

Synopsis on Dioxins and PCBs

Compiled especially for administrators by
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REPORT



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Structure of the booklet

The aim of this booklet is to give information on PCBs and dioxins as you need it, without having to read through all possible scientific details, but having an option to reach some whenever necessary. Therefore the structure is dictionary-like; after a short introductory chapter, all data are at specific entries in alphabetic order. Some references to further reading and the most essential sources are occasionally given. Since dioxin literature is full of phrases and definitions which are not part of everyday language, some crucial pieces of general information are also given, starting from the measures of picogram quantities all the way through some basic facts on pharmacokinetics, the fate and behaviour of chemicals in our body. The editors wish you an interesting journey rambling in the exiting world of the chemicals of the year. A www-version of this booklet will be available and updated at <http://www.thl.fi/dioxin/>. Therefore, comments and improvements will be appreciated: e-mail Jouko.Tuomisto(at)thl.fi.

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General introduction

Polychlorinated biphenyls (PCB-compounds) are a group of **oily stable chemicals**, which have been used because of their stability and low flammability as insulating materials in electrical equipment (transformers and capacitors), as plasticizers (softening materials) in plastic products, heavy duty hydraulic oils, and for a variety of other industrial purposes. Their **stability is a technical advantage**, but it also means that they are extremely **persistent in the environment**. They also contain **small amounts of dioxin-like PCBs as well as dioxin impurities** especially PCDFs, some of which are much more toxic than the main chemicals.

The production and use of PCBs have been discontinued in most countries, but large amounts remain in electrical equipment, plastic products, buildings (e.g. plastic carpeting, sealing materials), and in the environment. Because PCBs are considered problem waste, their disposal is expensive, and may sometimes lead to attempts to dispose of them by mixing them to other waste products. Two well-established **environmental accidents** leading to human suffering have occurred, called Yusho (Japan) and Yu-Cheng (Taiwan) poisonings. In both cases rice oil was contaminated and caused a number of health effects. Later contamination incidents have not lead to clear health consequences.

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and related halogenated aromatic hydrocarbons (e.g., PCDFs), often called “dioxins” as a group, are **ubiquitously present environmental contaminants**. Some of them, notably TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) belong to the most **toxic** synthetic compounds known. They are very stable against chemical and microbiological degradation and therefore **persistent** in the environment. They are fat-soluble and thus tend to **bioaccumulate** in tissue lipid and in the food chain. These factors increase their potential hazards to humans and animals.

Burning produces dioxins

The main new (*de novo*) sources of PCDD/Fs are **combustion** processes, such as burning of waste, and metal smelting and refining. In Europe, the Baltic Sea is an important sink of PCBs and dioxins. However, recent studies have revealed a major problem at localised spots, due to the

production and use of **chlorophenols** for impregnation of timber. In the most contaminated regions the concentration of PCDDs and PCDFs in soil and sediments appears to be incredibly high. An unpredictable source is old **transformers** and capacitors, each of which may contain several kilograms of PCBs and hundreds of milligrams of PCDD/Fs.

Food is the major source for human exposure to PCBs and dioxins, especially fatty foods: dairy products (butter, cheese, fatty milk), meat, egg, and fish. Food of animal origin accounts for 95 % of total exposure. The current average body burden of dioxins is about 5–50 ng/kg (as WHO-TEq in fat; pg/g = ng/kg) or 100–1000 ng (WHO-TEq) per person which is close to the lowest concentrations possibly causing health effects. Some **subgroups** within the society (e.g., nursing babies and people consuming plenty of fish) may be exposed to higher than average amounts these compounds and are thus at greater risk. Dioxin concentrations have been screened in five WHO international studies, and in Central Europe the concentrations have decreased in breast milk from about 40 ng/kg (as TEq in milk fat) in 1987 to below 10 ng/kg in 2006. PCBs have decreased at about the same rate. The decrease in environmental concentrations is due to cessation of PCB use and improved incineration technology.

Dioxins and some PCBs cause multiple toxic effects

Dioxins bring about a **wide spectrum** of biochemical and toxic effects in experimental animals. These effects depend on species, strain, gender, age and tissue. Various dioxin congeners (derivatives with the same basic structure) tend to elicit a similar battery of alterations, although the congeners are differently potent. TCDD serves as a surrogate for the whole group of chemicals. For the most part, the **mechanisms of these impacts are still obscure**. This hampers rational risk assessment. A common denominator appears to be the so called **AH receptor** (AHR), which mediates the biological effects of TCDD in cells. Some of the most toxic PCBs have dioxin-like toxicity based on AH receptor, but e.g. some effects of PCBs on the nervous system are believed to have a different mechanism.

A characteristic feature of the acute toxicity is an exceptionally **large variation in sensitivity** among species. To the guinea pig, TCDD is the most toxic synthetic compound known with an LD₅₀ value (dose lethal to 50% of animals) of only ca. 0.001 mg/kg, but the hamster tolerates 1 to 5 mg/kg. Even strains within the same species can show a similarly

wide difference: the LD₅₀ values for rats vary from 0.01 to >10 mg/kg. The reasons for these intra- and interspecies differences depend on the structure of the AH receptor, but many details remain to be studied. A peculiar wasting syndrome follows high single doses: the animals are anorectic and lose weight, followed by toxic effects in many organs. Some low-dose effects do not vary between species to the same extent as lethality and wasting. The most sensitive targets for TCDD appear to be various developing organs in the foetus and newborn.

Dioxins and PCBs accumulate in the human body

The fate of these chlorinated compounds in the body is unusual. Because they are fat-soluble and practically not at all water-soluble, they **cannot be excreted in urine**, some is excreted in faeces. Moreover, our body is hardly able to metabolise them. The excretion is so slow that their so called half-life is many years, which means that it takes years of our body to get rid of 50 % of the compound. Because dioxins are mixtures, every compound has a different half-life, but as a thumb rule one can say that an average half-life is five to ten years. This long half-life makes them highly cumulative compounds, i.e., they **accumulate in the body over the decades even at a low exposure**. Therefore it is important that the levels of these compounds in our food are minimised. Continuous exposures from contaminated food might lead in the long run to extremely high body burdens. On the other hand, the accumulation is so slow that it would take 40 to 50 years to reach a balance. During this ultimate **steady state**, the body burden (total amount of chemical in the body) is about 5000 daily doses. Therefore a short period of exposures exceeding the accepted limit values ten or even hundred times, would not remarkably change our body burden accumulated during the previous decades.

In humans, a **wide variety of health effects** have been linked to high exposure to dioxins, including mood alterations, reduced cognitive performance, diabetes, changes in white blood cells, dental defects, endometriosis, decreased male/female ratio of births and decreased testosterone and (in neonates) elevated thyroxin levels. Presently the effects have been proven only in the case of chloracne and disturbances in tooth development, and at very high accidental exposure levels other developmental effects. The effect that has caused the greatest public concern is cancer, and IARC classified TCDD as a human carcinogen in 1997. However, at the present dioxin levels the possibility of developmental effects is probably more relevant concern in the society.

Risk assessment is tricky

A problem in dioxin risk assessment is to evaluate the actual effect of the very low concentrations in the environment of these very toxic compounds. There is wealth of information on environmental concentrations, levels in humans, epidemiological studies with indirect exposure information, effects after different exposures in animals, and on certain aspects of biochemical pathways. However, there are **very few studies that are fully relevant for human risk assessment**. Therefore the scientific community remains divided in the issue of the true risk of the present environmental concentrations of dioxins, and recommendations for tolerable daily intake values have varied even thousand fold between countries. There is, however, an increasing agreement that the risk of cancer, while probably true at very high industrial or accidental exposures, is not relevant at the present levels of intake. The latest re-evaluation considered developmental effects as the most likely risk.

Common sources of errors and practical difficulties.

Dioxin literature may be confusing, and some factors may cause difficulties unless the reader is aware of them. Firstly, different measures are used for different purposes. The amounts of PCBs may be given as a sum of all PCB-derivatives (called *congeners*, see this and Σ PCB) in the sample, or as a sum of the six or *seven marker PCBs* (see this), which are the easiest to measure. The amounts of PCDD/Fs are usually given as a sum of the 17 most relevant congeners (see Σ PCDD/F), or as *TEqs* (see this), normalised to the equivalents of TCDD. Confusing between these may cause a hundredfold error. The transforming factors, *TEFs*, are based on convention, so they may change from time to time, and TEqs should not be used without giving information on the absolute amounts at the same time.

Secondly, different units are used for different purposes (see *units*). The amounts of dioxins in the body are sometimes given as ng/kg b.w. (nanograms per kilogram body weight), but more often as pg/g fat (picograms per gram fat). Because human body contains 10–20 % of fat tissue, the difference may be tenfold. Both absolute weights and TEqs may be given per body weight or per unit of fat, preferably per kilogram, but often per gram. Especially Americans also use non-standard units ppm (parts per million, $\mu\text{g/g}$ or mg/kg), ppb (parts per [American] billion, $\mu\text{g/}$

kg), and ppt (parts per [American] trillion, ng/kg). So please be careful, thousandfold errors are easy to make.

Thirdly, different measures are used for different matrices. In fish and other food items dioxins and PCBs are often expressed per wet weight (fresh weight), because it is then easy to calculate human intake via food. However, in contaminated soil or sediment samples they are usually expressed per dry weight. The difference between these two measures may also be formidable. A minimum requirement for accurate expression is weight of substance, weight of matrix, and quality, e.g. ng/kg (WHO-TEq in fat).

Fourthly, single acute dose and average daily dose mean very different things for the exposed person. Approximately similar body burden of dioxins could be achieved either by a single dose of 5,000 pg, or by a lifelong intake of 1 pg/day. Therefore one should be very careful in comparing the amounts in the body and the amounts in the food. This booklet will hopefully also clarify some of these pitfalls.

In this booklet we have used the following format for expressing units followed by their characterization and matrix information in parenthesis:

10 ng/kg (WHO-TEq in fat)

Encyclopaedia

Σ (sigma), sum. Ordered alphabetically at the main entry disregarding the prefix (e.g. **Σ7PCB**, see *PCB*).

absorption, uptake of digested nutrients or any chemical from the site of the first entry to the organism proper. The most common site of absorption is the gastrointestinal tract: stomach and the gut. Any unabsorbed material in the contents of the gastrointestinal tract is in principle outside the body. Therefore absorption is the first critical step towards toxicity of any chemical. The absorption of fat-soluble and poorly water-soluble dioxins and PCBs depends on the presence of fats: they are absorbed easily if they are dissolved in fats, but often poorly, if they are e.g. adsorbed onto soil material.

accumulation. See *cumulation*.

acute toxicity, short-term toxicity usually after a single dose of a chemical. This is usually measured during the observation period of 24 hours or sometimes up to 2 weeks, but in the case of PCBs and PCDD/Fs it must be observed for 4 or 6 weeks (see *PCB – acute toxicity*, *PCDD/F – acute toxicity*).

adsorption, attachment of material to a surface. In soil and sediments dioxins and PCBs adsorb tightly to the surface of organic material or clay particles, and may be poorly available for living organisms.

Agent Orange. See *chlorophenoxyacetic acid herbicides*.

AH receptor (AHR, dioxin receptor, aryl hydrocarbon receptor), a cell protein that initiates most of the effects of dioxin-like chemicals. Its primary function in the body is uncertain, and it is structurally related to many other important cell proteins involved for instance in rhythmic functions (clock proteins) and organ development.

Mechanism. When TCDD or other dioxins enter the cell, they bind to AHR, this moves from cellular cytoplasm to nucleus, forms a pair with another protein *ARNT* (see this), and this heterodimer (complex of two different proteins) binds to *DNA* (see this). This binding initiates the activation of a number of genes depending on the binding site of the dimer. Because it participates in the reading of a gene (transcription), it is called a *transcription factor* (see this). After a high dose of dioxin, AH receptor may activate or inhibit hundreds

of genes in rats (see *Tijet et al., Molec. Pharmacol. 2006:69:140–153*). One of the best studied of such genes is the gene of CYP1A1 enzyme, which is a xenobiotic metabolising enzyme. CYP1A1 oxidises many foreign chemicals and makes them more water-soluble usually aided by a second enzyme conjugating it to a water-soluble carrier molecule (see *metabolism*). Activation of CYP1A1 gene increases the enzymatic activity even by a factor of several hundred. It is not known which gene is (genes are) responsible for the toxic effects of dioxins (for more information on AHR, see *Lindén et al., Front. Neuroendocrinol. 2010:31:452–478*, <http://pubmed.gov/20624415>).

AH receptor nuclear translocator, see *ARNT*.

amino acid, the elementary unit of proteins. There are 20 common amino acids in proteins, and their order determines the character of the protein just as the order of the 26 letters of alphabet determines the contents of this text.

analysis, see *PCB – analysis, PCDD/F – analysis*.

Apiolio, a commercial PCB product. See *PCB – trade names*.

ARNT (Ah Receptor Nuclear Translocator), a protein in cell nucleus which acts as a partner of *AH receptor* (see this) and some other transcription factors. The complex of AHR + ARNT is called heterodimer, because it is a dimer of two different proteins. ARNT is in fact a misnomer, since it was previously thought to translocate AHR from the cytoplasm of the cell to the nucleus, but in fact it only binds AHR after this has entered the nucleus.

Aroclor, a commercial PCB product. See *PCB – trade names*.

aryl hydrocarbon receptor, see *AH receptor*.

Baltic Sea, an important sink of PCBs and PCDD/Fs in Europe. PCBs may have come mainly as air-borne pollution from Western Europe (see *PCB – sources, and incinerators*). PCDD/Fs (especially higher chlorinated PCDFs) may have their origin also in forest industries and their use of *chlorophenols* (see this). The levels in the Baltic Sea peaked during the 1970s, and have been decreasing since, albeit slowly. Baltic levels have caused a number of environmental toxicological effects, e.g. reproduction problems of seals and eagles.

Belgian chicken incident, a food contamination incident in Belgium. In January 1999 a large tank of recycled fats was contaminated by PCB oil. Refined fat was sold to more than ten animal feed factories (the contaminated lot probably only to two factories, both in

Belgium), which again sold their contaminated feed to farms, mostly chicken farms. The problem was noticed when the chickens showed symptoms of toxicity: low fertility and deformed chicks.

The total amount of PCB oil has been evaluated as 40–50 kg containing about 1 g (WHO-TEq) of dioxins and about 2 g (WHO-TEq) dioxin-like PCBs (*Debacker et al., Chemosphere 2007:67:S217–S223, <http://pubmed.gov/17208274>*). This could be the content of one or a few transformers.

The highest concentrations of PCBs found in chicken fat were 51 mg/kg (Σ 7PCB in fat) (51,000 ng/g) (see *seven marker PCBs*), and the highest dioxin concentration 0.0026 mg/kg (2613 ng/kg, as I-TEq or TCDD-equivalents in fat). PCBs were detected to a lesser extent in other farm animals. In chicken or chicken feed samples there were 50,000 times more PCBs (Σ 7PCB) than dioxin-TEqs, and the ratio was fairly constant. This means that monitoring in this specific case could be based on PCBs. As a screening analysis this could be performed in many laboratories, whereas dioxin analysis is extremely difficult and there were very few laboratories in Europe capable of performing them reliably. Also the cost of dioxin analysis was prohibitively expensive (of the order of 1000 euro per sample) and the analysis is time-consuming (about 1 month). Therefore routine monitoring could not be based on dioxin analyses or congener-specific PCB analysis using mass spectrometry.

Belgian PCB incident – risk evaluation. Dioxin concentrations that exceed the accepted limits in extreme cases by a hundredfold or more would cause a highly increased body burden in human beings, but slowly. Consuming 150 g of contaminated chicken (assuming 1000 ng/kg WHO-TEq in fat, 15 % of fat in the meat) twice a week would produce a body burden that would be hundredfold as compared with the present body burden of population (Figure 1). This would, however, require a continuous consumption during 30 to 50 years (see *cumulation*). In fact, an increase of 20 ng/kg (WHO-TEq in fat) would require 1 to 2 months of continuous consumption. Because the average young adult concentration in Central Europe in the period 1987 to 1993 decreased from 40 ng/kg to 20 ng/kg, the calculated consumption for one month would have meant going back to the levels prevalent in population during the 1980s.

Because it is unlikely that an individual would consume the worst contaminated chicken from week to week at this level, the true population effect is much less. This was later confirmed by actual measurements, where the congeners specific to the

contamination were traceable, but WHO-TEq values in the population did not increase significantly, in fact only from 22.9 to 23.1 ng/kg (*Debacker et al., Chemosphere 2007:67:S217–S223, <http://pubmed.gov/17208274>*). There may, however, be individuals who eat contaminated products from a single farm for some reason, and among those the prediction of maximal increase might hold. Even in such a case the time factor excludes any dramatic effects of dioxins. The contribution of non-dioxin-like PCBs is more difficult to assess. Particularly their poorly characterised neurodevelopmental effects are of concern. Also these compounds accumulate slowly.

The incident shows that due to the slow cumulation of dioxins, **long-term control** of food is of paramount importance. It also seems that the recycling and reuse system of fats, which as such is ecologically sound in reducing waste, has been too open and vulnerable.

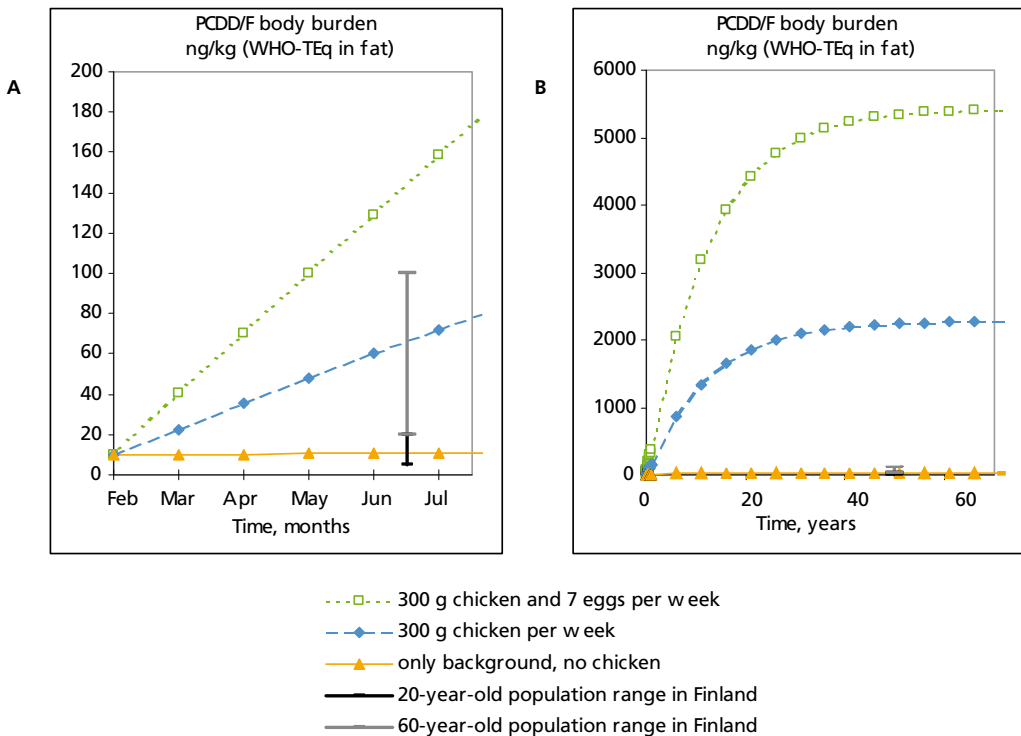


Figure 1. Modelled increase in the body burden of a person who consumes continuously the worst-contaminated chicken from Belgian chicken incident. A, six-month follow-up; B, 70-year follow-up. Assumptions: half-life: 8.6 years, body fat content: 15 kg, PCDD/F concentration in chicken: 1000 ng/kg (TEq in fat), chicken fat content: 15 % (per wet weight).

This risk evaluation means that food control should be very strict, and monitoring of concentrations in exposed population groups are highly advisable, but no individual health measures in those people who have consumed contaminated chicken for a limited time period can (nor need to) be recommended.

bioaccumulation (bioconcentration), property of a chemical to be concentrated from the surrounding environment to living organisms. Lipid-soluble, poorly water-soluble chemicals seek any lipid-containing material especially in water environment, e.g. plankton. Bioconcentration is strictly speaking a passive partition or diffusion between the media and the organism, bioaccumulation may also encompass uptake of compounds via feeding.

bioavailability, portion of a drug or chemical to enter the organism in active form. Bioavailability may be lowered by poor absorption or by metabolism in the gut or liver before passing to blood stream.

biomagnification, property of a chemical to be concentrated along the food chain. This requires that the chemical is not easily degraded chemically or biologically, and that it is bound to organisms or tissues so that it is carried from one species to the next species using it as its food. Lipid-soluble, poorly water-soluble chemicals are bioaccumulated by e.g. phytoplankton (plankton of plant character such as algae), this is consumed by animal plankton, this by invertebrates, further by fish and finally by seals. If the lipid-soluble chemical is very persistent, its concentration will increase stepwise at each level. That is why the species at the “top” of a food pyramid suffer most of persistent environmental chemicals. Chlorination of organic chemicals often increases both their persistence and their lipid solubility. Therefore PCBs and dioxins are bioaccumulated and biomagnified especially well. Increasing number of chlorines increases both lipid solubility and biomagnification. However, the optimal biomagnification capacity is at about 6 chlorines, probably because higher chlorinated congeners (esp. octa-) are so poorly water soluble that their bioavailability is low. Human beings are also at the top of the food chain, but because of the variety of foods from different sources humans consume, as compared with seals or eagles, bioaccumulation to humans is not so great.

biphenyl, C₁₂H₁₀, parent compound of polychlorinated biphenyls. See *chemical structures*.

body burden, the total amount of a chemical in the body. Average body burden of total sum of **PCBs** in industrialised countries range from

about 1 mg to 20 mg (Σ 6PCB) per person (0.1 to 1 mg/kg [Σ 6PCB in fat]). Average daily intake of the sum of PCBs is 10–20 ng/kg b.w. or about 1 μ g per person. As WHO-TEqs the PCB intake and body burden are comparable to those of PCDD/Fs.

Average body burden of **PCDD/Fs** in young western European population is about 100 ng (TEq) per person (0.000,000,1 g [TEq]); it can also be expressed as 5–10 ng/kg (TEq in fat) (Figure 2), in 60-year-old population about 500 ng (TEq per person). In *steady state* (see this) the body burden is about 5000 times the daily intake of dioxins. Average daily intake in many countries (see also *PCDD/F – sources*) is below 1 pg WHO-TEq/kg b.w., i.e. around 50 pg or lower (0.05 ng or 0.000,000,000,05 g) per person (see *TEq and units*). Further information *Liem et al. Food Addit. Contam.* 2000;17:241-259, <http://pubmed.gov/10912239>; *Patterson et al. Chemosphere* 2008;73:S261-S277, <http://pubmed.gov/18511103>; *Kiviranta* 2005, <http://bit.ly/ihD1j8>.

breast milk, one of the most important sources of dioxins and PCBs (see Fig. 2). Breast milk contains many lipid-soluble materials that are present in mother’s adipose tissue. In fact the concentrations of PCBs and PCDD/Fs are almost identical in mother’s adipose tissue, serum lipid and breast milk fat. This is an effective excretion method for the mother, who can lose even 25 % of her body burden of these substances during a long breast-feeding period. However, 25 % of

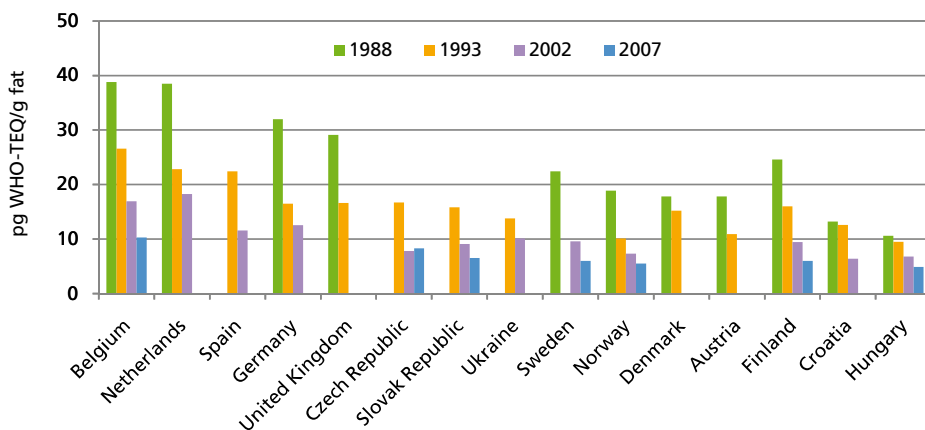


Figure 2. Changes in PCDD/F body burden in some countries measured from human milk samples of primipara mothers. (Data from ENHIS factsheet “Persistent organic pollutants in human milk”, 2009, with the permission of WHO Euro: <http://bit.ly/emTSPV>)

mother's body burden is then concentrated to a much smaller body, that of the baby. Therefore breast-fed babies are an obvious high-risk group for PCBs and PCDD/Fs. The dilemma of a risk assessor is that it is known with certainty that breast-feeding is beneficial for the baby, but there is no certainty that these chemicals would cause any harm at their present concentrations. Therefore most international expert groups have emphasised the importance of breast feeding and considered that whatever risks the dioxins may cause, they are not greater than the risks of not using the health advantages of mother's milk with its nutritional value, immunologically useful proteins and other health promoting factors. The latest dioxin risk assessment is based explicitly on the safety of the baby, and the tolerable daily intake (TDI) is calculated as a dose in mother's diet that would not cause too high exposure either to the foetus or a newborn breast-fed baby (WHO, *Food Add. Contam.* 2000:17:223-238, <http://pubmed.gov/10912238>).

b.w., body weight.

carcinogenicity, a property of a chemical to cause cancer. It is also called tumourigenicity to emphasise that a chemical may cause benign tumours and malignant tumours (such as carcinoma). Carcinogenic chemicals are often divided to genotoxic carcinogens (initiators) that can cause mutations (see *mutagenicity*) and initiate a cancer cell, and epigenetic carcinogens (see *promoters*) that are able to promote growth and/or differentiation of existing cancer cells.

carcinogenicity of dioxins, see *PCDD – carcinogenicity* and *PCDF – carcinogenicity*.

carcinogenicity of PCBs, see *PCB – carcinogenicity*.

carcinogenicity of PCDFs, see *PCDF – carcinogenicity*.

chemical structures. PCBs consist of 12 carbon atoms, forming two aromatic phenyl rings attached to one another through a carbon-carbon bridge, and 10 atoms that can be either hydrogens or chlorines (Figure 3). Theoretically 209 various combinations of chlorine and hydrogen are possible, and about 130 may be found in technical products. They are called congeners (see also *ortho-PCBs*). Chlorine increases the stability and decreases flammability of these compounds. The two phenyl rings of PCBs are able to rotate along the carbon-carbon bridge axis, and therefore they are flexible in the sense that they can assume a planar (flat) conformation similar to PCDDs, or a propeller-like conformation. *ortho*-Chlorines (in positions 2

and 6) may, however, prevent the planar conformation to a variable degree, and therefore *ortho*-congeners are less dioxin-like than non-*ortho*-congeners (see *ortho*-PCBs). Commercial PCBs contain PCDFs at levels up to 40 mg/kg, but usually not PCDDs.

PCDDs consist of 12 carbon atoms, forming two aromatic phenyl rings attached to one another through two oxygen bridges, and 8 atoms that can be either hydrogens or chlorines (Figure 4). Theoretically 75 various combinations of chlorine and hydrogen are possible, and the resulting dibenzo-*p*-dioxin derivatives are called *congeners* (see this). Chlorine increases the stability of these

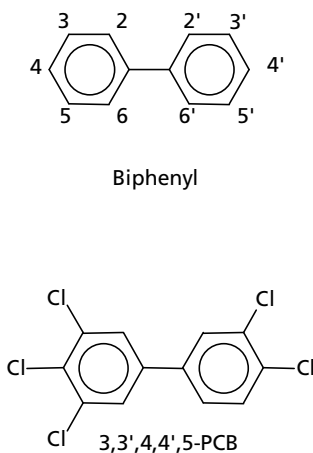


Figure 3. Structures of biphenyl and PCB.

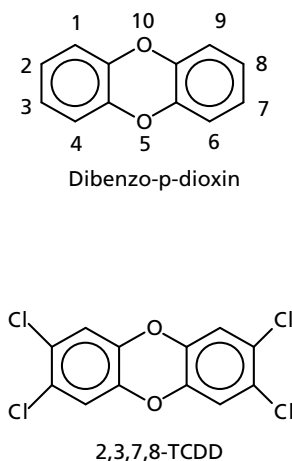


Figure 4. Structures of dibenzo-*p*-dioxin and TCDD.

compounds, and chlorines in positions 2,3,7, and 8 (lateral chlorines) are especially important, because they are essential for toxicity and also prevention of enzymatic destruction of PCDDs. Therefore the 7 congeners with 2,3,7,8-structure are toxicologically the most relevant. Each additional chlorine to 2,3,7,8-structure decreases toxicity, but the spectrum of adverse effects remains similar (see *TEF*). Tetra-, penta-, hexa-, hepta-, and octachloro-derivatives are often called TCDD, PeCDD, HxCDD, HpCDD and OCDD, respectively.

PCDFs consist of 12 carbon atoms, forming two aromatic phenyl rings attached to one another through one carbon-carbon bond and one oxygen bridge (Figure 5), and 8 atoms which can be either hydrogens or chlorines. Theoretically 135 various combinations of chlorine and hydrogen are possible, and the resulting dibenzofuran derivatives are called congeners. Chlorine increases the stability of these compounds, and chlorines in positions 2,3,7, and 8 (lateral chlorines) are especially important, because they increase toxicity and also prevent enzymatic destruction of PCDFs. Therefore the 10 congeners with 2,3,7,8-Cl-structure are toxicologically the most relevant. Most additional chlorines to 2,3,7,8-structure decrease toxicity (see *TEF*), but the spectrum of adverse effects remains similar. Tetra-, penta-, hexa-, hepta-, and octachloro-derivatives are often called TCDF, PeCDF, HxCDF, HpCDF and OCDF, respectively.

chloracne, a severe acneiform skin disease that is seen in humans after high industrial or accidental exposure to chlorinated compounds, esp. dioxins. A threshold level above which chloracne occurs has not been established. The dose range where chloracne was reported in Seveso, was 800 to 56,000 ng/kg (TCDD in fat), but some adults with levels up to 10,000 ng/kg did not have chloracne (see also *PCDD/F – acute toxicity*). Children seem to be more sensitive than adults to suffer from chloracne.

chlorophenols, a group of chemicals derived from phenol by chlorination. They are used mainly as antifungal impregnation agents

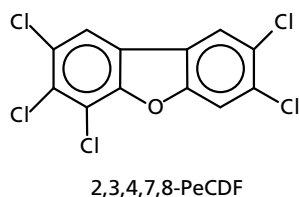


Figure 5. Structure of PeCDF.

in wood preservation, but previously their use has been widespread. The most common preparation is pentachlorophenol. Also tetrachlorophenol is the main chlorophenol in some preparations. Chlorophenols contain several other chlorinated compounds as minor contaminants, including PCDD/Fs. Chlorophenols may be a remarkable source of PCDD/Fs in waterways downstream of forest industries. In the most contaminated regions, the concentration of PCDDs and PCDFs in soil and sediments appears to be incredibly high, up to 10 mg/kg (10,000,000 ng/kg) dry weight, and as WHO-TEq 0.1 mg/kg dry weight (100,000 ng/kg). Chlorophenols have been banned in many European countries but not in all, and large amounts may exist in soil and sediments even after the discontinuation of their use. Some chlorophenols (esp. 2,4,5-trichlorophenol) were intermediates for further synthetic work.

chlorophenoxyacetic acid herbicides, a major class of weed-killers. They were once the most important class of herbicides, but their role has been decreasing. Some of them contained PCDD/Fs, 2,4,5-T in fact contained TCDD at relatively high concentrations during the 1970s. 2,4,5-T gained notorious reputation as an antifoliant agent (Agent Orange) in Vietnam War. It has later been claimed to have caused a number of side effects, including cancer and birth defects. Large epidemiological studies have not been able to substantiate these claims, but doubts have lingered ever since. Moreover, the Vietnamese have not been well studied. Also Swedish studies suggested increased cancer rates (soft-tissue sarcomas and non-Hodgkin lymphomas) in forest workers and others using these herbicides. Studies from other countries have not substantiated the high risk levels published in Sweden, but some studies suggest occupational risk. It is not clear whether this would be due to the herbicide itself or to dioxin impurities (for details, see Kogevinas *et al.*, *Am. J. Epidemiol.* 1997;145:1061–1075, <http://pubmed.gov/9199536>; Tuomisto *et al.* *Int. J. Cancer*, 2004;108:893–900, <http://pubmed.gov/14712494>).

citrus pulp pellet incident, a cattle feed contamination incident in 1997 and 1998. PCDD/F-contaminated lime was used in the drying process of pellets in one orange juice factory in Brazil. Pellets (dried orange peel) were imported to many European countries, and fed mainly to cattle. In Germany, a steady increase in dioxin concentrations in cow's milk was observed: average values were 0.62 ng/kg (I-TEq in fat) before August 1997; between September and December, 0.89; between January and February 1998, 1.38; and in March, up to 7.4 ng/kg (ITEq in fat). The pellets were

found to be the source of the contamination in April 1998.

The import of pellets from Brazil was banned for months, and a program for preventing further pellet contamination was set up. A provisional maximum level for PCDD/F in citrus pulp pellets was set at 0.5 ng/kg (I-TEq in d.w.) in EU. A major part of the feed was drawn from the market and destroyed. The total amount of the contaminated pellets was *ca.* 100,000 tons. A relatively small amount of heavily contaminated pellets had been mixed with this large stock during transportation, hence the concentrations varied greatly. The typical concentrations of PCDD/Fs in citrus pulp pellets were below 10 ng/kg (I-TEq in d.w.), but the highest concentrations were up to 32 ng/kg (ITEq in d.w.).

Clophen, a commercial PCB product. See *PCB – trade names*.

combustion, one of the major sources of PCDD/Fs. PCDD/Fs are formed during any unfavourable combustion process, if the required materials (chlorine, carbon, and certain metal catalysts such as copper) are present. This includes municipal waste incinerators, but also motor vehicles and **small-scale burning** of mixed materials. Especially unfavourable burning conditions prevail in accidental fires of landfill areas of municipal waste. On the other hand, a first-class incinerator (limit value 0.1 ng/Nm³ [WHO-TEq in exhaust gases], obtained by high enough burning temperature, good mixing, long enough residence time for burning gases, and “scrubbing” of the effluent gases to remove fly ash effectively) is an effective ultimate way to remove dioxin-like compounds from the environment.

congeners, chemicals derived from the same parent compound. PCBs, PCDDs and PCDFs are all mixtures of closely related compounds which are derivatives of biphenyl, dibenzo-*p*-dioxin and dibenzofuran, respectively (see *chemical structures*). Various number of hydrogen atoms in these parent compounds have been replaced with chlorine atoms, producing 209 possible PCBs, 75 possible PCDDs and 135 possible PCDFs. Derivatives in each group are called congeners in relation to other members of the same group. 17 PCDD/F congeners (7 PCDDs and 10 PCDFs) have “lateral” chlorines in positions 2,3,7 and 8, and are commonly measured and summed up by using *TEq* concept (see this). Similarly PCB-TEqs are used for “dioxin-like” non-*ortho* or mono-*ortho* PCB congeners (see *ortho-PCBs*).

conservative risk assessment, type of risk assessment which maximises the expectation of risk in order to make sure that the true risk is always below the estimate. In risk assessment one has often to

act in the state of uncertainty. Because many risk assessors prefer to err in the direction of exaggerating the risk rather than in the direction of not appreciating the risk, the worst possible prediction is often taken as the basis of risk evaluation in different steps of risk assessments. An example is using 95 % upper confidence limit rather than the most probable (average) risk level as the basis of likelihood of a deleterious effect. Another example is the so called *linear extrapolation* (see this) of cancer. It means that at one tenth dose of a carcinogenic chemical the number of cancers is also assumed to decrease to one tenth, at one hundredth dose to one hundredth, and so on all the way to zero level. An alternative way would be to assume a safe dose below which there is no cancer any more. Neither way of evaluation can be scientifically proved to be correct, but in conservative risk assessment the worst possibility is taken to be true. Conservative risk assessment has been criticised on several grounds. One is that crying the wolf all the time will inflate the message. The other point is an imbalance of risk evaluation, because conservative risk assessment is possible in some areas, e.g. in pesticide or dioxin risk assessment, but not in others such as air pollution or alcohol. This then may lead to wrong priorities, e.g. to overemphasising pesticide or dioxin risks while neglecting air pollution risks. Thirdly, the more uncertainty there is in the estimate, the higher the final estimate tends to be, while accurate estimates with little uncertainty tend to be lower. This results in systematic underrating of well-known risks, even if they were relatively high, and in exaggerating hypothetical risks.

cumulation, accumulation of a drug or chemical in the body. If a chemical enters the body continuously, its amount in the body increases until the elimination will reach the same rate as the intake; in other words the same amount of chemical is eliminated per unit of time, as is entering the body. This level is called the steady state. If elimination is very fast, this steady state level is reached quickly, but if elimination is very slow (in other words *half-life* [see this] is very long), a long time is needed to reach steady state. As a thumb rule, the body burden in steady state is the daily dose multiplied by 1.5 times half-life (in days), e.g. in the case of PCDD/Fs, about 5000 daily doses.

A bathtub with a leaking bottom plug can illustrate this. If the leak is large, pouring water from a tap to the bathtub at a constant rate will raise the water level rapidly to such a relatively low height that as much pours out through the leak as is coming in from the tap. But if the leak is little, water level will rise longer and to a higher level, until the pressure will increase the output of water through the

small leak to match the rate of the incoming water. Dioxins and PCBs leak out of the body very slowly, and therefore they keep cumulating even for decades until the elimination rate will finally be as great as the intake rate. The half-time of cumulation (the time during which 50% of steady state level will be reached) is the same as the half-life of elimination of the chemical. The half-life of TCDD is 7 to 8 years. This means that at a constant intake rate the body burden (the total amount of chemical in the body) will reach 50% of steady state in 7-8 years, 75 % in about 15 years and reach the steady state only in 40 to 50 years (see fig. 1 B).

CYP enzymes, a large group of enzymes metabolising drugs and foreign compounds (xenobiotics). AH receptor activated by dioxins initiates the expression of many CYP enzymes, i.e. it causes enzyme induction. This is in essence an adaptive and beneficial response, although in some cases it may lead to synthesis of carcinogenic intermediates (see *metabolism*)

2,4-D (2,4-dichlorophenoxyacetic acid), a *chlorophenoxyacetic acid herbicide* (see this).

daily intake, the amount of a contaminant that an individual is exposed to during one day, usually via food (see *PCB – sources, PCDD/F – sources*).

DDT [1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane], a well known insecticide (insect killer). DDT is not related to PCBs or dioxins, but it is also chlorinated, persistent organic compound which bioconcentrates in the environment and may cause problems to wildlife. Both DDT and PCDD/Fs are supposed to be *endocrine disrupters* (see that).

deka-, ten. E.g., dekachloro- ten chlorine atoms in a molecule.

developmental toxicity, toxic effects occurring during the developing period, especially during embryonal stages of development (see *embryo*). This period is often very sensitive to many chemicals, and the effect may range from reversible effects to embryonal or foetal death. Teratogenicity is one form of developmental toxicity, where a chemical causes permanent malformations. PCDD/Fs cause embryonal or foetal death at high exposures, teratogenicity such as cleft palate in some animal species, and they have been implied of being *endocrine disrupters* (see this).

di-, two. E.g., dichloro- two chlorine atoms in a molecule.

dibenzofuran, the parent compound of polychlorinated dibenzofurans (PCDFs), $C_{12}OH_8$. See *chemical structures*.

dibenzo-*p*-dioxin, the parent compound of polychlorinated dibenzo-*p*-dioxins (PCDDs), $C_{12}O_2H_8$. See *chemical structures*.

dioxane (1,4-diethylene dioxide), a ring-structured chemical, $C_4H_8O_2$. Used as stabiliser in chlorinated solvents and solvent for many organic compounds. Does not have dioxin-like effects.

dioxin, chemical name with multiple uses. In less careful language dioxin is used as a synonym of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), or any of the polychlorinated dibenzo-*p*-dioxins (PCDD) or dibenzofurans (PCDF), or the whole class of these compounds (see the specific entries). In strict chemical sense dioxin is a heterocyclic ring-structured chemical containing carbon, oxygen and hydrogen, $C_4H_4O_2$, forming e.g. the middle ring of dibenzo-*p*-dioxin (see *chemical structures*). It has no PCDD-like toxicity.

dioxin-like PCBs, PCB congeners able to assume planar conformation and bind to AH receptor. These include four non-ortho and eight mono-ortho congeners (see *ortho-PCBs* and *TEQ*).

dioxin receptor. See *AH receptor*.

dioxin responsive element. See *DRE*.

diphenyl (biphenyl), the parent compound of polychlorinated biphenyls (PCBs), $C_{12}H_{10}$.

DL-PCBs, see *dioxin-like PCBs*

DNA (deoxyribonucleic acid), the basic chemical structure of the genes. It is formed of four bases, adenine (A), guanine (G), cytosine (C), and thymine (T), a sugar deoxyribose, and phosphate. Its structure was found in 1953 by James Watson and Francis Crick. The smallest unit of DNA is a nucleotide, which consists of one base, one sugar, and phosphate. The base distinguishes the four different nucleotides from each other. Three successive nucleotides form a codon, which is the smallest code word unit of DNA. One codon determines one *amino acid* (see this) when the message of DNA is translated to a protein. The execution of protein synthesis according to the “blueprint” in DNA is called expression of the gene. First a blueprint is copied to RNA (see this) by transcription and then according to the directions in codons, amino acids are linked to form a *protein* (see this) chain by translation.

DRE (dioxin responsive element, XRE, xenobiotic responsive element), a short sequence of DNA which binds the dimer of AHR+ARNT and initiates the transcription of a gene. The structure of DRE in the case of CYP1A1 gene is 5'-TNGCGTG-3'.

d.w., dry weight.

elimination of chemicals, mechanism to get rid of drugs and chemicals (see also *PCB – elimination*, *PCDD/F – elimination*). Elimination out of the body takes place in two principal ways: excretion and metabolism (usually followed by excretion of the breakdown products). Only water-soluble materials can be excreted in the kidneys to urine, and many organic pollutants are lipid soluble and poorly water-soluble chemicals. Therefore they cannot be excreted practically at all as such, a little in faeces. Metabolism (see this) tries to make them more water soluble, but especially higher chlorinated PCBs (see *PCB – physicochemical properties*) and PCDD/Fs with “lateral” chlorine atoms (see this and *PCDD - chemical structure*, *PCDF – chemical structure*) are metabolised very poorly, and therefore cannot be effectively excreted even with the help of metabolism. They accumulate in body fats, and their *half-life* (see this) may be even several years. Elimination of drugs and chemicals usually obeys first order kinetics (see *half-life*, *cumulation*). This means that the rate of elimination directly correlates with the amount of the drug in the body (or the concentration in blood), i.e. a constant fraction (e.g. one per cent) of the chemical is eliminated in time unit (e.g. in an hour).

embryo, unborn offspring during the period of most rapid development until all major structures (limbs, inner organs) are represented, in man from two weeks after fertilization to the end of seventh or eighth week (see also foetus).

endocrine disrupters, chemicals or natural compounds that can interfere with the actions of hormones. Such chemicals have been known for decades, e.g. natural goitrogens (compounds in many plant species of *Cruciferae*-family that interfere with thyroid hormone synthesis), and many drugs that cause changes in the levels of pituitary hormone prolactin. Some PCBs and their metabolites bind to thyroid hormone binding protein and interfere with its function. Presently there is interest in many countries in chemicals that might interfere with the activity of sex hormones. *p,p'*-DDE, a metabolite of DDT is an antiandrogen: it antagonizes the effects of testosterone (male sex hormone). Estrogenic (female sex hormone) and antiestrogenic risks from the environment are less well characterised, but

environmental chemicals have been implied to cause “feminisation” or “demasculinisation”. In waterways the most important estrogenic compounds (e.g. causing sexual disturbances in fish) seem to be natural estrogens from humans and animals, and synthetic estrogens from contraceptive pills. Synthetic chemicals with postulated endocrine disrupting activity include phthalates, bisphenols, alkoxyphenols, organochlorine insecticides, some detergents, PCBs, and PCDD/Fs. Their effects on human male disorders (such as testis cancer, hypospadias, and semen quality) are under investigation, but so far there is no unambiguous evidence.

environmental persistence, ability of a chemical to continue existence in the environment (see *PCB – environmental persistence*, *PCDD/F – environmental persistence*).

epigenetic carcinogens, chemicals that cause tumours without causing mutations or other genetic damage. Instead they act by e.g. promoting the multiplication the initiated tumour cell and the growth of a tumour (see also *mutagenicity* and *promoters*).

equivalency factors. See *TEF*.

EU directives on dioxin. See *PCDD/F – limit values*.

expression of a gene, reading a genetic information from DNA to make a new protein (see *DNA* and *RNA*). Every cell contains every gene of the individual, but only some are expressed in any particular cell, and often only at a particular time. Proteins involved e.g. in the synthesis of skin pigment are expressed only in certain layers of the skin, and not in the gut; even in the skin the rate of expression depends on the stimulation by sunlight.

extrapolation, extending predictions outside the range of observations. In regulatory toxicology extrapolation means predicting an effect in such conditions that it is not possible to assess the effect experimentally. Extrapolation is used over dose, species, sex, age, or route.

Dose extrapolation means predicting an effect (e.g. the likelihood of cancer) below the range of doses that can be tested experimentally. In a group of 50 animals in a two-year cancer study, it is possible to detect a 10 % additional cancer risk, i.e. five cancers in addition to the typical background incidence of e.g. ten cancers. Ten per cent risk would be clearly unacceptable in humans. We would barely accept a risk of one in ten thousand of contracting cancer from a chemical. However, an experiment that could detect an increase in cancer risk from 20 % (background) to 20.01 % (background + chemical-

induced) would require more than 100,000 animals. This is clearly not feasible. Therefore the dose of the chemical is increased so that the effect is detectable, and the effect at the true level of human exposure is extrapolated mathematically. Because there is no obvious way to verify the correct formula for extrapolation, this is one of the most common sources of disputes in toxicology (see also *linear extrapolation*).

Another extrapolation is species extrapolation. If the chemical is studied in the mouse, one needs to know what dose in the mouse is equivalent to a dose in humans. This is one of the sources of confusion in dioxin risk assessment, because TCDD kills a guinea pig at a dose of 0.001–0.002 mg/kg, but a hamster only at a dose of several mg/kg. So it is important to know, which is a better model for human being, the guinea pig or the hamster. Some effects of TCDD, such as developmental toxicity, are seen at low doses both in guinea pigs and hamsters, however.

Fenchlor, a commercial PCB product. See *PCB – trade names*.

first order kinetics, see *elimination*.

foetus, fetus, unborn offspring after all major structures have been outlined, in man from seven or eight weeks after fertilization until birth (see also embryo).

gas chromatography-mass spectrometry (GC-MS), a method for analysing concentrations of, e.g., PCDD/Fs, PCBs, and other organic compounds in a sample. The method has two phases: first, separation based on differential movement of compounds in hot flowing gas in a long quartz capillary; second, detection based on the molecular mass of the compounds. The method is very sensitive and it can detect as little as 0.5–100 pg, depending on the resolution of mass spectrometer and the matrix..

GC-MS, gas chromatography- mass spectrometry, see this

genotoxic carcinogens, cancer-causing substances that cause mutations, chromosomal damage or other kind of damage to the genetic material in cells. They are thus able to transform a normal cell to a cancer cell (see *mutagenicity*).

geological sources. See *natural sources*.

German dioxin incident, animal feed contamination incident near Hamburg in November, 2010. A routine analysis in a feed factory revealed PCDD/Fs in fats to be used for animal feed. Technical fatty acids had been mixed with other fats in a recycling firm, and this caused

a concentration of about 60 ng/kg in one batch of fat. The highest concentration in the produced feed was about 1.5 ng/kg, exceeding the maximum limit of 0.75 ng/kg. In some eggs concentrations over 12 ng/kg were found, but most eggs produced contained less than 3.0 ng/kg, the maximum limit of European Union. So this incident is not comparable to the Belgian PCB chicken incident (see this).

half-life, time needed to decrease the amount of chemical to one-half (see also *PCB – half-life*, *PCDD/F – elimination*). Most chemicals are eliminated out of the body by the so-called first-order elimination. This means that a fixed proportion (e.g. one per cent) of the chemical remaining in the body is eliminated per unit of time (e.g. per hour). Therefore more is eliminated in absolute terms (e.g. milligrams of chemical), when the concentration in the body is high, than later, when the concentration has already decreased.

A convenient measure for the rate of elimination is the half-life: this is the time during which the amount of chemical in the body will decrease to 50% of the amount in the beginning of the observation. The half-life is a constant for a chemical, so during the first half-life the amount decreases to 50%, during the next to 25%, during the next to 12.5% and so on. As a practical rule it is considered that a substance is totally eliminated within 5 half-lives (in fact about 3% of it still remains). Elimination half-life is equal to cumulation half-time. This means that with a constant intake, body burden increases practically 5 half-lives, after which a steady state is achieved.

hepta-, seven. E.g., heptachloro- seven chlorine atoms in a molecule.

herbicides, see *chlorophenoxyacetic acid herbicides*.

hexa-, six. E.g., hexachloro- six chlorine atoms in a molecule.

HpCDD, heptachlorodibenzo-*p*-dioxin. See *chemical structures*.

HpCDF, heptachlorodibenzofuran. See *chemical structures*.

HxCDD, hexachlorodibenzo-*p*-dioxin. See *chemical structures*.

HxCDF, hexachlorodibenzofuran. See *chemical structures*.

incinerator, a furnace to burn completely waste materials. Incinerators of mixed municipal waste have been one of the most important sources of PCDD/Fs in Western Europe and America (see fig 6). PCDD/Fs are formed, if there is chlorine (especially from polyvinyl chloride plastics, PVC) and certain metals present which catalyse their formation, and thermal conditions are favourable. Incinerators may also vaporise PCDD/Fs, PCBs and their contaminants from the

fuel, if the burning conditions are not adequate. Incinerating is a completely valid means of disposing of PCDD/Fs (and PCBs), but the requirements of the incinerator are demanding. The temperature must be high enough, and there must be a proper filtering system to collect fly ash that may still contain some PCDD/Fs formed after cooling. It should be noted that dioxins may be formed during any unfavourable combustion process, if the required materials are present, including motor vehicles and small-scale burning of mixed materials (see also *combustion*).

I-TEq (international TCDD-equivalent quantity), see *TEq*.

IUPAC, International Union of Pure and Applied Chemistry. IUPAC has standardised the names of all PCB and PCDD/F congeners and given them reference numbers that are widely used due to their simplicity compared to their proper names. E.g., PCB126 denotes 3,3',4,4',5-pentachlorobiphenyl.

Kanechlor, a commercial PCB product. See *PCB – trade names*.

lateral chlorines, the four chlorine atoms in a PCDD/F molecule in positions 2, 3, 7, and 8 (see *chemical structures*). These four chlorines are required for binding to the AH receptor and toxic effects. They also stabilise the molecule against metabolism, which increases their half-life and tendency for accumulation. PCDD/Fs without lateral chlorines are rapidly metabolised, which prevents their accumulation in the food chain.

LD50 (median lethal dose), a dose which is lethal to 50 % of animals usually in an acute experiment (a single dose experiment).

levels of dioxins, see *PCDD/F – concentrations in humans and body burden*.

linear extrapolation, a straight-line projection of an effect to smaller doses (see also *extrapolation*). Linear extrapolation is a simple way of quantifying a toxic effect (usually cancer) at low doses, which cannot be tested reliably. Cancer rate is measured at a high dose, and found to be e.g. 10 % (a cancer in one animal out of ten). An assumption is made that the rate decreases towards low-dose range linearly at the same rate as the dose. In other words, one hundredth dose gives the number of tumours that is one hundredth of the measured number (one hundredth of 10 % is then one out of 1000), and so forth. Linear extrapolation means that there is no safe dose (“one molecule can cause a cancer”). While intuitively attractive, this theory is probably false in most cases thanks to our defence mechanisms, and carcinogenicity

is not different from any other form of toxicity. The actual risk is probably lower than the estimate achieved by linear extrapolation, hence this method is conservative. In theory also one tuberculosis bacillus can cause the disease, but experience has taught us that the dose of bacteria is highly relevant, and in real life one bacillus is easily destroyed by the body and cannot cause tuberculosis.

lipids, one of the principal classes of macromolecules in our body (the others are proteins and carbohydrates). Lipids include fats and oils (triglycerides), fatty acids, waxes, steroids, phospholipids, glycolipids and lipoproteins.

lipophilicity, having a strong affinity to fats and other lipids (rather than to water). This property of a chemical is often described by the octanol-water partition coefficient P_{ow} . It is the proportion of the concentrations of the dissolved chemical in octanol (a lipophilic solvent) and water phases in a test tube. The more lipophilic chemical, the more it moves to the octanol phase and the higher is the P_{ow} value.

LOEL (LOAEL), lowest observed (adverse) effect level. A common term in regulatory toxicology to define the lower limit of toxic or biochemical effects in animal studies. This time-honoured term is a poor and inaccurate way of defining toxicity, because toxicity is not a threshold phenomenon but fades away gradually when the dose decreases. Therefore LOEL depends on the number and size of doses selected, number of animals (the more animals, the lower the LOEL is likely to be), and inaccuracy caused by chance. Errors can be easily an order of magnitude (tenfold) or greater. There is a trend to replace LOEL with a “benchmark dose”, which is defined as a dose causing 5 % or 10 % of the maximal effect. It is much more accurate, because it is not based on just one dose but a dose response curve derived from several dose levels.

Love Canal, a residential area at Niagara Falls, New York. Housing and a school were constructed over an old hazardous waste site containing many chemicals including dioxins. This was revealed in 1979, and the population evacuated. There is no unambiguous evidence of human illness due to this incident.

maximum limits, see PCDD/F – limit values

metabolism, processes by which a particular substance is handled in the body. Chemical transformation of foreign chemicals (xenobiotics) occurs especially in the liver, but to some extent in all tissues. Usually the main purpose is to transform the chemicals to a more water-

soluble form so that they can be excreted via urine or faeces. Often this drug or xenobiotic metabolism occurs in two steps, in the first phase usually oxidative enzymes (often *CYP-enzymes*, see this) attach a “handle”, a suitable group such as hydroxyl, to the chemical, and secondly a water-soluble molecule (such as a sugar or amino acid) is tied to this handle to increase water-solubility. Often the metabolised products are less toxic, but in occasional cases metabolism may increase toxicity.

microgram (μg), 0.000,001 g. See *units*.

mono-, one. E.g., monochloro- one chlorine atom in a molecule.

mono-ortho-PCB. See *ortho-PCB*.

municipal waste incineration. See *incinerator*.

mutagenicity, a property of a chemical to cause genetic damage (damage of DNA). If the error is caused to a critical gene (such as in a so-called proto-oncogen or “cancer gene”, or in an anticancer gene), the result may be carcinogenicity. Therefore mutagenicity tests are done as cheap preliminary tests to assess the possibility of cancer risk of a chemical. PCBs and PCDD/Fs are not mutagenic, and thus they are not likely to initiate a cancer, but they may promote the development of cancer initiated by other factors.

nanogram (ng), 0.000,000,001 g. See *units*.

natural sources of dioxins, sources not associated with human activities. Few exhaustive analyses have been performed on old samples, but it seems on the basis of both soil samples in museums and sea and lake bottom sediment samples that pre-industrial PCDD/F levels are detectable but low. These may be due to forest fires and later due to combustion of natural items such as wood and peat. A drastic increase is seen after 1940's, and this coincides with a change in congener profiles. PCBs are not detected in pre-industrial samples.

ng, nanogram. See *units*.

NOEL (NOAEL), no-observed-(adverse)-effect level. The largest dose in an animal experiment that does not cause an effect (see *LOEL*).

nona-, nine. E.g., nonachloro- nine chlorine atoms in a molecule.

non-ortho-PCB, see *ortho-PCBs*.

OCDD, octachlorodibenzo-*p*-dioxin. See *chemical structures*.

OCDF, octachlorodibenzofuran. See *chemical structures*.

octa-, eight. E.g., octachloro- eight chlorine atoms in a molecule.

octanol, octyl alcohol, C₈H₁₇OH.

ortho-PCBs, congeners of PCBs that have one or more chlorines in *ortho*-position (positions 2 or 6; see *chemical structures*). Position of a group in aromatic ring as related to some other group can be *ortho*-, *meta*- (positions 3 or 5), or *para*- (position 4). In PCB congeners (see *congener*) this is counted from the carbon-carbon bridge between the two phenyl rings. *ortho*-Congeners mean congeners that have one (mono-*ortho*) or several (di-*ortho*, tri-*ortho*, tetra-*ortho*) chlorines in *ortho* positions. *ortho*-Positions affect the conformation of the molecule; non-*ortho* PCBs can assume a completely flat (planar) conformation, which is close to that of dioxins. Space-requiring *ortho* chlorines are a steric hindrance for the flat conformation, and therefore only non-*ortho* or to some extent mono-*ortho* PCBs can mimic PCDDs to have similar toxic effects based on binding to *AH receptor* (see this). Non-*ortho*-congeners are present in the environment at much lower concentrations than *ortho*-congeners.

PBBs (polybrominated biphenyls), compounds that are used as flame retardants and fire extinguishers. They may have some of the same effects as PCBs. They also bioaccumulate as lipid soluble and persistent chemicals.

PBDEs (polybrominated diphenylethers), compounds that are in wide use as flame retardants. They may have some of the same effects as PCBs, but they are generally less potent. They also bioaccumulate as lipid soluble and persistent chemicals.

PCB, *polychlorinated biphenyl* (see that). See also *PCB – specific items*.

ΣPCB, the sum (total weight) of all PCB congeners.

Σ7PCB, the sum (total weight) of the *seven marker PCBs* (see this).

PCB – acute toxicity, toxicity occurring after a single dose within a few weeks. It is generally low, but it depends on the mixture of congeners, because dioxin-like (non-*ortho*, see *ortho-PCBs*) PCBs are much more toxic than other congeners. Their toxicity resembles that of dioxins (see *PCDD/F – acute toxicity*).

PCB – analysis, measurement of concentration of a compound in a sample. The marker PCBs can be analysed by gas chromatography by using electron capture detector. This is a fairly widely available method, but if absolute accuracy and congener-specific analysis is needed, *gas*

chromatography-mass spectrometry (see this) may be needed. This is a very expensive method not available in many laboratories.

PCB – biomagnification, property of PCB compounds to concentrate from one trophic level to the next (see also *biomagnification*). Many PCBs are extremely persistent in the environment. Increase in chlorination (see *PCB – physicochemical properties*) increases both stability and lipophilicity. Therefore they concentrate along the food chain, and species at the “top” of the food chain (such as seals or eagles) are in special danger.

PCB – carcinogenicity, capacity of PCBs to cause cancer. A number of long-term carcinogenicity studies have been carried out in mice and rats. Interpretation is complicated by the lack of information of minor impurities, especially PCDFs. In many of these studies hepatocellular adenomas and/or carcinomas (tumours of the liver) were found although the increase was not always significant. The most recent studies conclude that carcinogenicity of PCBs can be totally or almost totally attributed to dioxin-like PCBs or PCDD/F impurities (*Knerr & Schrenk Crit.Rev. Toxicol. 2006:36:663-694*, <http://pubmed.gov/17050081>). PCB mixtures are considered non-genotoxic, PCBs do not cause mutations or chromosomal damage. Therefore rodent tumourigenicity is considered to be of epigenetic nature (promoting rather than initiating effect, see *mutagenicity, promoters*). IARC classifies PCBs as probable human carcinogens on the basis of animal data. Remarkable caution is needed in extrapolating the available animal data to humans. None of the available epidemiological studies provide conclusive evidence of an association between PCB exposure and increased cancer mortality. (For more information, see *International Programme on Chemical Safety, Environmental Health Criteria 140, WHO, Geneva, 1993*, <http://bit.ly/fubDjv>).

PCB – chemical structure, see *chemical structures*.

PCB – contaminants, by-products found unintentionally in PCB products. Technical PCBs contain a number of various chlorinated byproducts, e.g. about 40% chlorobenzenes, a few percent chloronaphthalenes, and also small amounts of PCDDs and PCDFs (93% PCDFs and 7% PCDDs of the total PCDD/F content in the PCB product which caused the Yusho Rice Oil accident, pentaPCBs, tetraPCBs and hexaPCBs dominating). PCDFs have been detected up to 40 mg/kg (Σ PCDF) in PCBs. Because commercial products were not sold according to composition but according to their physical

properties, there may be large variations both between preparations and between batches of a preparation.

PCB – disposal of PCB oils cannot be burned in usual conditions, because they burn poorly and evaporate to the environment along with their PCDD/F impurities. PCDFs may also be formed during PCB burning. Therefore PCBs are considered problem waste, which must be incinerated by a well-controlled process in a high-quality waste incinerator at the temperature of 1000–1200 °C, and with an effective fly-ash filtering system (see also *incineration*).

PCB – elimination, process of discharging PCB out of the body. Elimination of chemicals out of the body is usually based on two mechanisms, excretion (such as in urine or faeces) or metabolism (see this; chemical breakdown, often in the liver). Only water soluble materials can be excreted in the kidneys to urine, and PCBs as lipid soluble and poorly water soluble chemicals cannot be excreted practically at all as such. Metabolism tries to make them more water soluble, but especially higher chlorinated PCBs (see *PCB – physicochemical properties*) are metabolised very poorly, and therefore cannot be effectively excreted even with the help of metabolism. Therefore they accumulate in body fats, and their *half-life* (see this) may be even several years. *para*-Positions (4 or 4', see fig. 3) seem to be preferably hydroxylated, unless prevented by chlorines in both 3 and 5. Metabolism is favoured by availability of two neighbouring non-chlorinated carbon atoms. As the rate of chlorination increases, the rate of metabolism decreases.

PCB – environmental persistence, ability of PCBs to continue existence in the environment. The stability of PCBs is a technical advantage, but it also means that they are extremely persistent in the environment. Increase in chlorination (see *PCB – physicochemical properties*) increases both stability and lipophilicity. Neither soil microbes nor animals are able to break down effectively the highly chlorinated PCBs. This causes very slow elimination (see *PCB – elimination*). Because some PCBs are more persistent than others, the spectrum of congeners in the environment, animals and humans is never quite identical to that in the original commercial product. In water, PCBs are adsorbed on sediments and organic matter. This decreases the rate of volatilisation, but also slows down the degradation.

PCB – half-life, time needed to decrease the amount of PCBs to one-half. The half-lives of the most toxic non-*ortho* PCBs have been

estimated to vary from 0.1 to 7.3 years (see *Milbrath et al. Environ. Health Perspect.* 2009;117:417-425, <http://pubmed.gov/19337517>). Somewhat fragmentary information suggests that the half-lives of other PCBs are from a year to about 20 years. See also *half-life*.

PCB – physicochemical properties. All PCBs are lipophilic (soluble in fats and oils) and practically insoluble in water, but lipophilicity increases by increasing rate of chlorination (see *PCB – chemical structure*). Technical mixtures are mobile to viscous oils depending on the rate of chlorination, and their boiling point varies from 300 to 400 °C. They resist high temperatures and oxidising conditions without breaking down. Their electrical conductivity is very low which made them suitable cooling liquids for electrical equipment.

PCB – sources. Emissions. PCBs were manufactured from 1930 to 1970s or 1980s (varying in different countries), and the total production was in excess of a million tonnes. Production of PCBs was banned by Stockholm convention (*see this*) in 2001. They have spread to the environment in accidents (such as transformer fires or leaks), by volatilisation from waste landfills and during incineration of mixed municipal waste (e.g. plastic materials). The virtually universal distribution of PCBs suggests transport in air.

Human exposure. Food is the major source for human exposure to PCBs and dioxins, especially fatty foods: dairy products (butter, cheese, fatty milk), meat, egg, and fish. Some subgroups within the society (e.g., nursing babies and people consuming plenty of fish) may be highly exposed to these compounds and are thus at greater risk. Average daily intake of PCBs is about 1 µg per person. PCB concentrations have been screened in four WHO international studies, and in Central Europe the concentrations have decreased in breast milk from 400–800 µg/kg (sum of *six marker PCBs* [see this] in milk fat) to 100–200 µg/kg from 1984 to 2003. The decrease in environmental concentrations is partly due to prohibition of the use of PCBs, partly due to improved incineration technology (see also *PCDD/F – sources*).

PCB – toxicity in humans. This is difficult to evaluate, because the exposure has usually been to a mixture of different congeners and also impurities such as PCDFs. Occupational exposure may be to different congeners than exposure of general public through food, because some congeners are more easily degraded in the environment than others. In occupational conditions skin rashes, itching, irritation of the conjunctivae, pigmentation of fingers and nails, chloracne, liver

problems and neurological and unspecific psychological symptoms have been seen. In *Yusho* and *Yu-Cheng* incidents (see these) also various skin and nail problems were seen, as well as liver enlargement and immunological problems. In children among *Yusho* and *Yu-Cheng* patients skin problems, oedematous eyes, dentition at birth and lowered birth weight were seen, among others. Total exposures in these cases have been estimated at 600 to 1,800 mg per person (Σ PCB). The daily intake of PCBs in general population in most industrialised countries is of the order of 1 μ g per person (Σ PCB). Such levels have not been associated with disease. (For a review, see *Ulbrich & Stahlmann, Arch. Toxicol. 2004;78:252-268*, <http://pubmed.gov/15064922>; for detailed evaluation, see *International Programme on Chemical Safety, Environmental Health Criteria 140, WHO, Geneva, 1993*, <http://bit.ly/fubDjv>).

PCB – trade names. Many companies in several countries have manufactured PCBs. The trade names include Apirolio, Aroclor, Clophen, Fenchlor, Kanechlor, Phenoclor, Pyralene, Pyranol, Pyroclor, Santotherm FR, and Sovol. Sometimes the trade name indicates the degree of chlorination, e.g. Aroclor 1254 contains 54 % of chlorine, 12 indicates the number of carbon atoms.

PCB – use. PCBs were used since 1930 because of their stability and low flammability (see *PCB – physicochemical properties*) as insulating materials in electrical equipment (electrical capacitors, transformers), as plasticizers (softening materials) in plastic products, and for a variety of other industrial purposes (in gas-transmission turbines, vacuum pumps, hydraulic fluids, adhesives, fire retardants, wax extenders, lubricants, cutting oils, oils in heat exchangers etc.). The total production was in excess of a million tonnes. Common trademarks included Aroclor, Clophen, and Kanechlor (see *PCB – trade names*).

PCDD, polychlorinated dibenzo-*p*-dioxin. See this and *PCDD – specific items*.

PCDD – carcinogenicity, capability of dioxins to cause cancer. TCDD has been shown to be carcinogenic (causing cancer) in several species of experimental animals. TCDD is not mutagenic, i.e. it does not cause mutations which may initiate a cancer cell by changing the genetic information of the cell. Rather TCDD is a promoting agent: it promotes the growth and transformation of already initiated cancer cells (*Dragan & Schrenk, Food Addit. Contam. 2000;17:289–302*, <http://pubmed.gov/10912243>). It has also been proposed that

TCDD may metabolically activate polyaromatic hydrocarbons to form reactive intermediates, or induce active oxygen radicals, which may secondarily cause genetic damage. Such mechanisms and recent studies suggest that there is a practical threshold level or dose, below which TCDD will not cause cancer (*Walker et al., Environ. Health Perspect., 2005:113, 43–48; <http://pubmed.gov/15626646>*).

In human beings cancer assessment has proved difficult, because, with the possible exception of *Seveso accident* (see this), the groups investigated have always been exposed to many chemicals simultaneously. Some of these (such as chlorophenols and several solvents) may be carcinogenic in their own right, and it is hard to know which chemical is responsible for the effect. In short, human carcinogenicity is likely, but very high exposures to TCDD and other dioxins are needed to cause a modest increase in cancer incidence. The maximum TCDD concentrations in Seveso were 56,000 ng/kg (TCDD in fat), in occupational studies max. 32,000 ng/kg (TEq in fat) and average 2,000 ng/kg (while the average concentrations in the population are 5 to 50 ng/kg, as WHO-TEq in fat). Regardless of the high concentrations, the increases in cancer rates were barely detectable (e.g. in the latest occupational study 13 % increase in total cancer). This means that dioxins are relatively weak carcinogens in humans (More information on this topic in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 69, Lyon, 1997, <http://bit.ly/ieqeDt>; Kogevinas, *Food Addit. Contam.* 2000:17:317-324, <http://pubmed.gov/10912245>; Pesatori et al., *Environ. Health* 2009:8:39, <http://pubmed.gov/19754930>; Tuomisto et al. *Int. J. Cancer*, 2004:108:893-900, <http://pubmed.gov/14712494>).*

PCDD – chemical structure. See *chemical structures*.

PCDD/F, an abbreviation for PCDDs and PCDFs.

ΣPCDD/F, the sum (total weight) of the 17 PCDDs and PCDFs with a TEF value >0.

PCDD/F – acute toxicity. This is quite variable in different animal species (Table 1). Lethal dose of TCDD to guinea pigs is about 0.001 mg/kg b.w., and to Rhesus monkeys 0.07 mg/kg b.w., but hamsters can tolerate over 1 mg/kg b.w. Even strains within the same species can show a similarly wide difference: the LD50 values for rats vary from 0.010 to >10 mg/kg.

Human lethal dose is not known. In Seveso accident, the highest human TCDD concentrations were 56,000 ng/kg (in fat). No people died in the accident, but lots of small animals such as rabbits were

Table 1. Acute toxicity (measured as median lethal dose) of TCDD in animal species and strains. The LD50 values (see this) are based on the administered dose in mammals and birds and measured concentrations in fish.

Species (strain)	LD50 (mg/kg)
Lake trout sack fry	0.000074
Guinea pig	0.002
Zebra fish sack fry	0.0025
Rat (Long-Evans)	0.018
Chicken	<0.025
Rat (Sprague-Dawley)	0.06
Rabbit	0.115
Mouse (C57BL/6)	0.182
Mouse (DBA/2)	2.57
Hamster	>3
Rat (Han/Wistar)	>10

found dead at the accident area. In Vienna in 1998 two women were poisoned with huge doses of TCDD, in one of them the concentration was 144,000 ng/kg fat, the highest ever measured. This is equivalent to a dose of 0.02–0.03 mg/kg b.w. She suffered from chloracne for several years, but other symptoms were few. In 2004 Ukrainian presidential candidate Victor Yushchenko was deliberately poisoned with TCDD, and his TCDD concentration was 108,000 ng/kg. After initial malaise, the most remarkable symptom was chloracne. These findings show that human being is not among the most sensitive species (see *Geusau et al. Environ. Health Perspect. 2001:109: 865–869*, <http://pubmed.gov/11564625>; *Sorg et al. Lancet 2009:374:1179–1185*; <http://pubmed.gov/19660807>).

No dose will kill the animal immediately, but a high dose causes the so called “wasting syndrome”, the animal is anorectic and eats less than a quarter of the normal food intake, and dies after two to three weeks when the body weight has decreased by 30–50 %. In some animals there may be liver damage including porphyria (disturbance of the synthesis of heme, the pigment of haemoglobin). Other typical features are atrophy of the thymus, disturbances in the levels of some amino acids and lipids, and induction of many oxidative enzymes. Other PCDD/Fs induce similar toxic effects, but they are less potent in line with their TEF (For details, see *Pohjanvirta & Tuomisto, Pharmacol. Rev. 1994:46:483-549*, <http://pubmed.gov/7899475>. See also *PCDD/F - toxicity in animals*).

PCDD/F – analysis. At the concentrations present in the environment or in living tissues, PCDD/Fs can be reliably analysed only by using *gas chromatography-mass spectrometry* (see this) with high resolution. This is an expensive method and because of extensive sample purification steps, the procedure will take two weeks. A bioassay based on binding of dioxins to AH receptor after thorough purification may be used to analyse the sum of dioxin-like activity in the sample.

PCDD/F – biomagnification, property of PCDD/F compounds to concentrate from one trophic level to the next (see also *biomagnification*). Many PCDD/Fs are extremely persistent in the environment. Increase in chlorination (see *PCDD/F – physicochemical properties*) increases both stability and lipophilicity. Therefore they concentrate along the food chain, and species at the “top” of the food chain (such as seals or eagles) are in special danger.

PCDD/F – concentration in humans. Dioxins in the body are almost exclusively in fat because of their lipid solubility and poor water solubility. In some tissues dioxins may also be bound to specific proteins. The most reliable method to measure dioxin levels is to measure their concentrations in fat. Dioxin levels are the same on fat basis in most organs of the body, so there is plenty in very fatty tissues and little in lean tissues. Importantly there is the same concentration of dioxins in milk fat as in the fat of serum or of adipose tissue. This gives a possibility to measure dioxin levels without invasive methodology. WHO has organised five rounds of international human milk analysis dioxin studies (see Fig. 2). However, since the *cumulation* (see this) of dioxins is very slow, the concentrations will increase during most of the lifetime. In Finland, the level in 20 year old population is 5–10 ng/kg (TEq in fat), but in 60 year old population it is 20–100 ng/kg. In chemical industries concentrations of up to several thousand ng/kg have been measured, and the highest measured concentrations in accidents or poisonings (see *PCDD/F – acute toxicity*) were 56,000–144,000 ng/kg (TCDD in fat). Dioxin concentrations have decreased during 1980s to 2000s (see also *body burden* and *PCDD/F – sources*).

PCDD/F – elimination, process of discharging PCDD/Fs out of the body. This is very slow in all mammals, because these compounds are lipophilic, and cannot be excreted in urine, and also poorly degradable by the enzymatic machinery of the body (see also *PCB – elimination*). Generally, PCDFs are eliminated a little faster than PCDDs. Half lives of the 17 most important PCDD/Fs are shown in Table 2 (from *Milbrath et al. Environ. Health Perspect. 2009;117:417–*

Table 2. Elimination half-lives of the most important PCDD/Fs (Milbrath et al. 2009, <http://pubmed.gov/19337517>)

Congener	Half-life, years
2,3,7,8-TCDD	7.2
1,2,3,7,8-PeCDD	11.2
1,2,3,4,7,8-HxCDD	9.8
1,2,3,6,7,8-HxCDD	13.1
1,2,3,7,8,9-HxCDD	5.1
1,2,3,4,6,7,8-HpCDD	4.9
OCDD	6.7
2,3,7,8-TCDF	2.1
1,2,3,7,8-PeCDF	3.5
2,3,4,7,8-PeCDF	7.0
1,2,3,4,7,8-HxCDF	6.4
1,2,3,6,7,8-HxCDF	7.2
1,2,3,7,8,9-HxCDF	7.2
2,3,4,6,7,8-HxCDF	2.8
1,2,3,4,6,7,8-HpCDF	3.1
1,2,3,4,7,8,9-HpCDF	4.6
OCDF	1.4

425, <http://pubmed.gov/19337517>). After a very high exposure, the half-life of e.g. TCDD may shorten even to about 1 year probably due to induction of metabolising enzymes. This must be taken into account, if historic exposures are back-calculated.

PCDD/F – environmental persistence, ability of PCDD/Fs to continue existence in the environment. Many PCDD/Fs are extremely persistent in the environment. Increase in chlorination (see *PCDD/F – physicochemical properties*) increases both stability and lipophilicity. Neither soil microbes nor animals are able to break down effectively those PCDDs with “lateral” chlorines, i.e. chlorines in positions 2,3,7, and 8. This causes especially slow elimination (see *PCDD/F – elimination*), and due to biomagnification (see *bioaccumulation, biomagnification*) those particular compounds are present in the organisms of higher trophic levels (such as birds and mammals). Since the same group of PCDDs with chlorines in 2,3,7,8-positions are also more toxic than others, they are toxicologically the most important congeners.

PCDD/F – half-life, time needed to decrease the amount of chemical to one-half (see *PCDD/F – elimination*).

PCDD/F – limit values, concentrations that are not to be exceeded in a matrix. European Union established maximum values for all important food items in 2001. These vary from 1 pg/g WHO-PCDD/F-TEq in fat (e.g. pork, animal fat) to 6 pg/g (liver), or to 4 pg/g wet weight in fish. These are set as low as reasonable for each type of product. In 2006 dioxin-like PCBs were included and the maximum limits for total dioxins vary from 1.5 to 6 pg/g fat, except for fish 8 pg/g ww. In animal feed the maximum limits for total dioxins are 1.25 to 4.5, in fish oil 24 ng/kg feed (for details see *Commission Regulation 1881/2006*, <http://bit.ly/gcwyJa>). For waste incineration exhaust gases, there is a limit value of 0.1 ng/Nm³ (I-TEq in normalised cubic meter).

PCDD/F – physicochemical properties. All PCDD/Fs are non-volatile, lipophilic (soluble in fats and oils) and poorly water soluble, but lipophilicity increases by increasing rate of chlorination (see *PCDD – chemical structure*, *PCDF – chemical structure*). Their octanol/water partition coefficient (indicating relative lipid to water solubility, see *lipophilicity*) is of the order of a million to hundred million ($\log P_{ow}$ 6.5 to 8.8) explaining the high tendency to move toward lipids from water.

PCDD/F – risk assessment. This has been very difficult for several reasons. Mechanisms of toxicity are not yet fully understood. Large variations of acute toxicity between laboratory species have added to uncertainties in species extrapolation. Also elimination rate varies remarkably between species; the half-life of TCDD in rats is 3 weeks, in humans 7–8 years. Therefore long-term effects are more difficult to evaluate than short-term effects (see *tolerable daily intake*). Until recently cancer risk was considered the most important risk, and there was uncertainty and disagreement of the dose extrapolation. Recent studies after high occupational and accidental exposures have, however, shown the cancer risk to be rather small, and in the general population it is probably not a relevant risk. If there is any risk at the present background levels, it is likely to be that of developmental effects. One of the most sensitive effects seems to be the mineralization defect in teeth of children with the highest exposure via breast milk.

WHO scientific panel reassessed dioxin risks in 1998, and the new recommendation for tolerable daily intake level is 1 to 4 pg/kg/day (in TEq per b.w.) during continuous exposure. This TDI for women was calculated to give a reasonable safety margin for a child during pregnancy and during breast feeding (*WHO, Food Add. Contam. 2000:17:223-238*, <http://pubmed.gov/10912238>). For adult effects the safety margin is higher. Two further points are important. One is that

some of the most important sources are beneficial for health for other reasons, e.g. breast milk and fish. It is not rational to limit their use on the basis of theoretical risks. The second is that PCDD/Fs accumulate very slowly (see *cumulation*). Therefore only exposures over years are important, unless the exposure is very high (such as an accident). Therefore emission control rather than exclusion of important food items is the most logical way to further decrease dioxin intake.

PCDD/F – sources. *Formation.* PCDD/Fs will form in small amounts, if carbon, oxygen and chlorine are available in the presence of metal catalysts at suitable temperatures, which optimally means 400 to 700 °C. The most important sources of PCDD/Fs have been incineration of mixed waste at too low temperatures, metal smelting and refining, and chlorine bleaching of pulp (Figure 6). Another mostly local source has been occurrence as impurities

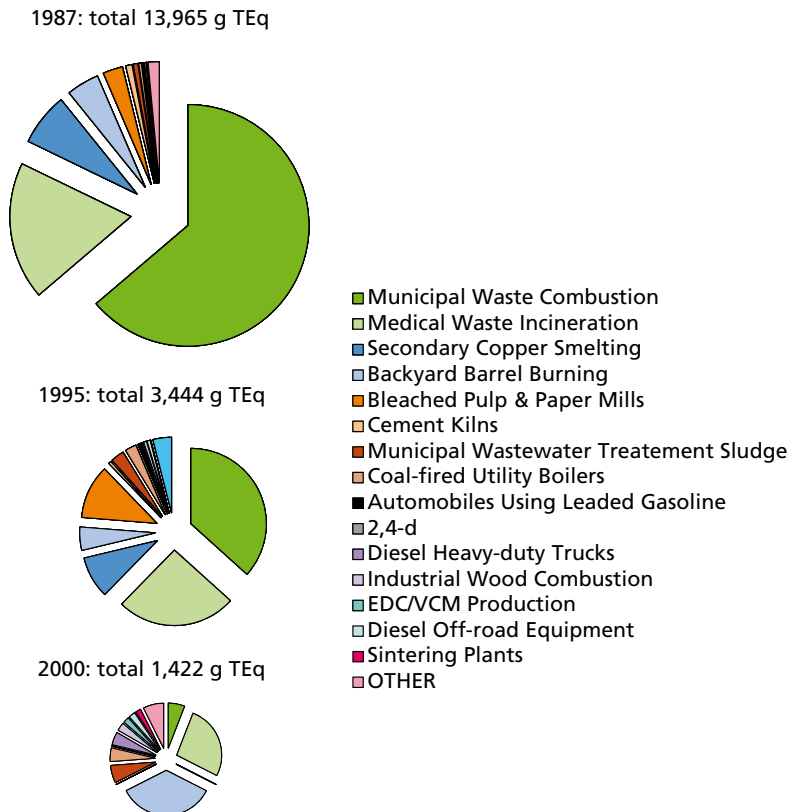


Figure 6. Emission sources of PCDD/F in the United States in 1987-2000. National Center for Environmental Assessment, Washington, DC; EPA/600/P-03/002F. (<http://1.usa.gov/YP8d9>)

of many chlorinated chemicals such as PCBs, chlorophenols, phenoxy acid herbicides, and hexachlorophene. Most sources except local small-scale burning have decreased dramatically (Fig. 6).

Human exposure. Food is the major source for human exposure of PCBs and dioxins, especially fatty foods: dairy products (butter, cheese, fatty milk), meat, egg, and fish (Figure 7). The current average body burden of PCDD/Fs + DL-PCBs is 10–100 ng/kg (TEq in fat) or 100–1000 ng (TEq per person), in children 2–15 ng/kg fat (see *body burden*). Average daily intake in many countries is about 1 pg/kg (TEq per b.w.), or about 50–100 pg per person. Some subgroups within the society (e.g., nursing babies and people consuming plenty of fish) may be highly exposed to these compounds and their body burden is closest to the lowest concentrations possibly causing health effects. Dioxin concentrations have been screened in five WHO international studies, and in Central Europe the concentrations have decreased in breast milk from 30–40 ng/kg (TEq in milk fat) to 5–20 ng/kg from 1987 to 2006. The decrease in environmental concentrations is due e.g. to improved incineration technology (see figs. 6 and 7).

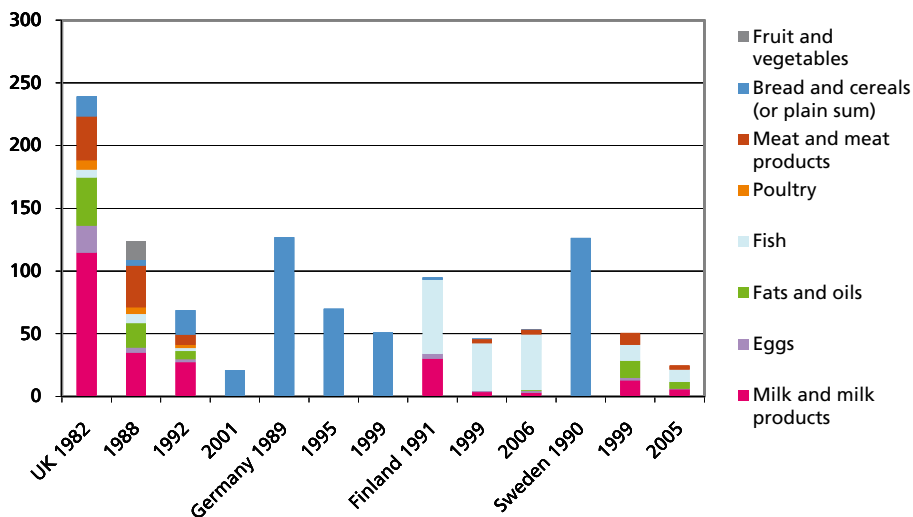


Figure 7. Different food items as sources of PCDD/Fs (pg/day I-TEq) in some European countries and the time trends. Sources: King, K. Compilation of EU Dioxin Exposure and Health Data, Task 4 - Human Exposure. AEA Technology 1999, <http://bit.ly/hyVngV>; Kiviranta H. Exposure and human PCDD/F and PCB body burden in Finland, Publicat. Natl. Public Hlth Inst. A14/2005, <http://bit.ly/iHD1j8>; Törnkvist A. et al. Chemosphere 2011:83:193, <http://pubmed.gov/21269658>.

PCDD/F – tooth effects. These were clearly shown in *Yusho incident and Seveso* (see these). At lower concentrations in 1980s in Finland, defective mineralization of the first permanent molar teeth, which are formed during the two first years of life, correlated with PCDD/F exposure during breast-feeding. If real, this may be the most sensitive effect of PCDD/Fs ever seen in humans.

PCDD/F – toxicity in animals. Dioxins bring about a wide spectrum of biochemical and toxic effects in experimental animals. These effects depend on dose, species, strain, gender, age and tissue. Various *dioxin congeners* (see this) tend to elicit a similar battery of alterations, although the congeners are differently potent. TCDD serves as a surrogate for the whole group of chemicals. For the most part, the mechanisms of these impacts are still obscure. This hampers rational risk assessment. A common denominator appears to be the so called *AH receptor* (AHR) (see this), which mediates the biological effects of TCDD in cells. Some of the most toxic PCBs have dioxin-like toxicity based on AH receptor, but e.g. some effects on the nervous system are believed to have a different mechanism.

A characteristic feature of the acute toxicity is an exceptionally large variation in sensitivity among species (see *PCDD/F – acute toxicity*). To the guinea pig, TCDD is the most toxic synthetic compound known with an LD50 value (dose lethal to 50% of animals) of only ca. 0.001 mg/kg, but the hamster tolerates a thousandfold higher dose. The reasons for these intra- and interspecies differences are unclear, but some are due to differences in the AH receptors. One of the most sensitive targets for TCDD appears to be the reproductive organ system in the developing foetus (Table 3). (For detailed information, see *Pohjanvirta & Tuomisto, Pharmacol. Rev. 1994;46:483-549*, <http://pubmed.gov/7899475>; *Birnbaum & Tuomisto, Food Addit. Contam. 2000;17:275-288*, <http://pubmed.gov/10912242>).

PCDD/F – toxicity in humans. Acute toxicity after large doses was best seen after the *Seveso accident* (see this) and two cases of individual poisoning (see *PCDD/F-acute toxicity*). The most remarkable effect was *chloracne*, especially in children exposed to high doses appearing between two weeks and two months, and sometimes continuing for years.

Chloracne has regularly been described even after heavy occupational exposures to PCDDs and other chlorinated chemicals. Also elevations of liver enzymes in blood were seen in Seveso victims indicating liver damage. There were signs of disturbed porphyrin metabolism (synthesis of heme, the pigment of haemoglobin) and

Table 3. Examples of toxic and biochemical effects after TCDD, and body burdens related to the effects.

Effect	Species	Body burden (ng/kg b.w.)
Adverse (toxic) effects		
Immunological (viral sensitivity)	Mouse	10 (LOEL)
Developmental neurotoxicity (object learning)	Rhesus monkey	42 (LOEL) (maternal)
Reproductive toxicity (decreased sperm count)	Rat	28 (LOEL) (maternal)
Hormonal (endometriosis)	Rhesus monkey	69 (LOEL)
Chloracne	Human	95–3000
Tumour promotion	Rat	2500
Thyroid hormone (T4) decrease	Rat	3000 (ED50)
Immunotoxicity (thymus atrophy)	Rat	5000 (ED50)
Wasting syndrome	Rat	10,000–50,000
Biochemical effects		
EGF receptor induction	Rat	3 (LOEL)
IL1beta expression increase	Mouse	10 (LOEL)
CYP1A1 enzyme induction	Mouse	3 (LOEL)
	Rat	3 (LOEL)

LOEL: lowest observed effect level; ED50: median effective dose (causes 50 % of maximum effect). Data e.g. from WHO, *Food Add. Contam.* 2000:17:223-238, <http://pubmed.gov/10912238>; DeVito et al., *Environ Health Persp* 103 : 820-8 31, 1995, <http://1.usa.gov/fiQJWC>.

increases in serum lipids (both triglycerides and cholesterol). A number of other health effects have been linked to high exposure to dioxins, including mood alterations, reduced cognitive performance, diabetes, changes in white blood cells, endometriosis, decreased male/female ratio of births and decreased testosterone and (in neonates) elevated thyroxin levels. As yet such effects have not been proven as caused by PCDD/Fs. The effect that has caused the greatest public concern is cancer, and IARC classified TCDD as a human carcinogen in 1987 (see *PCDD – carcinogenicity*). Another concern in the society are the possible developmental effects. There is recent data that dioxin exposure from breast milk is associated with abnormal development and mineralization of teeth (see *PCDD/F – tooth effects*).

PCDD/F – use. PCDD/Fs have never been synthesised for any other purpose than research, but they are formed as unintentional by-products in chemical syntheses of 2,4,5-trichlorophenol (an intermediate of antiseptic hexachlorophene and herbicide 2,4,5-T) and in many burning processes (see *PCDD – sources*).

PCDF, *polychlorinated dibenzofuran*. See that and *PCDF – specific items*; since the properties are usually very close, a treatise is usually given under PCDD/F.

PCDF – chemical structure. See *chemical structures*.

PCDF – carcinogenicity, capacity of PCDFs to cause cancer. Animal carcinogenicity of 2,3,4,7,8-PeCDF seems to be in line with its TEF value in rats. In Japan (*Yusho incident*, 22 year follow-up) there is some indication on increased liver cancer in men, but in Taiwan (*Yu-Cheng incident*) after 12 year follow-up there is no increase (see these). Therefore evidence is scarce, but due to the fact that PCDFs bind to the AH receptor and the assumption that the carcinogenicity of dioxins is mediated by this receptor, PCDFs are usually considered carcinogens in decision-making (see also *PCDD – carcinogenicity*).

penta-, five. E.g., pentachloro- five chlorine atoms in a molecule.

pentachlorophenol. See chlorophenols.

Phenoclor, a commercial PCB product. See *PCB – trade names*.

phenoxy acids. See *chlorophenoxyacetic acid herbicides*.

physicochemical properties. See *PCB – physicochemical properties*, *PCDD/F – physicochemical properties*.

picogram (pg), 0.000,000,000,001 g. See *units*.

polychlorinated biphenyls (PCB-compounds), a group of oily stable chemicals, which are mixtures of many congeners (see *chemical structures*). They are very poorly water soluble and lipophilic (see *PCB – physicochemical properties*), and therefore accumulate in lipids (fats) of living organisms (see *PCB – environmental persistence*), and bioaccumulate in trophic levels (see *PCB – biomagnification*). They contain small amounts (1 to 40 mg/kg) of PCDFs as impurities (see *PCB – contaminants*). (For detailed information, see *International Programme on Chemical Safety, Environmental Health Criteria 140*, WHO, Geneva, 1993, <http://bit.ly/fubDjv>; *Safe, Crit. Rev. Toxicol.* 1994:24:87-149, <http://pubmed.gov/8037844>).

polychlorinated dibenzofurans (PCDFs), a group of related chemicals that are usually present in mixtures and usually as minor impurities among other chemicals such as PCBs and chlorophenols. They are quite similar to PCDDs both chemically and biologically (see *PCDF* and *PCDD – specific items*; since the properties are usually very close, a treatise is mostly given under *PCDD/F*). (For detailed

information, see *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 69, pp. 345-423, Lyon, 1997, <http://bit.ly/ieqeDt>).

polychlorinated dibenzo-p-dioxins (PCDDs), a group of related chemicals which are usually present in mixtures and usually as minor impurities among other chemicals such as PCBs, chlorophenols, phenoxy acid herbicides, hexachlorophene antiseptic etc. They are poorly water soluble and lipophilic (see *PCDD/F – physicochemical properties*), and therefore accumulate in lipids (fats) of living organisms (see *PCDD/F – environmental persistence*), and bioaccumulate in trophic levels (see *PCDD/F – biomagnification*). (For detailed information, see *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 69, pp. 33-343, Lyon, 1997, <http://bit.ly/ieqeDt>).

ppb, parts per billion (American). A non-standard concentration unit equal to ng/g or µg/kg or 10⁻⁹ g/g.

ppt, parts per trillion (American). A non-standard concentration unit equal to pg/g or ng/kg or 10⁻¹² g/g.

precautionary principle, administrative principle to act even without full proof of danger, if the consequences would be serious (see also *conservative risk assessment*).

profile of congeners (spectrum of congeners, congener profile), the variety of different congeners of PCB or PCDD/F in a particular sample. The proportion of each congener in the total PCB or PCDD/F may change along the food chain, because different congeners are differently metabolised and taken up by organisms, and therefore the spectrum in human beings (see *TEq, Figure 8*) is very different from that of the original source, e.g. a commercial PCB mixture. To help risk assessment, the use of relative intake fraction has been proposed. It means calculating the intake of a certain congener by population, compared with the intake of TCDD from the same source. Relative intake fraction of a congener may be 10-100 times less than that of TCDD, in other words it is not carried from the source to people as effectively as TCDD.

promoters, a class of chemicals that promote the development of cancer. Usually the development of cancer is divided to the stages of initiation and promotion. Some chemicals may cause an error in the genetic message of a cell (see *mutagenicity*), and the cell will be transformed to a cancer cell. A single cancer cell will usually

not develop to a full-blown cancer, unless other factors promote its growth and development. Promoters are a large class of chemicals that cause promotion by several mechanisms, the simplest is just a tissue damage that makes the cells divide to replace destroyed cells. Dioxin-like chemicals are strong promoters of cancer development, but they are not mutagenic.

proteins, a class of the most important macromolecules of our body and all living organisms. They are formed of *amino acids* (see this), and usually synthesised in ribosomes, small cell organelles, by the code transferred by messenger RNA (see *RNA*).

Pyralene, a commercial PCB product. See *PCB – trade names*.

Pyroclor, a commercial PCB product. See *PCB – trade names*.

Ranch Hand, a U.S. military operation during Vietnam War, where antifoliant agents were spread over large areas to kill vegetation. One of the compounds used was Agent Orange, which contained mostly 2,4,5-T and was contaminated by PCDD/Fs. (See also *chlorophenoxyacetic acid herbicides*).

ribosome, a cell organelle where protein synthesis takes place. Ribosomes themselves are formed of several protein molecules.

risk assessment. See *PCDD/F – risk assessment, conservative risk assessment*.

RNA (ribonucleic acid), a nucleic acid similar to *DNA* (see this), but instead of thymine, one of the bases is uracil. There are three kinds of RNA. **Messenger RNA** is a copy of one gene copied during transcription from DNA, and it usually gives a code for one protein molecule. **Transfer RNA** transfers one amino acid at a time to a nascent protein in the ribosome. **Ribosomal RNA** functions in ribosomes. To learn more of these, grab any modern biology or biochemistry textbook.

Santotherm FR, a commercial PCB product. See *PCB – trade names*.

seven marker PCBs ($\Sigma 7$ PCB), a selection of PCB congeners. $\Sigma 7$ PCB denotes the sum of the seven marker PCBs. In a sample containing PCBs, there are often several dozens of different congeners. For practical reasons, all of them are not always measured, but the most important congeners are used as indicators. In Belgian chicken incident, only seven abundant congeners were usually measured: congeners with IUPAC numbers 28, 52, 101, 118, 138, 153, and 180 (2,4,4'-TriCB, 2,2',5,5'-TCB, 2,2',4,5,5'-PeCB, 2,3',4,4',5-PeCB, 2,2',3,4,4',5'-HxCB, 2,2',4,4',5,5'-HxCB, 2,2',3,4,4',5,5'-HpCB, respectively). The seven

congeners are estimated to constitute about one third of all PCBs in the contaminated feed.

Seveso accident, the best-known dioxin accident in 1976 in Italy. In Seveso, 20 km north of Milan, a trichlorophenol production reactor in a chemical factory blew up and released kilogram quantities of TCDD to the environment. The cloud of chemicals spread as far as 6 km from the factory, and settled on the ground. Within 5 weeks the area was subdivided into three subareas based on soil concentrations: zone A (87 hectares, over 50 µg/m² of TCDD), zone B (270 hectares, over 5 µg/m²), and zone R (1430 hectares, below 5 µg/m²). From zone A over 730 inhabitants were evacuated, and strict hygienic regulations were set for other zones. In a selected group of highly exposed persons, TCDD concentrations up to 56,000 ng/kg (TCDD in fat) were detected. In randomly sampled persons, the calculated median concentrations were 390 ng/kg (TCDD in fat) (zone A), 78 ng/kg (zone B) and in the reference population 5.5 ng/kg.

Chloracne was observed in about 200 persons, most of them children, but no other direct adverse health outcomes were noted. After 20 years there was no health difference between these chloracne patients and controls. Changes in tooth development and decreased male offspring of persons exposed as small children were noted later. In 25-year mortality and 20-year incidence follow-up studies, no increased total mortality nor increased all cancers were observed (in zones A and B about 300 cancers as expected). There seems to be an increase of lymphatic and haematopoietic malignancies in zone B (29 cases, 28 deaths, about 1.5-fold risk), among them increases in myeloid leukaemia (7 cases, 6 deaths), and myeloma (6 cases, 5 deaths). There were similar increases in zone A, but this population was quite small for reliable analysis. One may conclude that the increase of specific cancers is likely to be real, but considering the high exposure, the risk of cancer is not very high (for details, see *Consonni et al., Am. J. Epid.* 2008;167:847-858, <http://pubmed.gov/18192277>; *Pesatori et al., Environ. Health* 2009;8:39, <http://pubmed.gov/19754930>).

six marker PCBs (Σ 6PCB), a selection of PCB congeners. Σ 6PCB denotes the sum of the six marker PCBs. In a sample containing PCBs, there are often several dozens of different congeners. For practical reasons, all of them are not always measured, but the most important congeners are used as indicators: congeners with IUPAC numbers 28, 52, 101, 138, 153, and 180 (2,4,4'-TriCB, 2,2',5,5'-TCB, 2,2',4,5,5'-PeCB, 2,2',3,4,4',5'-HxCB, 2,2',4,4',5,5'-HxCB, 2,2',3,4,4',5,5'-HpCB, respectively).

soft-tissue sarcoma, a malignant tumour that is often attributed as a “dioxin cancer”. However, in a large case-control study the risk of this cancer was not found increased when dioxin concentration in the body increased, rather the risk was highest at the lowest body burden of total TEQs (Tuomisto *et al.*, *Int. J. Cancer*, 2004:108:893-900, <http://pubmed.gov/14712494>). Also the Seveso studies do not favour the hypothesis of dioxins increasing the risk of this cancer.

sources of PCBs and PCDD/Fs. See *PCDD/F – sources* and *PCB – sources*.

Sovol, a commercial PCB product. See *PCB – trade names*.

spectrum of congeners. See *profile of congeners*.

steady state, the state during which the amount of chemical in the body stays constant, i.e. the same amount is eliminated per unit of time as is entering the body (see *cumulation*).

Stockholm convention. Agreement to stop producing persistent organic pollutants. The Convention (2001) originally included 12 pollutants or groups of pollutants including PCDD/Fs and PCBs, signed by 151 parties as of 2011 (details see <http://www.pops.int>).

2,4,5-T (2,4,5-trichlorophenoxyacetic acid), a herbicide presently banned in many countries. See *chlorophenoxyacetic acid herbicides*.

TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the most potent of polychlorinated dibenzo-*p*-dioxins. For properties, see *PCDD/F – specific items*).

TDI, *tolerable daily intake* (see that).

TEF (TCDD equivalency factor, toxic equivalency factor), a relative toxicity factor of a PCDD/F or PCB congener as related to TCDD. TEF values vary from 1 to 0.00003 (Table 4; see also *TEQ*). Various TEF values have been developed, e.g. WHO-TEF, Nordic TEF and international TEF or I-TEF. WHO-TEF values are based on the most recent scientific consensus. The differences between the respective TEFs are not great. The latest re-evaluation of TEF values was that by WHO in 2005, and these TEF values have been used in this booklet as WHO-TEF for PCDD/Fs and PCB-TEF for PCBs. $TEQ = \sum TEF_i * C_i$, where C_i is the amount (or concentration) of congener i . (Further details in Van den Berg *et al.*, *Toxicol. Sci* 2006:93: 223-241, <http://pubmed.gov/16829543>).

Table 4. Toxic equivalency factors for all PCDD/Fs and PCBs that have a TEF>0. Other congeners are not assumed to have dioxin-like effects. IUPAC numbers for PCBs are given in parenthesis.

Congener	WHO-TEF 2005
PCDDs	
2,3,7,8-TCDD	1
1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-HxCDD	0.1
1,2,3,7,8,9-HxCDD	0.1
1,2,3,4,6,7,8-HpCDD	0.01
OCDD	0.0003
PCDFs	
2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-PeCDF	0.3
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	0.0003
Non-ortho-PCBs	
3,3',4,4'-TCB (77)	0.0001
3,4,4',5-TCB (81)	0.0003
3,3',4,4',5-PeCB (126)	0.1
3,3',4,4',5,5'-HxCB (169)	0.03
Mono-ortho-PCBs	
2,3,3',4,4'-PeCB (105)	0.00003
2,3,4,4',5-PeCB (114)	0.00003
2,3',4,4',5-PeCB (118)	0.00003
2',3,4,4',5-PeCB (123)	0.00003
2,3,3',4,4',5-HxCB (156)	0.00003
2,3,3',4,4',5'-HxCB (157)	0.00003
2,3',4,4',5,5'-HxCB (167)	0.00003
2,3,3',4,4',5,5'-HpCB (189)	0.00003

TEq, TCDD equivalent quantity, toxicity equivalent (see also *TEF*). Different congeners of dibenzo-*p*-dioxins and dibenzofurans have many of the same biological effects but they are differently potent, meaning that different doses are needed to cause the same effect (Figure 8). E.g. 1,2,3,4,7,8-hexachlorodibenzo-*p*-dioxin (HxCDD) is one tenth as toxic as TCDD. To be able to assess the effects of a mixture, all congeners are “normalised” to the effects of TCDD, e.g. the amount or concentration of HxCDD is multiplied by the equivalency factor 0.1 (its TEF is 0.1). When all congeners are expressed as “equivalents of TCDD” they can be simply added and the sum gives the total toxicity of the mixture. Also the most important dioxin-like

PCBs have been given TEF values, but it should be appreciated that PCBs may have other effects that cannot be expressed by a TCDD-equivalency. (For more information on TEq concept and its use, see *Van den Berg et al., Toxicol. Sci., 2006: 93: 223-241*, <http://pubmed.gov/16829543>; Tuomisto, in R. Pohjanvirta (ed.) *The AH Receptor in Biology and Toxicology*, John Wiley & Sons, 2011).

tetra-, four. E.g., tetrachloro- four chlorine atoms in a molecule.

Times Beach, a village in Eastern Missouri where salvage oil containing over 30 mg/kg TCDD, was used to spray a horse arena and 23 miles of roadways as dust suppressant in 1971. Hundreds of birds and rodents died in the neighbourhood, as well as 48 of the 85 horses exercised in the arena. Three children and one adult developed chloracne. The source was ultimately traced to the distillation bottom sludges of a hexachlorophene manufacturer. The incident led to evacuation of the population and a buyout of the whole community by U.S. Federal Government.

tolerable daily intake dose (TDI), a theoretical concept of regulatory toxicology giving the highest dose of a chemical which can be assured to be safe even if one is exposed to the chemical through the whole

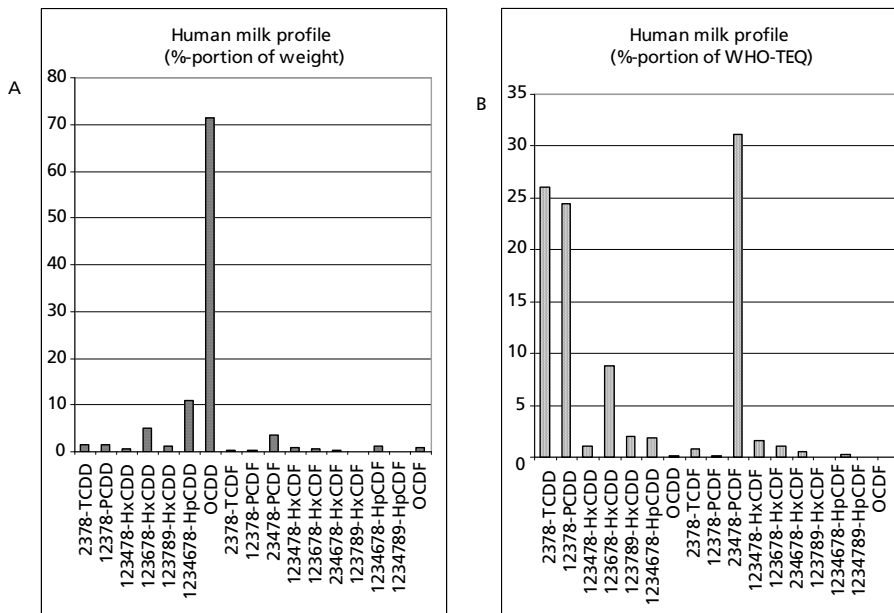


Figure 8. Congener profile of human milk samples (17 dioxin-like PCDD/Fs). A, weight basis (describes the amount); B WHO-TEq basis (describes the toxic potency).

lifetime. Most TDI values have been estimated on the basis of animal experiments. Usually the TDIs include safety margins to guarantee safety even if human being should be more sensitive than the animal. The safety margin is often 100-fold, but could be larger, if research data is not satisfactory. If the chemical is *carcinogenic* (see this), different methods are used in different countries. Some countries use large safety margin (e.g. 1000-fold), some use mathematical *extrapolations* (see this) to reach a level deemed safe (e.g. a maximum likelihood of one in a million chance of contracting cancer due to a lifetime exposure to the chemical). The important point is that the purpose of TDI is to serve regulators in administrative work, and not individual persons. It does not predict the likelihood of individual's health effect in any reliable way, if the limit is exceeded. TDIs of dioxins set by various authorities in different countries vary by more than thousandfold, which illustrates the difficulties in dioxin risk assessment. The latest recommendation for TDI for the sum of dioxins and dioxin-like PCBs is 1 to 4 pg/kg/day (WHO-TEq per b.w.), in other words, in 70-kg person 70 to 280 pg/day. This should be understood as the average intake over a long period of time, notably of a woman in fertile age to guarantee the safety of the newborn (see *cumulation*).

toxicity in humans, see *PCB – toxicity in humans, PCDD/F – toxicity in humans*.

transcription, reading the genetic message from *DNA* (see this) to *RNA*.

transcription factor, a cell protein that can bind to specific sites at *DNA* (see this) or a member of a set of such proteins, which after binding to *DNA* initiate a chain of events leading to expression of a particular gene. This usually leads to the synthesis of a protein determined by that gene.

translation, reading the message in messenger *RNA* (see *RNA*) to make a protein.

tri-, three. E.g., trichloro- three chlorine atoms in a molecule.

trophic levels, ecological levels of nutrition. In the Baltic Sea white-tailed eagle feeds on salmon, which feeds on herring, which feeds on small crustaceans and animal plankton, which feeds on phytoplankton. Chemicals may be transferred and bioconcentrated along such trophic levels.

units. Concentrations and amounts of dioxins and PCBs are very small, and therefore units to measure them do not belong to

Table 5. Weight units.

1 kg (kilogram)	1000 g	10 ³ g
1 g (gram)	1 g	10 ⁰ g
1 mg (milligram)	0.001 g	10 ⁻³ g
1 µg (microgram)	0.000,001 g	10 ⁻⁶ g
1 ng (nanogram)	0.000,000,001 g	10 ⁻⁹ g
1 pg (picogram)	0.000,000,000,001 g	10 ⁻¹² g
1 fg (femtogram)	0.000,000,000,000,001 g	10 ⁻¹⁵ g

everyday vocabulary (Table 5.). One picogram per gram results, if 10 g (a spoonful of sugar) is dissolved in a lake 10 m deep and one square kilometre large. These small concentrations we are dealing with explain why relatively small amounts of chemicals can contaminate large amounts of feed, for instance.

PCDD/F concentrations are often expressed as *TEq* (see this). PCB is usually expressed as sum of all PCBs (Σ PCBs) or as sum of marker PCBs analysed (e.g. Σ 7PCBs, sum of *seven marker PCBs* [see this]).

Concentrations of PCBs or PCDD/Fs can be expressed per wet weight (w.w.) (e.g. in fish), per dry weight (d.w.) (e.g. in soil), per normalised cubic meter (Nm³) (e.g. in exhaust gases), or per fat. Many organisms contain about 10 % fat, then the difference between concentrations per fat and per wet weight is about tenfold. However, especially fish may be very different in their fat content, and usually PCBs and PCDD/Fs in fish are given per wet weight. Human PCBs and PCDD/Fs are mostly expressed per gram fat, because the concentrations are comparable regardless of if it was measured in serum, adipose tissue or milk. Human body contains about 15 % (10–12 kg) fat, but the variation is large, especially upward. See also *Common sources of errors and practical difficulties in the General introduction*.

use of PCBs, see *PCB – use*.

xenobiotic, foreign chemical. See also *metabolism*.

Yu-Cheng incident, contamination of rice oil with PCB in Taiwan. In 1979, 2061 persons were determined to be victims of PCB poisoning, and the affected persons had been using rice-bran oil contaminated (53–99 mg/kg [Σ PCB in fat]) by PCBs used in heat transfer system. The PCB intake was estimated to be 700 to 1,800 mg (Σ PCB per person) and the average estimated PCDF intake 3.8 mg (Σ PCDD/F per person). Average blood levels were 50–100 µg/litre (Σ PCB). The congener-specific analysis is available only from samples collected in 1994-1995. Then PCDFs accounted for 44% of TEq, non-ortho-

PCBs 24%, mono-ortho-PCBs 20%, and PCDDs 12%, mean total TEq was still over 1300 ng/kg fat. As in the earlier *Yusho incident* (see this) the main signs were eye problems (swelling, hypersecretion of Meibomian glands), abnormal pigmentation, decreased nerve conduction velocities, hyperpigmentation and tooth deformities of babies born to affected mothers.

Yusho incident, contamination of rice oil with PCB in Japan. In the year 1968, patients with chloracne came to the dermatology clinic in Fukuoka, and this disease was connected with the consumption of a batch of rice oil which was contaminated (2000–3000 mg/kg [Σ PCB in fat]) with Kanechlor 400, a PCB used in the heat exchanger leaking to the rice oil. The average estimated intake per person was 633 mg PCBs and 3.4 mg PCDFs among some other chemicals. This has been estimated to be 154,000 pg/kg/day (I-TEq per body weight per day) or 100,000 times higher than average background intake. The earliest signs of toxicity were enlargement and hypersecretion of Meibomian glands in the eyes, swelling of the eyelids and pigmentation of skin and mucous membranes. Many different skin problems followed, including darkening of the skin, hyperkeratosis and chloracne. Babies born to Yusho mothers were smaller than normal, they showed a dark brown pigmentation, and some of them had gingival hyperplasia and dentition at birth. The total number of patients was about 1,200 which is rather small number to evaluate effects on cancer reliably, but there seems to be an excess of cancer deaths among the male patients. Japanese research groups have concluded that the main signs and symptoms were due to the minor contaminants, i.e. PCDFs of the PCB contaminating rice oil. International Programme on Chemical safety concluded in 1993 that the intoxications of Yusho and Yu-Cheng were caused mainly by a combined effect of PCBs (especially coplanar ones) and PCDFs. For more information on Yusho see “*Yusho; A human disaster caused by PCBs and related compounds*”, ed. By M. Kuratsune, H. Yoshimura, Y. Hori, M. Okumura, Y. Masuda, Kyushu Univ. Press, Fukuoka, 1996.

Σ (sigma), sum. Ordered alphabetically at the main entry disregarding the prefix.