

First Consensus Workshop on Food Safety

Brussels, Belgium, 10-12 July 2002

Environmental issues and food safety - the case of dioxin

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Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs) are referred to as dioxins. There are 75 PCDD and 135 PCDF congeners. They are not produced by intention but they have an ubiquitous distribution as contaminants of the environment due to their formation as unwanted and often unavoidable by-products in a number of anthropogenic activities. They are formed during incomplete combustion processes, industrial as well as natural. Waste incineration is thought to be a major source. They also occur as contaminants during various industrial processes, e.g. the manufacture of some chlorinated chemicals and chlorine bleaching of paper pulp.

The toxicity of individual dioxins differs considerably. The congeners that are of toxicological importance are substituted in each of the 2-, 3-, 7- and 8-positions. Thus, from 210 theoretically possible congeners, only 17 are of toxicological concern. These compounds have a similar toxicological profile to that of the most toxic congener 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD).

The toxic responses of dioxins include dermal toxicity, immunotoxicity, carcinogenicity, reproductive and developmental toxicity and most, if not all, are mediated *via* the aryl hydrocarbon (Ah) receptor present in most tissues of animals and humans.

Technical mixtures of polychlorinated biphenyls (PCBs) have been widely used in a number of applications such as use in hydraulic and heat transfer systems as well as cooling and insulating fluids in transformers and capacitors. Typical open applications have been the use of PCBs in pigments, dyes, repellents and carbonless copy paper or as plasticizers in paints, sealings, plastics and rubber products. The production and use of PCBs has been discontinued in most countries, but large amounts remain in electrical equipment, plastic products, buildings and the environment.

Among the many PCBs the so-called non-*ortho* and mono-*ortho* substituted PCBs show toxicological properties that are similar to dioxins. They are therefore often termed “dioxin-like PCBs” and they are included in the risk assessment of the dioxins.

Dioxins and PCBs are lipophilic (fat soluble) compounds. They are extremely resistant towards chemical and biological degradation processes and therefore persist in the environment and accumulate in the food chains in fatty foods. Therefore, the highest levels of

dioxins can be found in foods derived from fatty fish, poultry, and mammals. Products of vegetable origin (cereals, fruit and vegetables) exhibit low dioxin contamination levels. More than 90% of human dioxin exposure derives from food. Of this, about 90% normally comes from foods of animal or fish origin. As a rule of thumb, products from fish, milk and meat contribute equally to the intake of dioxins in the Western European countries.

Toxic Equivalency Factors

In all foods, dioxins and PCBs are found as complex mixtures. In order to compare analytical and exposure data, the analytical results are converted into toxic equivalents (TEQ). This conversion is based on the assumption that all 2,3,7,8-substituted PCDDs and PCDFs, as well as the dioxin-like PCBs, bind to the same receptor, the Ah receptor, and show comparable qualitative effects, but with different potencies. These differences in toxicity are expressed in the toxic equivalency factors (TEFs), estimated from the weaker toxicity of the respective congener in relation to the most toxic congener 2,3,7,8-TCDD, which is assigned the arbitrary TEF of 1. By multiplying the analytically determined amounts of each congener by the corresponding TEF and summing the contribution from each congener the total TEQ value of a sample can be obtained using the following equation:

$$\text{TEQ} = \sum (\text{PCDD}_i \times \text{TEF}_i) + \sum (\text{PCDF}_i \times \text{TEF}_i) + \sum (\text{PCB}_i \times \text{TEF}_i)$$

Several different TEF schemes have been proposed. The most recent TEFs for PCDDs, PCDFs and dioxin-like PCBs were established by WHO in 1998 (WHO-TEFs, Table 1).

Toxicological evaluation

The EC Scientific Committee on Food (SCF) evaluated dioxins in 2000 and updated the evaluation in 2001 because new toxicological data became available. The most sensitive adverse effects reported are developmental and reproductive effects in rats and monkeys and an increase in the incidence of endometriosis in monkeys. The studies demonstrate reduction in daily sperm production, cauda epididymal sperm number and epididymis weight as well as accelerated eye opening, reduction in anogenital distance and feminised sexual behaviour in the male offspring associated with maternal steady state body burdens in the range of 39 – 99 ng 2,3,7,8-TCDD/kg bw. Reduction in weights of testes and size of sex-accessory glands, such as the ventral prostate in the male offspring, and development of external malformations of genitalia in female offspring as well as reduced male and/or female fertility require higher maternal body burdens. Table 2 gives a summary of the NOAEL and LOAELs for the most sensitive adverse effects of 2,3,7,8-TCDD on developmental endpoints in experimental animals.

In the evaluation of the toxicity of dioxins and dioxin-like PCBs, the SCF applied the body burden approach, and arrived at a temporary tolerable weekly intake (t-TWI) of 14 pg/kg bw for 2,3,7,8-TCDD. For 2,3,7,8-TCDD and related compounds, such as other dioxins and dioxin-like PCBs that have very long half-lives in the human body, the Committee found it more appropriate to establish a temporary tolerable weekly intake (t-TWI) instead of a tolerable daily intake (TDI).

The t-TWI for 2,3,7,8-TCDD was extended to include all 2,3,7,8-substituted PCDDs and PCDFs, and the dioxin-like PCBs, and a group t-TWI of 14 pg WHO TEQ/kg bw was established for these compounds.

Although the International Agency for Research on Cancer (IARC, 1997) has classified 2,3,7,8-TCDD as a human carcinogen it was concluded that 2,3,7,8-TCDD is not a direct-acting genotoxic agent. It has not shown effects in the majority of assays for genotoxicity and it does not bind covalently to DNA. Based on the available information, the application of a threshold model was considered to be appropriate for the indirect and non-genotoxic action of 2,3,7,8-TCDD. It was also noted that the 2,3,7,8-TCDD body burdens in female rats showing an increased incidence in liver tumours and the 2,3,7,8-TCDD body burdens associated with an increased cancer risk in human cohorts occupationally or accidentally exposed, were several orders of magnitude higher than the background dioxin body burdens seen in the general population.

Intake of dioxins and risk groups

The average dietary exposure of PCDDs and PCDFs for an adult person has been estimated to be between 0.4 and 1.5 pg TEQ/kg bw/day. An additional average dietary exposure to dioxin-like PCBs appears to be between 0.8 and 1.5 pg TEQ/kg bw/day.

The estimated average human intakes in the European countries of 1.2-3.0 pg WHO TEQ/kg bw/day would produce body burdens of 2.4-6.0 ng WHO TEQ/kg bw (see Section 3.2). A steady state body burden of 4 ng WHO TEQ/kg bw would be produced at an intake at the group t-TWI.

Using the current database of dietary exposures to dioxins and dioxin-like PCBs it was concluded that a considerable proportion of the European population would exceed the group t-TWI of 14 pg WHO-TEQ/kg bw. However, the SCF emphasised that a TWI is not a lower bound of toxicity, it is an estimate of a safe level of intake and is derived conservatively using uncertainty factors applied to no observed adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAELs). Therefore, exceedence of the group t-TWI does not necessarily mean that there is an appreciable risk to the health, but rather that exposure above this tolerable weekly intake leads to an erosion of the protection embedded in the group t-TWI.

Meat, eggs, milk, farmed fish and other food products may be contaminated above background by dioxins from feedingstuffs. Such contamination may be due to a high level of local environmental contamination, for example from a local waste incinerator, or to incidents, such as the Belgian episode, where animal feedingstuffs were contaminated, or to a high content of dioxins in fishmeal and fish oil. Wild fish from certain polluted areas may be highly contaminated.

Various risk assessments of PCDDs, PCDFs and dioxin-like PCBs have identified groups of the population that may experience higher than average exposure through high consumption of heavily contaminated food, human milk (breast-fed infants), or occupational exposure. It is important to note that the sensitive endpoints that drive the derivation of the t-TWI relate to the body burden of dioxin in fertile women. Except for promotion of endometriosis, the group at risk is the unborn foetus, the exposure of which depends on the mother's body burden. It also has to be recognised that, for the general population, this body burden is the result of dioxin exposure *via* the food over many years. The long half-lives in humans of the compounds involved mean that the steady-state body burdens usually reflect a stable situation in which brief exposures above background will not result in changes.

During the nursing period, breast-fed infants may have intakes of these compounds on a body weight basis estimated to be 1 to 2 orders of magnitude higher than the average adult intake. The intake by the breast-fed infants was mimicked in the studies that were considered during the derivation of the t-TWI, in which the offspring was exposed through the suckling phase. In this context, the SCF reiterated the conclusions of WHO meetings on the health significance of contamination of human milk with dioxins and PCBs, namely that the current evidence does not justify altering recommendations on the promotion of, and support for, breast-feeding.

Recommendations

Continuing efforts should be made to limit release of PCDDs, PCDFs and dioxin-related compounds to the lowest levels that are technically achievable. This is the most efficient way to reduce the presence of these compounds in the food chain and to ensure continued reductions in human body burdens.

There is clear evidence of a decrease within the last 10 years in dioxin levels in foods and human milk in almost every region of Europe for which suitable data exist. This can be attributed most probably to the enhanced identification and control of input to the environment. The relationship between average dietary exposure to dioxins and the resulting tissue levels in humans is illustrated by data from Germany, which showed that decreases in average TEQ intake over the course of 7 years (1989-1996) resulted in similar declines in the concentrations in human milk and blood.

The consumption of food with average contamination levels already results in a weekly intake that is in the range of, or exceeds, the t-TWI value for dioxins and dioxin-like PCBs. Therefore, setting maximum levels that will considerably reduce human exposure would result in a considerable part of the present food supply being declared unfit for human consumption. Therefore the SCF recommended to set action thresholds and target values for those food groups that contribute most to the human body burden. In this context, target values indicate the average levels of contamination of food products required to bring the exposure down to the TWI value. An action threshold is a level of contamination that triggers specific risk management actions. Action thresholds are higher than target values.

Target values would normally be lower than the actual average background levels for the respective food commodity and therefore can only be reached after a further reduction of the emissions of dioxins and dioxin-like PCBs into the environment. Consequently, target values will be the driving force behind measures necessary for a further reduction of emissions into the environment. With increasing decline of emissions, the distribution of the contamination levels for the different food groups will show a shift to lower levels and will slowly come closer to the target values. As a result of this, the action thresholds might be revised after a certain period of time.

TABLE 1. Comparison of the most widely used TEFs for dioxins and dioxin-like PCBs.

PCDDs and PCDFs	Toxic Equivalency Factor (TEF)	
	I-TEF (NATO/CCMS, 1988)	WHO-TEF (van den Berg <i>et al.</i> , 1998)
2,3,7,8-TCDD	1	1
1,2,3,7,8-PnCDD	0.5	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.001	0.0001
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PnCDF	0.05	0.05
2,3,4,7,8-PnCDF	0.5	0.5
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.01	0.01
OCDF	0.001	0.0001

PCBs (IUPAC number)	Toxic Equivalency Factor (TEF)	
	PCB-TEF (Ahlborg <i>et al.</i> , 1994)	WHO-TEF (van den Berg <i>et al.</i> , 1998)
<i>Non-ortho PCBs</i>		
3,3',4,4'-TCB (77)	0.0005	0.0001
3,4,4',5'-TCB (81)	-	0.0001
3,3',4,4',5'-PnCB (126)	0.1	0.1
3,3',4,4',5,5'-HxCB (169)	0.01	0.01
<i>Mono-ortho PCBs</i>		
2,3,3',4,4'-PnCB (105)	0.0001	0.0001
2,3,4,4',5'-PnCB (114)	0.0005	0.0005
2,3',4,4',5'-PnCB (118)	0.0001	0.0001
2,3,4,4',5'-PnCB (123)	0.0001	0.0001
2,3,3',4,4',5'-HxCB (156)	0.0005	0.0005
2,3,3',4,4',5'-HxCB (157)	0.0005	0.0005
2,3',4,4',5,5'-HxCB (167)	0.00001	0.00001
2,3,3',4,4',5,5'-HpCB (189)	0.0001	0.0001
<i>Di-ortho PCBs</i>		
2,2',3,3',4,4',5'-HpCB (170)	0.0001	-
2,2',3,4,4',5,5'-HpCB (180)	0.00001	-

Abbreviations: PnCDD, pentachlorodibenzo-*p*-dioxin; HxCDD, hexachlorodibenzo-*p*-dioxin; HpCDD, heptachlorodibenzo-*p*-dioxin; OCDD, octachlorodibenzo-*p*-dioxin; PnCDF, pentachlorodibenzofuran; HxCDF, hexachlorodibenzofuran; HpCDF, heptachlorodibenzofuran; OCDF, octachlorodibenzofuran; TCB, tetrachlorobiphenyl; PnCB, pentachlorobiphenyl; HxCB, hexachlorobiphenyl; HpCB, heptachlorobiphenyl.

TABLE 2. Estimated animal steady state body burdens of 2,3,7,8-TCDD and associated estimated human daily intakes (EHDI) at NOAELs and LOAELs in the pivotal studies

Study	Endpoint	NOAEL	LOAEL	Estimated maternal steady state body burden ¹⁾ (ng/kg bw)	Associated EHDI (pg/kg bw)
Mably <i>et al.</i> , 1992	Holzman rats: Decreased sperm count in male offspring		64 ng/kg bw single bolus dose by gavage	99 ²⁾	49.5
Gray <i>et al.</i> , 1997a	Long Evans rats: Accelerated eye opening and decreased sperm count in male offspring		50 ng/kg bw single bolus dose by gavage	79 ²⁾	39.5
Faqi <i>et al.</i> , 1998	Wistar rats: Decreased sperm production and altered sexual behavior in male offspring		Maintenance of 25 ng/kg bw by subcutaneous injections	39 ²⁾	19.5
Ohsako <i>et al.</i> , 2001	Holzman rats: Decreased anogenital distance in male offspring	12.5 ng/kg bw single bolus dose by gavage		19 ³⁾	9.5
			50 ng/kg bw single bolus dose by gavage	79 ³⁾	39.5

¹⁾ Increment over background. Background body burden in rats is about 4 ng TEQ/kg bw (WHO, 2000).

²⁾ Composite value resulting from of pseudo steady state body burden and acute body burden on GD 15.

³⁾ Maternal body burden at gestation day 16.