore the WHO European Centre for Environment and Health and the International Programme of Chemical Safety reassessed the health risk of dioxins in 1998 *(74,75)*. The consultation concluded that the human data do not lend themselves to be used as the basis for setting a tolerable daily intake (TDI). However, they were considered to constitute an important reference for comparison with a health risk assessment based on animal data. Consequently the TDI was based on animal data. It was further decided that body burdens should be used to scale doses across species. Human daily intakes corresponding with body burdens similar to those associated with lowest adverse effect levels in rats and monkeys could be estimated to be in the range of 14–37 pg/kg bw/day. By applying an uncertainty factor of 10 to this range of LOAELs, a TDI expressed as a range of 1–4 TEQ pg/kg bw was established for dioxins and dioxin-like compounds.

The consultation emphasized, that 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. Although not explicitly stated, the TDI can be looked upon as applicable to the total intake of TEQs, both via the oral and inhalation route, derived from PCDDs and PCDFs and other dioxin-like compounds that act by the same mechanisms and cause similar types of toxicity. The average daily intake by all routes of exposure to PCDDs and PCDFs calculated as TEQs is in the same range as the current TDI. When the contribution from dioxin-like PCBs is taken into account, the intake increases by a factor of 2–3. There are, however, groups with specific dietary habits (e.g. a high intake of contaminated food) or occupational exposure, that may have exposures in excess of the TDI for PCDDs and PCDFs.

The daily intake of PCDDs and PCDFs in breastfed infants in industrialized countries has been calculated in TEQs to range from about 20 pg/kg bw in less industrialized areas up to about 130 pg/kg bw in more industrialized areas. When the contribution from dioxin-like PCBs is taken into account, the intakes may be up to twice these figures. This indicates intakes being far above the TDI. However, WHO noted that the TDI should not be applied to breastfed infants because the concept of TDI relates to a dose ingested throughout a lifetime *(32)*. In general, the quantity of PCDDs and PCDFs ingested over a 6-month breastfeeding period would be less than 5% of the quantity ingested over a lifetime.

The TEQ contribution from inhalation exposure is on average approximately 1% of the dietary intake but may in certain extreme situations (areas close to point emission sources or contaminated indoor air) approach the dietary intake.

Guidelines

An air quality guideline for PCDDs/PCDFs is not proposed because direct inhalation exposures constitute only a small proportion of the total exposure, generally less than 5% of the daily intake from food.

Urban ambient TEQ air concentrations of PCDDs and PCDFs are estimated to be about 0.1 pg/m^3. However, large variations have been measured. Although such an air concentration is only a minor contributor to direct human exposure, it is a major contributor to contamination of the food-chain. It is difficult, however, to calculate indirect exposure from contamination of food via deposition from ambient air. Mathematical models are being used in the absence of experimental data, but these models require validation. Air concentrations of 0.3 pg/m^3 or higher are indications of local emission sources which need to be identified and controlled.

Although indoor air levels of PCDDs and PCDFs are generally very low, in certain instances, TEQ levels of up to 3 pg/m^3 have been detected. Such levels will constitute an exposure ranging from 25% up to 100% of the current TDI of 1–4 pg TEQ/kg bw (equivalent to 60–240 pg TEQ per day for a 60 kg person).

Owing to the potential importance of the indirect contribution of PCDDs and PCDFs in air to the total human exposure to these compounds through deposition and uptake in the food chain, measures should be undertaken to further reduce emissions to air from known sources. For risk reduction, it is important to control known sources, i.e. both combustion processes and chemicals, as well as to identify new sources.

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