WikiJournal Preprints/Dioxins and dioxin-like compounds

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Dioxins and dioxin-like compounds comprise a group of chemicals including polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF), as well as certain dioxin-like polychlorinated biphenyls (dl-PCB), and potentially others. They act via a common mechanism, stimulation of aryl hydrocarbon receptor (AHR), a vital transcription factor in cells. There are very high differences in potency among these compounds, i.e. in the ability to stimulate the receptor. This leads to ten thousand fold or higher differences in doses causing similar toxic effects. Most of these compounds are eliminated very slowly in the environment, animals, or humans, which makes them persistent. They like fat much more than water, and therefore they tend to accumulate in lipid or fatty tissues, and concentrate along the food web (bioaccumulation and biomagnification).

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PCDD/PCDFs are formed mostly as side products in burning processes, but PCBs were oils manufactured for many purposes. Because of toxicity and persistence, dioxin-like compounds have been regulated strictly since 1980s, and their levels in the environment and animals have decreased by an order of magnitude or more. Therefore the effects on wildlife have clearly decreased, and even populations at the top of the food web such as fish-eating birds or seals have recovered after serious effects on their reproductive capacity and developmental effects in their young especially in 1970s and 1980s.

In humans the intake is mostly from food of animal sources, but because our diet is much more diverse than that of such hallmark animals as white-tailed eagles or seals, the concentrations never increased to similar levels. However, during 1970s and 1980s slight effects were probably also seen in humans, including developmental effects in teeth, sexual organs, and the development of immune systems.

Both scientists and administrative bodies debate at the moment about the importance of remaining risks. This is very important, because the AH receptors seem to be physiologically important regulators of growth and development of organs, immunological development, food intake and hunger, and in addition regulate enzymes protecting us from many chemicals. Thus a certain level of activation is needed, and only inappropriate stimulation of the receptor is likely to be harmful. This emphasizes the importance of benefit versus risk analysis. As a whole, regulating the emissions to the environment may be considered more important presently than limiting consumption of important and otherwise healthy food items and e.g. breast feeding.

Distinct toxic effects of very high doses of dioxins in humans have been clearly demonstrated by frank poisonings and the highest occupational exposures. Hallmark effects have been skin lesions called chloracne, various developmental effects of children, and a slightly increased risk of total cancer rate.

General introduction

"Dioxins" is an imprecise term including structurally related groups of chemicals such as polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). Certain polychlorinated biphenyls (dl-PCBs) and many other chemicals[1][2][3] have dioxin-like properties. The term "dioxin-like" is used because these chemicals have a common mechanism of action, i.e. inappropriate stimulation of aryl hydrocarbon receptor (AHR, AH receptor, "dioxin receptor").[4][5]

Among compounds binding to the AHR, the higher the binding affinity, the higher will be the toxicity. High toxicity means that even low doses or low exposure levels are sufficient to produce toxic responses. Compounds with lower affinity for the AHR require higher doses to elicit similar toxic effects. Low-affinity compounds (e.g. some PCBs, usually at relatively high doses) can elicit toxic effects that are different from those of classic dioxin-like effects of chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

Dioxins are a puzzling group of chemicals that have widely diverse effects in different cell-types, tissues and animal species. Many consider them dreaded environmental "superpoisons". But they are also highly interesting tools for studying the mechanisms of intracellular receptors, gene expression, growth and development of organs, metabolism of chemicals in the body, carcinogenesis, food intake and hunger, as well as interactions of chemicals, microbes and immunological systems. The AH receptor, the mediator of dioxin toxicity seems to be an important physiological actor in the body, a ligand-activated transcription factor functionally similar but structurally unrelated to intracellular

receptors such as steroid or thyroid receptors. This reminds us of the ultimate principle of Paracelsus: all things are poisons, only the dose makes that a thing is not a poison. AH receptors are necessary for many normal biological functions,[6][5] and their physiological activation regulates our wellbeing, but their inappropriate activation leads to multiple forms of toxicity.

The best studied compound is the most toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The toxicity of other congeners is compared with this prototype. TCDD is assigned a toxicity equivalence factor (TEF) of 1. The potency and toxicokinetics of other compounds vary over orders of magnitude, and therefore each compound is assigned its own TEF that may range from 1 to 0.000 03 (or lower for fish, see below). The TEF for each compound forms the basis for defining toxic equivalency (TEQ) when assessing the toxicity of mixtures.

The metabolism and excretion of dioxins in mammals is generally very slow. Dioxins are also persistent and accumulate in the biosphere. Therefore delayed toxicity is the typical mode of harmful effects and the delay between exposure and effect complicates the assessment of risk from dioxins. Developmental adverse effects are seen at the lowest doses.

A few dramatic cases of accidental or deliberate acute poisoning are known. Two women were poisoned in Vienna, Austria, in 1998 by huge doses of TCDD. In 2004 Victor Yushchenko, then presidential candidate of Ukraine, was deliberately poisoned with a huge dose of TCDD. A widely known dioxin accident took place in Seveso, Italy in 1976. These high-dose incidents have somewhat delineated the acute effects on humans. As described in detail later in this article it is more difficult to ascertain, precisely, what are the human health effects of chronic low-dose exposures to dioxin-like compounds. This remains a contentious issue of importance to regulatory agencies as well as to the general public.

For a short account of historical legacies of dioxins see Weber et al.[7] Due to intensive research efforts dioxin toxicity is known and understood better than that of most environmental toxic agents. On the other hand, it is beguilingly complicated.

Chemistry

There are 75 possible congeners of polychlorinated dibenzo-*p*-dioxins (PCDD) and 135 possible congeners of polychlorinated dibenzofurans (PCDF). So-called lateral chlorine substitutions at the positions 2,3,7, and 8 (Fig. 1) allow the dioxins to bind to the AH receptor with high affinity. They also prevent enzymatic attacks on the molecule causing persistence both in human body and in the environment. Such compounds are particularly toxic and constitute the prototype for dioxin-like toxicity. TEF values have been assigned to 17 congeners (seven dibenzo-*p*-dioxins and ten dibenzofurans) having four to eight chlorine substitutions. Chlorines in excess of the four (2,3,7 and 8) decrease the potency, but the type of toxic effects remains mainly the same.[8]

There are 209 PCB-compounds. Four non-ortho compounds that have no chlorine substitution in any o-position to the inter-ring C-C-bridge (2, 2', 6 or 6') have the greatest dioxin-like potency (Fig. 2). The toxicity of 3,3',4,4',5-penta-CB (PCB126) is comparable to those dioxins assigned the TEF value[8] although high toxicity in humans has been challenged.[9] Eight mono-ortho PCBs have very low activity. All other PCBs are devoid of noticeable dioxin-like effects.

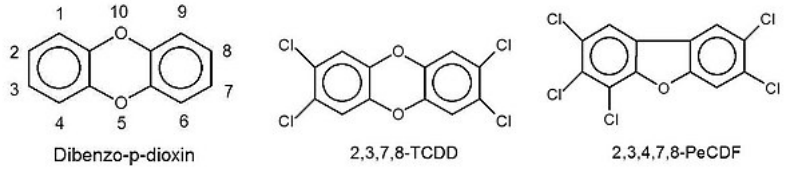


Figure 1 | Structures of dibenzo-p-dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,4,7,8-pentachlorodibenzofurane

Only compounds that are able to assume a planar (flat) conformation can bind to the AH receptor. Non-ortho compounds rotate relatively freely along the C-C-bridge between the rings, but each o-chlorine causes a steric hindrance and makes it more difficult for the molecule to assume a planar conformation (Fig. 2).

Brominated dioxins, furans and biphenyls, as well as mixed halogenated congeners, may share the toxicity and the ability to bind to AH receptor. They probably deserve TEF values as well, but lack sufficient data.[10] Many other compounds bind to AH receptors, e.g. polyaromatic hydrocarbons and polychlorinated azoxy-benzenes and naphthalenes.[1]

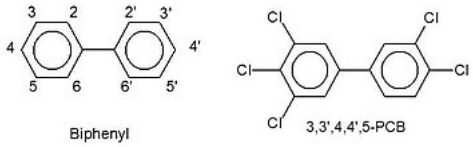


Figure 2 | Structures of biphenyl and 3,3',4,4',5-pentachlorobiphenyl (PCB 126)

Surprisingly, many natural compounds have very high affinity to AH receptors. These include e.g. indoles, flavones, benzoflavones, imidazoles and pyridines (for review, see Denison and Nagy[2]; DeGroot et al.[11]). They are usually metabolized rapidly, but due to continuous intake from food, especially vegetables, they may cause receptor activation at the same level as or higher than the present background concentrations of contaminant dioxins.[12] Short-acting stimulations of the receptor may, however, be qualitatively different from the persistent stimulation of dioxins.[13] Intriguingly many of these vegetables are considered very healthy.

Sources

Sources of different dioxin-like chemicals are different depending upon the chemical class. PCDD/F compounds are unwanted side products in burning processes or are impurities in the synthesis of PCBs, chlorophenol fungicides and phenoxy acid herbicides.[14] Due to control measures, main sources are very different today than they were 30 or 40 years ago. The decrease in environmental levels is clearly demonstrated by concentrations in sea bottom sediments.[15]

Any burning will produce PCDD/Fs if chlorine (particularly along with metal catalysts) is available, even burning wood[16] and burning incense.[17] Poorly controlled urban waste incineration was one of the most important sources in past. This can be technically solved by ensuring high incineration temperature (1,000 °C or higher), long burning time, and effective flue gas filtration. In modern good-quality incinerators PCDD/Fs are not a problem.[18] On the other hand, accidental dumpsite fires and backyard burning of waste are much more problematic and poorly controlled. In poor burning conditions the production of PCDD/Fs can be very high.[19][18]

Many previous sources of PCDD/Fs are presently in reasonable control (e.g. decreased chlorine bleaching of pulp, syntheses of PCBs, chlorophenols and phenoxy acids etc.). Metal industries and local burning of solid fuels remain as sources.[18] Emissions decreased between 1985 and 2004 by about 80 % in Europe (from 14 kg per year I-TEQ [a] to 2–4 kg),[20] in the USA between 1987 and 2000 even more (from 14 kg to 1.4 kg)[21] (Fig. 3). In the USA the top three current sources of dioxin emissions to air are forest fires, backyard burning of trash, and medical waste incinerators.[22] The trend is not good in all countries, however.[23][14] Electronic waste recycling in poorly-controlled conditions is a recent additional concern as a source of dioxin-like compounds.[24][25] It should be noted that there are also natural sources of PCDD/Fs such as kaolinic clay and volcanic eruptions.[26][27][28]

PCB compounds were in wide use from 1930s to 1980s for multiple purposes because they are technically excellent oils, resistant to pressure, chemically resistant, non-flammable, and do not conduct electricity. Although their production was discontinued in most countries in the 1980s, these compounds still linger in many products such as electrical transformers and plastic materials. Some of it ends up to the general environment. Only a minor portion of PCBs in mixtures are dioxin-like, depending on the

matrix, for example non-ortho congeners are of the order of 0.1 % and mono-ortho congeners 10 % of the total amount of PCBs.[29]

I-TEQ (international TEQ for PCDD/Fs) was used before present TEQs were agreed under the auspices of the World Health Organization. The differences are minor. The TEQs used in this text are sometimes called WHO-TEQs.

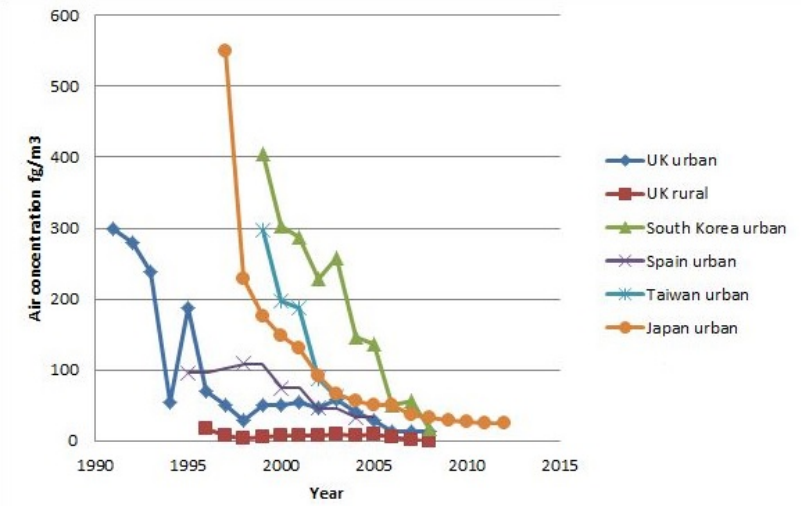


Figure 3 | Decrease of dioxins in ambient air in different regions *(redrawn from Dopico and Gomez, 2015).*[19]

Environmental fate

Dioxins tend to accumulate in the environment, because they are persistent and not easily degraded by environmental microbes. Because dioxins are much more soluble in lipids than in water, they tend to accumulate in e.g. plankton (bioaccumulation). The concentration tends to magnify at each trophic level (biomagnification), which leads to high concentrations at the highest trophic levels, e.g. seals and predatory birds. Human concentrations are not nearly as high as in the most endangered wild species, because the human diet is quite diverse. However, there have been concerns regarding the safety of wild and farmed fish in our diet (see below).

TCDD has been long known to be sensitive to photochemical dechlorination. If exposed to direct sunlight or UV-radiation, it will decompose in a matter of hours.[30] Photocatalysis and other methods have also been tested in attempts to remove dioxins in soils and other environments.[14][28] Because dioxins adsorb tightly to soil particles, and microbial degradation (mostly via dehalogenation) of dioxins is very slow, researchers have actively tried to search for mechanisms to increase degradation[31] or to find especially active microbial species for the purposes of bioremediation.[32][14][28] By and large, this has not been very successful. Also interactions with the microbiome in the intestines are poorly known.[33]

Dioxin literature is confusing to many because units used may be less known and they are sometimes used in a confusing manner. Some dioxins are very potent and therefore the amounts of our concern are very small, usually measured as picograms or nanograms. Concentrations in animal or human tissues are usually expressed as pg/g lipid or ng/kg lipid. Some authors use non-standard expression ppt (parts per trillion). This is confusing and should be avoided, since trillion may mean 10^{12} or 10^{18} in different countries depending on the use of short scale or long scale system, resp. Picogram is 0.000 000 000 001 g.

To make it clear, weight units are g (gram), mg (milligram, 10^{-3} g), µg (microgram, 10^{-6} g), ng (nanogram, 10^{-9} g), pg (picogram, 10^{-12} g), fg (femtogram, 10^{-15} g).

Toxicokinetics: absorption, distribution and elimination

The main source of dioxins in animals and humans is food.[34][35] Oral absorption of dioxins depends on the carrier. Dioxins in the fat of fish or meat are well absorbed, but those in e.g. soils poorly. After absorption they are distributed mostly to adipose tissue and to the liver.[36][37][38] Liver sequestration increases at high dose levels due to induction of CYP1A2 binding dioxins.[39]

Elimination of dioxins is slow, because they are not easily metabolized and urinary excretion is negligible. Elimination is mainly via faeces after slow metabolism in the liver, followed by biliary excretion into the gut. Variation between species is large, e.g. the half-life of TCDD in rats is about 3 weeks, in man about 7 years.[36] Elimination half-lives of various congeners in people may vary tenfold (Table 1). There may be high individual variation.[40] Very high concentrations seem to induce metabolizing enzymes and shorten the half-lives.[41][42]

Table 1. Elimination half-lives in humans of some PCDD/Fs.[43]

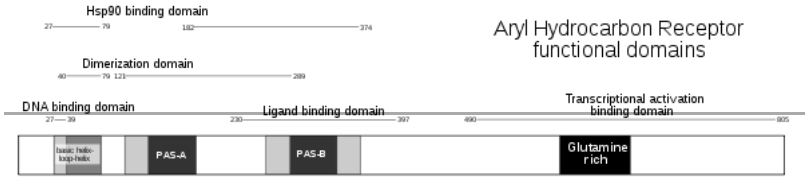
Congener	Half-life, years
2,3,7,8-TCDD	7.2
1,2,3,7,8-PeCDD	11.2
1,2,3,4,7,8-HxCDD	9.8
1,2,3,6,7,8-HxCDD	13.1
1,2,3,7,8,9-HxCDD	5.1
1,2,3,4,6,7,8-HpCDD	4.9
OCDD	6.7
2,3,7,8-TCDF	2.1
1,2,3,7,8-PeCDF	3.5
2,3,4,7,8-PeCDF	7.0
1,2,3,4,7,8-HxCDF	6.4
1,2,3,6,7,8-HxCDF	7.2
1,2,3,7,8,9-HxCDF	7.2
2,3,4,6,7,8-HxCDF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

Nursing mothers excrete dioxins in milk fat at approximately the same concentrations as their own level in body fat. This means that maternal dioxin levels decrease during the lactation period (even by 20%).[44] Also placental PCDD/F concentrations are in the same range as in maternal body or breast milk (as pg/g fat)[45] and placental transfer to the foetus occurs.[46] Each delivery and lactation decreases the mother's body burden by 25–30%. In children elimination is faster than in adults, initially with a half-life of months rather than years,[47][48][49] probably due to several factors, faster rate of faecal lipid excretion, and increased metabolism.[50] Rapid growth and dilution decrease the concentrations as well, even if the body burden does not change to the same extent.

Mechanism of action: the Aryl Hydrocarbon Receptor (AHR)

Most biological actions of dioxins, including their toxicity, are mediated by the AHR (Fig. 4). The AHR is an evolutionarily ancient receptor, an over 600-million-year old protein occurring in all vertebrates. Homologs of the AHR have also been discovered in invertebrates and insects. These primitive AHR-homologs do not bind dioxins or other external ligands. They seem to play important developmental roles in neuronal differentiation and regulation of feeding-related aggregation behaviour or in regulation of normal morphogenesis.[51][52][53][54][55]

The AHR belongs to the family of basic Helix–Loop–Helix-PAS (bHLH/PAS) proteins, which have important roles in e.g. regulation of neural development, in generation and maintenance of circadian rhythms, in sensing cellular environment, and as transcriptional partners and co-activators. Although it is structurally



different, the AHR acts as a transcription factor analogously to the nuclear receptors such as steroid receptors or thyroid receptors. The AHR is a ligand-activated transcription factor that integrates environmental, dietary, microbial and metabolic cues to control complex transcriptional programmes in a ligand-specific, cell-type-specific and context-specific manner.[5]

Figure 4 | The structure of AHR. The approximate sites for DNA binding, ligand binding, HSP90 binding, heterodimerization, and transactivation are shown

Jeff Dahl, CC BY-SA 4.0

The AHR exists in the cytosol in a protein complex including several proteins (Fig. 5). These chaperones keep the AHR in a conformation able to bind a ligand but unable to enter the nucleus. After ligand binding, the protein complex enters into the nucleus. The AHR releases its chaperones and heterodimerizes with another bHLH/PAS protein, ARNT (AHR nuclear translocator). The AHR/ARNT dimer binds to DNA at the major groove of the DNA helix at specific sites, AHR response elements (also known as dioxin response elements, DREs, or xenobiotic response elements XREs).

In addition to this canonical pathway, some actions of dioxins and AHR are mediated via non-canonical pathways. These may be involved e.g. in interactions with other receptors, such as estrogen receptor, other transcription factors such as NFκB signalling complex, different kinases, and various epigenetic mechanisms.[51][56][5][57][58]

In response to activation by dioxins, the AHR signalling pathway modifies the expression levels of numerous genes. The best characterized of these at the molecular level is the induction of the gene for a Phase I cytochrome P-450 drug-metabolizing enzyme, CYP1A1.[59][60][61]

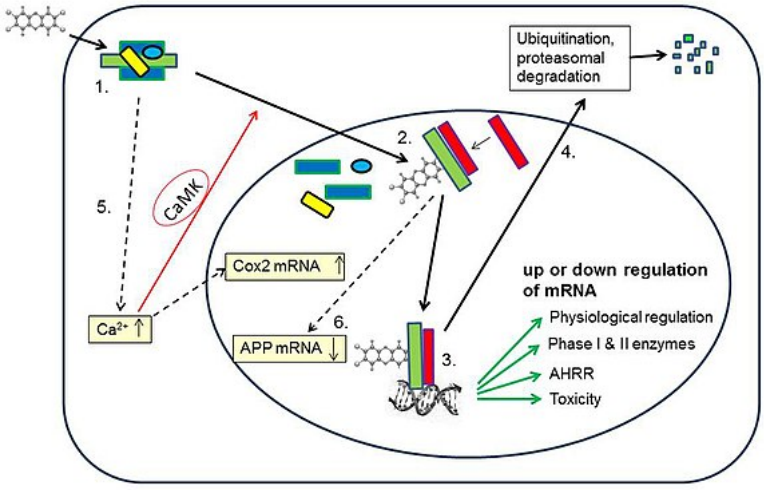


Figure 5 | A schematic diagram of some AHR signaling pathways. The canonical pathway is depicted with solid black arrows, alternative pathways with dashed arrows, and an intersection of these two with a solid red arrow. The green bars represent the AHR, red bars ARNT, yellow bars ARA9 (AIP, Xap2), blue bars HSP90 and the blue ovals p23. Dioxin binding to the AHR (1.) leads to its translocation into the nucleus by importin-β, (2.) heterodimerization with ARNT and binding to the DNA at DREs, (3.) modulating expression levels of target genes (green arrows). One of the gene products elevated by this mechanism is AHRR, a repressor protein which forms a feedback loop that inhibits AHR action. The AHR is finally degraded by the ubiquitin–proteasome system (4.). AHR activation can also rapidly increase intracellular Ca2+ concentration (5.) which in turn may ultimately result in augmented Cox2 gene expression. Elevation of Ca2+ activates CaMKs, which appear to have a critical role in the translocation of the AHR. Another example of effects mediated by the AHR via non-

Dioxin-activated AHR induces other Phase I and II enzymes that metabolize chemicals in the liver including CYP1A2, CYP1B1, CYP2S1, CYP2A5, ALDH3, GSTA1, UGT1A1, UGT1A6, UGT1A7 and NQO1. Probably this induction system evolved as a mechanism to enhance the elimination of foreign fat-soluble chemicals. In addition to xenobiotic-metabolizing enzymes, TCDD exposure modifies the expression of a large number of other genes. For example, in adult mouse or rat liver, hundreds of genes are affected.[62][51][5] It is still unclear which genes are the most important for the main toxic effects such as lethality, anorexia and wasting syndrome, and various hyperplastic and atrophic tissue changes.

The role of AH receptor predominantly as an inducer of metabolic enzymes to protect us from xenobiotics is rapidly changing. Mice lacking

AHR (AHR knockout) have clearly demonstrated the necessity of AHR activation for normal physiology, and these animals are severely sick with e.g. cardiac hypertrophy, liver fibrosis, reproductive problems, and impaired immunology. AH receptors participate in many regulatory functions in the body (the reader is referred to recent reviews).[51][63][64][65][66][67][68][69][70][55] An important area seems to be antibacterial and antiviral defence mechanisms[71][72] and the regulation of innate immunity.[73][74][5] AHR ligands are important at intestinal epithelial cells which serve as gatekeepers for their supply, and if AHR activation is too low, loss of important lymphoid cells and subsequent susceptibility to infections follow.

canonical pathways is suppression of acute-phase proteins (6.) which does not involve DNA binding.

(simplified and modified from Lindén et al.).[51], *Jouko Tuomisto*

Toxicity equivalents

Dioxins and dioxin-like compounds vary in their potency and fate in the organisms. The toxicity of mixtures cannot be assessed by simply adding up the amounts or concentrations of all chemicals in the mixture. However, if the amount of a compound is standardized to the toxicologically equivalent amount of TCDD, chemicals with different potencies can be summed up and this equivalent quantity is very useful for regulatory and even some scientific purposes.[8][75] Several versions of TEF have been used since 1984, proposed by Ontario Ministry of Environment, U.S. Environmental Protection Agency, and Nordic Countries, respectively. International harmonization was undertaken by NATO/CCMS, and most recently the World Health Organization organized re-evaluations of TEF values in 1998, 2005 and 2013.[75][10]

The toxicities can vary by a factor of 30,000, and TCDD is assigned a TEF of 1. Other chemicals are given TEF values of 1 to 0.000 03 (in fish down to <0.000 005) (Table 2). The amount of a given compound is multiplied by its TEF, resulting in the amount toxicologically equivalent to that of TCDD. These partial equivalent amounts are then added up to make the sum toxic equivalent (TEQ) of the mixture. This can be used as a proxy of the total dose of dioxin-like compounds. This is a consensus value based on several assumptions and not a strictly scientific fact.[8] Therefore they should be regularly updated to reflect new and more accurate information.

Table 2. Toxic equivalency factors for PCDD/Fs and PCBs. Other congeners are not assumed to have dioxin-like effects. IUPAC numbers for PCBs are given in parenthesis.[76][8]

Class	Congener	WHO-TEF 2005	WHO-TEF fish 1998	WHO-TEF birds 1998
PCDDs	2,3,7,8-TCDD	1	1	1
	1,2,3,7,8-PeCDD	1	1	1
	1,2,3,4,7,8-HxCDD	0.1	0.5	0.05
	1,2,3,6,7,8-HxCDD	0.1	0.01	0.01
	1,2,3,7,8,9-HxCDD	0.1	0.01	0.1
	1,2,3,4,6,7,8-HpCDD	0.01	0.0001	<0.001
	OCDD	0.0003	<0.0001	0.0001
PCDFs	2,3,7,8-TCDF	0.1	0.05	1
	1,2,3,7,8-PeCDF	0.03	0.05	0.1
	2,3,4,7,8-PeCDF	0.3	0.5	1
	1,2,3,4,7,8-HxCDF	0.1	0.1	0.1
	1,2,3,6,7,8-HxCDF	0.1	0.1	0.1
	1,2,3,7,8,9-HxCDF	0.1	0.1	0.1
	2,3,4,6,7,8-HxCDF	0.1	0.1	0.1
	1,2,3,4,6,7,8-HpCDF	0.01	0.01	0.01
	1,2,3,4,7,8,9-HpCDF	0.01	0.01	0.01
	OCDF	0.0003	<0.0001	0.0001
Non-ortho-PCBs	3,3',4,4'-TCB (77)	0.0001	0.0005	0.1
	3,4,4',5-TCB (81)	0.0003	0.0001	0.05
	3,3',4,4',5-PeCB (126)	0.1	0.005	0.1
	3,3',4,4',5,5'-HxCB (169)	0.03	0.00005	0.001
Mono-ortho-PCBs	2,3,3',4,4'-PeCB (105)	0.00003	<0.000005	0.0001
	2,3,4,4',5-PeCB (114)	0.00003	<0.000005	0.0001
	2,3',4,4',5-PeCB (118)	0.00003	<0.000005	0.00001
	2',3,4,4',5-PeCB (123)	0.00003	<0.000005	0.00001
	2,3,3',4,4',5-HxCB (156)	0.00003	<0.000005	0.0001
	2,3,3',4,4',5'-HxCB (157)	0.00003	<0.000005	0.0001
	2,3',4,4',5,5'-HxCB (167)	0.00003	<0.000005	0.00001
	2,3,3',4,4',5,5'-HpCB (189)	0.00003	<0.000005	0.00001

PCDD/F congeners usually seem to act additively, which justifies the use of TEFs.[77] With less potent compounds, partial antagonism is possible.[78][79][80] This may lead to overestimation of the total toxicity.[80] In fact, some in vitro results indicate that there may be significant deviations in human sensitivity from the TEF values based mostly on rodent data.[9]

If toxicity studies, such as on lethality, immunotoxicity and reproductive toxicity, are available, TEF values are based on them. If they are lacking, it may be necessary to base the values on *in vitro* information. Most studies are based on oral intake, so the values correlate best with oral toxicity. Internal TEF values based on concentrations in the body would be preferable, but there is not enough data to formulate them. Different endpoints of toxicity may lead to different TEF values; hence the values are always balanced compromises and show only the order of magnitude.

Slightly different TEF values have been assessed for fish and birds, in addition to those of humans and other mammals (Table 2).[76]

Toxic effects in wild animals

Toxic effects in wildlife are difficult to sort out, because usually the exposures have been to mixtures of quite different chemicals such as PCDD/Fs, dioxin-like PCBs as well as simultaneous exposure to non-dioxin-like PCBs, DDT and other chlorinated insecticides such as aldrin, dieldrin, lindane and others. Effects of individual chemicals on animals have been studied in laboratory conditions, but ecological impact is more difficult to assess. High-dose effects on wildlife and domestic animals have been reviewed, e.g.[81]

Developmental and embryotoxicity are the most sensitive effects of dioxins. Trout and other salmonids are the most sensitive species of fish. Sensitivities among fish species vary up to 120-fold.[82][83] Typical findings are excess mortality, oedema, haemorrhages, and craniofacial malformations. So-called blue sac disease of early embryos is associated with high concentrations of TCDD.[84] Adult fish are less susceptible showing wasting syndrome, fin necrosis, liver toxicity, and loss of weight at high doses, and impaired reproduction especially in females.[83] Dioxins, along with overfishing, are considered a reason for the lake trout population crash in the Great Lakes in the U.S.A. and Canada in mid-twentieth century. Experimentally the mechanisms of toxicity in fish have been studied in zebrafish, especially cardiovascular toxicity, craniofacial malformations, and reproductive toxicity (reviewed by King-Heiden *et al.*).[83]

A number of bird species have also been shown to be sensitive to embryonal toxicity and problems in reproduction. High concentrations of dioxins, PCBs and DDT in fish have threatened the populations of fish-eating birds, especially eagles and ospreys with incredible total PCB levels of up to 1,000 μg/g in fat, due to the position of these birds at the top of the food chain.[85]

Marine mammals are also on top of the food chain, highest are polar bears. On the other hand, polar bears also metabolize polychlorinated compounds fairly effectively.[86] PCB concentrations seem to be 2–5-fold higher than in seals, their main food source. In Canadian seals total PCB levels vary from 300 to 1,000 ng/g (wet weight in blubber), and TEQs are of the order of 0.5–0.6 pg/g.[86] In the Baltic Sea, which is the most contaminated brackish water area in the world, total PCB levels in ringed seals are presently about 5,000 ng/g (in fat) and PCDD/F levels about 40 pg/g TEQ (in fat). The levels were 8-fold and 20-fold higher, resp., in 1970s, and at that time POPs are considered having been an important reason for their poor reproductive success.[87] POPs are also implicated in bone deformities in seals[88] and polar bears.[89]

In addition to marine mammals, developmental effects were shown in bank voles living in an environment contaminated by chlorophenols and their dioxin impurities: they had third molars reduced in size.[90] In laboratory rats, TCDD reduces dose-dependently the size of molars, most severely the third lower molars.[91]

As in humans, the concentrations of dioxins (as well as DDT and its metabolites) in wildlife have clearly decreased over the years,[86] e.g. in seals of the Baltic sea,[87] in eggs of herring gulls of the Great Lakes,[92][93] in eggs around contaminated harbour sites,[94] and guillemot eggs of the Baltic sea,[95] in white-tailed eagles in Scandinavia,[85] as well as in salmon and Baltic herring in the Baltic sea.[96][97][98] When the organochlorine levels have decreased, populations have recovered, e.g. white-tailed eagle[85][99] and osprey.[100] Brominated compounds have not decreased much so far, but they only contribute about 1 % of TEQs.[87]

Concentrations in fish and in birds are dependent on the age of the animal. Correcting for this is necessary to reliably calculate time trends in trout.[101] In Baltic herring, concentrations of both PCBs and PCDD/Fs increase several fold from age 1 year to age 8–15 years.[102][96] In adult glaucous gulls, however, no age-correlation was found, suggesting that steady state levels are reached early in life.[103] This implies relatively rapid elimination and a short half-life. In eagle nestlings, PCB concentrations decrease after hatching[104] indicating that maternal load transferred to eggs is initially more important than the content of PCBs in their diet during the rapid growth.

Human intake and concentrations

Food from animals is the most important source of dioxins for humans.[34] Fish is very important, and although meat and milk products have dominated in most countries, the concentrations in farming products have now declined.[105] In all foods the concentrations have decreased remarkably in the Western countries during the last 30 to 40 years, and the present daily intake is 1–2 pg/kg bw (TEQ). Human exposure from contaminated soil is very limited.[106]

Dioxins accumulate during the whole lifetime, because their half-lives are very long (Fig. 6). PCDD/F concentrations in young people are 5–10 pg/g TEQ in fat, but 40–100 pg/g in older generations.[107] Additionally, there is carry-over in older generations from earlier decades when the intake was 5 to 10 times higher than presently.[108][109] For this reason concentrations cannot be compared without information on age and the year of sampling.

Dioxin concentrations (but not all PCBs) in humans have been decreasing for over 30 years, in line with decreasing environmental levels.[110] The World Health Organization has organized dioxin follow-up measurements in breast milk since 1987. In more recent surveys also PCBs and some other persistent chlorinated compounds have been measured.[111] This information is crucial, because transgenerational effects are possible (see below), and if true in humans, the impact of high concentrations in 1970s would be seen during the 21st century.

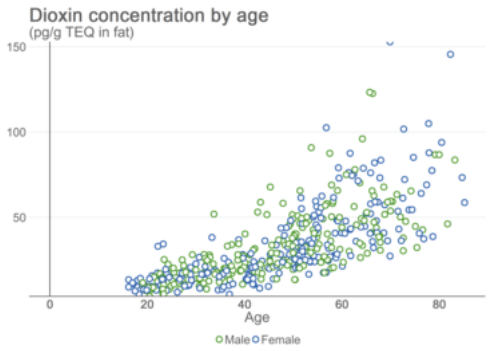


Figure 6 | Dioxin concentrations are high in older generations for two reasons: dioxins accumulate over years, because their elimination is slow and half-lives are long, and the intake was much higher in the past than presently.[108]

Breast milk concentrations were very high in 1970s (Fig. 7), about 50 pg/g for PCDD/Fs and 50 pg/g for dl-PCBs (TEQ in fat).[112] During the first systematic round of breast milk measurements in 1987, PCDD/F concentrations in many countries were between 30 and 40 pg/g TEQ in milk fat[113] and during the last round in 2005–2010 between 5 and 10 pg/g in many European countries, and low in many African countries, but still high in e.g. India, Egypt and the Netherlands (over 20 pg/g).[111] Thus the concentrations have decreased by 80–90 % in many but not all countries.

Toxic effects in humans

Accidents, contamination episodes and occupational risks

A few dramatic accidental or deliberate cases of acute poisoning have taken place. Two women were poisoned in Vienna, Austria, in 1998 by huge doses of TCDD. Dioxin concentration in one of them was 144,000 pg/g in serum fat, the highest ever measured in humans.[114] The dose must have been about 25 µg/kg. Contemporary concentrations in young people are 5–10 pg TEQ/g fat, and in older people 50 pg TEQ/g fat or more (Fig. 6), and daily intake is 1–2 pg TEQ/kg body weight. This victim survived despite the extraordinarily high levels of TCDD in her serum, but had severe chloracne lasting for years and weight loss. There were few other symptoms or laboratory findings: mild gastrointestinal symptoms and amenorrhea.[114] Victor Yushchenko, then presidential candidate of Ukraine, was deliberately poisoned in 2004 with a huge dose of TCDD; the concentration in fat was 108,000 pg/g. He suffered from severe

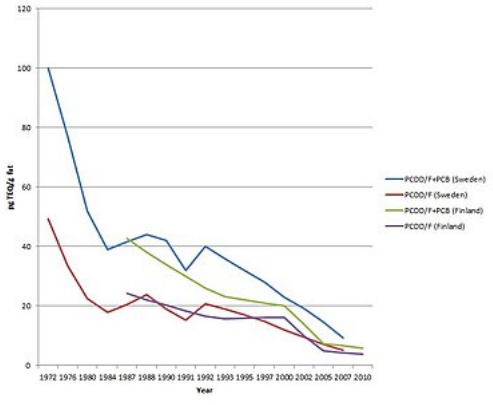


Figure 7 | Decrease of dioxin concentrations in breast milk in Sweden and Finland (Sweden, early data from Norén and Meironyté, 2000, others from van den Berg et al, 2017 and WHO database of the Institute for Health and Welfare, Finland, Hannu Kiviranta).[112][111]

gastrointestinal symptoms, indicating pancreatitis and hepatitis, and then developed severe chloracne, but survived.[42][115] In both the Vienna poisoning and the Yushchenko poisoning the details of TCDD intake are unknown.

Perhaps the best known dioxin accident took place in Seveso, Italy in 1976.[116][117] The town was contaminated by TCDD, after a tank containing 2,4,5-trichlorophenol released its contents to air. The highest levels (up to 56,000 pg/g in serum lipid) were found in children who ate local food and played outdoors. About 200 cases of chloracne occurred; other detectable human effects were few, although a number of animals such as rabbits died.[116] Cancer studies have suggested a slightly increased number of hematopoietic and lymphatic tissue malignancies.[118][119] In a cohort of women with measured individual TCDD levels a slightly increased risk of all cancers was found (1.8 fold risk vs. tenfold increase in TCDD concentration) as well as a non-significant increased risk of breast cancer.[120]

Several developmental consequences were detected after the Seveso incident. Dental aberrations associated with TCDD levels were found 25 years after the accident in persons who had been less than five years old at the time of the accident.[121] Lowered male/female sex ratios were found in the offspring of males exposed to high concentrations of TCDD.[122] Decreased sperm quality was observed in young men exposed to TCDD in utero and during lactation or during infancy or prepuberty.[123][124] Slightly increased risk of endometriosis[125] as well as a dose-dependently increased time to pregnancy and infertility were found among the most heavily exposed women.[126] However, in 30 years' follow-up no association between TCDD exposure and adverse pregnancy outcomes were detected except for a non-significant decrease in birthweight.[127] Some metabolic and endocrine effects were seen for a limited time period.[128] Neonatal thyroid stimulating hormone levels were increased in newborns of mothers with high body burdens of TCDD.[129]

There have also been several cases of food contamination. In Japan (Yusho incident, 1968) and in Taiwan (Yu-cheng incident, 1979) PCB oil used in heat exchangers leaked to rice bran oil. Consumption of contaminated oil caused over 2000[130] and about 2000[131] cases of poisoning, respectively. Most of the toxic effects have been attributed to PCDFs and dl-PCBs. The most dramatic health effects were caused by developmental toxicity during pregnancy. The average daily intake was calculated to have been 154,000 pg I-TEQ/kg in the Yusho incident,[132] 100,000 fold higher than average background intake at present. The Yu-cheng incident was roughly similar, and the concentrations were still over 1300 pg I-TEQ/g fat about 15 years later.[133] There were many skin problems such as hypersecretion of Meibomian glands in the eyes, swelling of eyelids, abnormal pigmentation of skin, hyperkeratosis and chloracne. Babies born to Yusho and Yu-cheng mothers were smaller than normal. They had dark brown pigmentation, gingival hyperplasia, and sometimes dentition at birth or other tooth deformities. Foetal deaths and miscarriages were common.[40] Cancer studies initially gave inconsistent results in spite of the heavy exposure.[134][131] Later, a combined analysis of both episodes indicated increased mortality from all causes, all cancers, lung cancer, and heart disease in men, and liver cancer in women.[135]

Several feed and food contamination episodes with dioxin-like compounds have occurred also in Europe and elsewhere.[136][26] A tank of recycled fats was contaminated with at least 160 kg PCB oil in 1999 in Belgium, and used for animal feed. Low fertility of chickens and deformed chicks were noted. About 1 g of dioxins and 2 g dl-PCBs (TEQ) were involved.[137] This caused a major dioxin alarm, and European Union set very strict limits for dioxins in food and feed. Due to fairly rapid intervention, total dioxin concentrations in the population did not increase even in Belgium: 23.1 versus 22.9 pg TEQ/g fat.[137] No health effects have been noted. Similar conclusions were drawn after a food contamination incident in Ireland: a short term exceedance of limit values is not likely to lead to health effects.[138] The incidences show that careful food controls are necessary, but no individual health measures (e.g. abortions) are rational in case of short moderately increased intake, because human dioxin body burden (accumulated during the whole lifetime) is large compared with short-term additional exposures, and therefore levels increase very slowly.

Phenoxy acid herbicides (Agent Orange and others, contaminated by dioxins, especially TCDD) were used in large quantities during the Vietnam War. The veterans have been thoroughly studied, but variable levels complicate assessments. There is some evidence for increased cancer, diabetes,[139] and hypertension[140] in the most highly

exposed groups. However, causal relationship has been difficult to prove, and e.g. in case of diabetes a reverse causality has been suggested,[141] and dose-responses do not support causality.[142][143][109] Effects on local population have been less scrutinized.[144] Tooth enamel defects were found to be more common in dioxin-affected regions,[145] as well as borderline impaired neurodevelopment[146][145] and eating disorders.[147] Both modelling and monitoring results suggest that although somewhat higher than normal, highly elevated exposures to TCDD are not common in local people occasionally exposed to spraying.[148] However, there are remarkable differences in PCDD/F levels in breast milk in different locations.[149]

Several industrial settings have caused high exposures to dioxins when synthesizing chlorophenols or phenoxy acid herbicides.[150][151][152][153] Chloracne is a hallmark characteristic at the higher end of exposure levels. Occupational cancer studies have been pooled in a large international combined cohort, suggesting an increased risk of all cancers and of soft-tissue sarcoma.[154] The difficulty in interpreting the effects is that exposure levels were not measured directly and appear to be highly variable, i.e. very high industrial levels and marginally increased levels in workers spraying phenoxy herbicides.[155] The study[154] was crucial for IARC evaluations,[156][157] which have also been criticized.[158][159][160] Especially the evidence on soft-tissue sarcoma is weak and based on very few cases,[155] but a slight increase of all cancers is likely to be real considering recent new evidence on Yusho, Yu-cheng and Seveso accidents. An increase in lung cancer risk would be logical among smokers due to promotion.

A review of high-exposure studies suggests that dioxin exposure is associated with increased mortality from cardiovascular disease and, especially, ischemic heart disease.[161] High industrial male dioxin levels were associated with lowered male/female ratio of offspring agreeing with the Seveso results.[162]

sks connected with low exposures of general population

An international panel met in 1998, organized by the World Health Organization and International Programme on Chemical Safety, to give guidance for assessing tolerable daily intake (TDI) values.[163] Critical body burdens were compared in humans and animals, and the respective estimated human intake was calculated. The most relevant effects were found to be sperm count, immune suppression, genital malformations, and neurobehavioural effects in offspring and endometriosis in adults.[164] Thus the safety margins for different developmental effects were considered lowest. The TDI recommendation was 1-4 pg/kg TEQ, with an ultimate goal to reduce it to 1 pg/kg.

This recommendation was based on the intake of dioxins by women in fertile age subsequently delivering dioxins during pregnancy and breast feeding to the child. Dioxin concentration in breast milk fat is about the same as in mother's adipose tissue. Considering the amount of fat transported from mother to child during a long breast feeding period, this was considered the most vulnerable situation. Therefore the TDI does not directly guide intake in any other population group, including children.[164] It should be noted that the body burden of dioxins at steady state is about 5000 daily doses meaning that only long-term intake is important.[3]

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) derived in 2001 a provisional tolerable monthly intake (PTMI) of 70 pg TEQ/kg body weight.[136] The Scientific Committee on Food applied a TDI of 2 pg TEQ/kg, which is very close to the JECFA PTMI.[165] The U.S. Environmental Protection Agency (U.S. EPA) established an oral reference dose (RfD) of 0.7 pg/kg b.w. per day for TCDD.[166] In view of different approaches European Food Safety Authority (EFSA) recommended a new comprehensive risk assessment,[165] and recently EFSA Panel on Contaminants in the Food Chain (CONTAM) recommended a tolerable weekly intake (TWI) of 2 pg TEQ/kg which is pending.[105]

Table 3. Tolerable intake estimates by different agencies in Europe and the United States.

Agency	Tolerable dose	Tolerable dose expressed as TDI
WHO 2001		1-4 pg TEQ/kg
JECFA 2001	70 pg TEQ/kg monthly	2.3 pg TEQ/kg
USEPA 2012	0.7 pg TCDD/kg daily (reference dose)	
EFSA-SCF 2015		2 pg TEQ/kg
EFSA CONTAM Panel 2018	2 pg TEQ/kg weekly	0.29 TEQ/kg

Tooth deformities have been considered a plausible developmental effect in a general population after a long breast-feeding with relatively high dioxin concentrations in breast milk (range 7.7–258) pg/g TEQ in fat.[167][168] The effects were no longer seen when dioxin levels in milk decreased over the years. Cryptorchidism did not associate with placental levels of dioxins and PCBs,[45] but adipose tissue levels at the time of operation may support an association.[169] Sperm counts at age 18–19 years were inversely associated with dioxin levels at age 8–9 years in a cohort of Russian boys.[170] The range of PCDD/F+PCB TEQ was 4.88–107 pg/g lipid, or relatively high for age due to local industrial emissions. Maternal levels of dioxins were 5 to 173 pg TEQ/g fat, but the levels in babies are not known.[171] Several endpoints in male sexual development including those in the Russian Children study have been reviewed and the most sensitive endpoint was interpreted to be sperm count due to epididymal factors.[172] It was hypothesized that the mechanism is associated with sperm DNA methylation in young adults.[173]

The CONTAM panel of EFSA recommended a TWI of 2 pg/kg based heavily on the Russian Children Study.[105] The problem is that we do not know the sensitive time period, and if it is e.g. two first years of life associated with breast feeding, we do not know the concentrations that may have been higher than at 8–9 years. Modelling is limited by the lack of exact information on kinetics in small children. Decreasing sperm counts in many countries while the concentrations of dioxins have been decreasing do not support a causal role of present dioxin intake. If multigenerational mechanisms are involved, it would be more important to evaluate the concentrations some decades back, and contemporary restrictions no longer help. Setting strict arbitrary limits may fire back, and changes in diet, e.g. avoiding fish consumption could lead to harmful health effects. It is also a problem that harmful effects may only concern certain age categories (esp. young women before their first pregnancy), and for others fish consumption means a health benefit.

Cancer risk from dioxin exposures has been hotly debated. IARC[156][157] has deemed TCDD and 2,3,4,7,8-TCDF as carcinogenic to humans (class 1). However, the assessments are based on animal experiments and high accidental or occupational exposures.[174] IARC only assesses the certainty of evidence regardless of the dose, and it remains unclear what is the risk for the general population. The high-exposure populations[175] were exposed to 100–1000 or more times higher levels than the general population. The assessment has been challenged in several papers on various grounds.[158][159][160][155]

It may be concluded that dioxins are carcinogenic in animals and probably carcinogenic at high dose levels in humans. However, there is no good evidence that there would be any significant increase in cancer risk at the present levels detected in the general population. The WHO consultation group[164] concluded that the potential cancer risk is taken care of, if TDI is determined on the basis of developmental effects.

A population risk in humans is unlikely on several grounds. Dioxins do not cause carcinogenic mutations of DNA.[157] Therefore linear extrapolation is not likely to be valid, and safety margins can be applied as in other forms of toxicity. The important physiological role of the AH receptor means that an appropriate receptor activation is beneficial. Only inappropriate stimulation is harmful, which is the case with other receptors such as steroid and thyroid receptors.[155]

Cancer interpretation based on case-control studies relying on exposure assessment by questionnaires after diagnosing cancer is problematic because of recall bias.[176] Cohort studies give equivocal results.[155] A specific cancer that many studies associate with dioxins is soft tissue sarcoma. In a large case-control study with individual measured concentration data, no positive associations were found between soft-tissue sarcoma and TEQs or individual dioxins

or PCBs.[108] Rather there was a trend of decreasing risk at higher exposure groups suggesting a hormetic effect.[177] Other side of the coin may even be that AH receptor agonists could be used in search for drugs in treating cancer.[70] Recently a few among a large number of POPs analysed were found to correlate with breast cancer metastasis.[178] In addition to chance effects there is a problem of causality: what is primary and what is secondary.[109]

Recently a number of cross-sectional studies have shown associations between type 2 diabetes and several POP compounds including dioxins (reviewed by Magliano et al.).[179] Their significance remains uncertain, however, because ecological observational studies cannot prove causality, and prospective studies have been inconsistent.[179][180] One of the problems is that similar results have been obtained with a large variety of chlorinated pesticides, non-dioxin-like PCBs, dl-PCBs, PCDDs and PCDFs. These compounds have different mechanisms of action, and the only common dominator is long half-life leading to unpredictable toxicokinetics. This suggests that the results may be confounded by diet and obesity which are by far the most important risk factors of type 2 diabetes.[179][109][180] Well-planned controlled studies are clearly needed.[143]

In conclusion the safety margins seem to be lowest for developmental effects. Sex ratio changes were seen at concentrations about 20 times the present levels,[122] and for enamel defects in teeth and the sperm quality the margin may be slightly lower.[167][121][170][172] These are in line with the assessment by the WHO panel.[164]

The WHO panel based their assessment in the exposure of child-bearing women who excrete much of their body burden to the child during pregnancy and lactation. In other population groups the risks are low. The panel concluded that even if the safety margin concerning the child is fairly narrow, the benefits of breast feeding clearly exceed the risks. Similarly, the health benefits of fish consumption clearly exceed the risks of dioxins or other persistent organic compounds.[181] In case of competing risks (e.g. cardiovascular disease) the application of precautionary principle may be dangerous.

Laboratory studies and their relevance in risk assessment

Effects in animals can be broadly divided to clearly toxic effects (such as lethality, wasting syndrome, liver injury, developmental toxicity), and metabolic effects that often can be classified as adaptive responses (such as induction of enzymes metabolizing xenobiotic chemicals). Highly detailed descriptions can be found in several reviews.[1][36][182][183][60][81][51][64] A wasting-syndrome-like poisoning has never been seen in humans even after huge doses (see above).[42][115]

The most conspicuous acute toxic effects in adult animals

Acute toxicity of dioxins differs highly among species (Table 3). Guinea pig is considered to be the most sensitive mammal; the LD50 of TCDD is about 1-2 µg/kg. Hamsters tolerate more than a thousand fold dose. The differences between and within species are sometimes based on different ligand binding affinities (e.g. C57BL/6 mice and ten times more resistant DBA2/2J mice), sometimes to the structure of the transactivation domain of the receptor (such as a thousand fold difference between Long-Evans and Han/Wistar/Kuo rats, and possibly between guinea pig and hamster). These differences clearly complicate risk assessment on the basis of animal studies.

It is typical that even after a high single dose the animals do not die immediately, but following a reduced feed intake and wasting (so called wasting syndrome) in two to three weeks.[36] The syndrome is associated with decreased appetite and food intake, but the exact mechanism is not clear.[51] At very low doses there is a clear aversion response to novel foods which may not be related to the fatal wasting syndrome, but is rather an adaptive safety response preventing consumption of toxic food items.[184][185]

Table 4. Lethal dose in some animal species[36]

Species	LD50 (µg/kg body weight)
Guinea pig	2
Rat	10-60
Rhesus monkey	~70
Rabbit	115
Mouse	100-300
Dog	>300
Bullfrog	>500
Hamster	~3,000
Han/Wistar(Kuopio) rat	>10,000

Some changes in the transactivation domain of AH receptor influence drastically the wasting syndrome and lethality whereas biochemical effects such as CYP1A1 enzyme induction are unaffected as well as AHR binding.[186] Therefore two types of dioxin effects have been proposed. Type I responses include developmental effects, aversion to novel foods, and the typical induction of CYP1A1 and other oxidative enzymes which occur at the same dose levels regardless of the structure of the AHR. Type II responses with great variation between species and strains include several high-dose effects such as wasting syndrome, lethality, and liver toxicity.[187][188] There is some evidence that tumour promotion might belong to type II responses.[189]

Table 5. Examples of adaptive and toxic responses to TCDD in very differently sensitive rat lines, the resistant Han/Wistar Kuopio and the sensitive Long-Evans strains[183] *(novel food aversion, resistant line A and sensitive line C developed from H/W and L-E strains*[185]*).*

Response	H/W or line A	L-E or line C
Adaptive responses and the most sensitive toxic effects (type I)		
Enzyme induction	0.1-1 µg/kg	0.1-1 µg/kg
Aversion to novel foods[184][185]	0.1-0.6 µg/kg	0.2-0.4 µg/kg
Developmental effects (teeth)[91][190]	0.1-1 µg/kg (dam)	0.1-1 µg/kg (dam)
Clearly toxic outcomes (type II)		
Lethality	> 10,000 µg/kg	10 µg/kg
Liver damage	mild	severe
Severe anorexia and wasting syndrome	transient	to lethality
Tumour promotion	>100 µg/kg	>1 µg/kg
Other		
AH receptor binding	23 fmol/mg	20 fmol/mg

Thus type I effects are relatively similar among species or strains, but type II effects cannot be reliably predicted over species. It is of interest that many of the type I responses can be interpreted as defence mechanisms toward noxious chemicals via the AH receptor (induction of metabolism, aversion of toxic foods) and can therefore be considered adaptive and protective.

Dioxins cause various pleiotropic effects. There may be both proliferative responses and atrophic responses. Thymic atrophy and some immunological effects are consistent findings in multiple laboratory species. Liver toxicity is variable, it is typical in rabbits, but some effects are seen in other species, e.g. disturbances of porphyrin metabolism,

oxidative damage, and fatty infiltration. There are also multiple high-dose effects on the nervous system, such as tryptophan metabolism or neuropathies.[191] Generally speaking, adverse effects at low doses in adult animals are few.[1][36]

Developmental effects

Developmental effects have been found to be the most sensitive adverse effects of TCDD in several animal species. Transfer of dioxins through placenta varies by compound and animal species,[192] and the amount transferred by lactation in rodents seems to be more than placental transfer.[193][192] Comparison of single-dose studies to continuous daily intake studies resulting in a similar body burden is problematic, because distribution of dioxins during the peak concentration in the dam is different from long-term distribution.[194]

Some of the effects are observed at exposure levels indicating relatively small safety margins to the human background exposure.[182][57] The sensitive targets include developing male and female reproductive system, immune system, nervous system, and teeth and bone. Clear teratogenic effects such as cleft palate and hydronephrosis were detected only after relatively high doses in mice.[195][196] Some developmental effects may be caused by indirect mechanisms, e.g. enzyme induction may lead to accelerated metabolism of thyroid hormones resulting in decreased hormone levels. Thyroid hormones are essential for normal development, notably the development of the nervous system. In many other cases the mechanisms seem to involve local growth factors, and the phenomenon cannot be described as endocrine disruption in strict sense.

Development of teeth and the skeleton are highly sensitive targets of dioxin toxicity in several vertebrate species.[197] Teeth are useful indicators of developmental toxicity, because they do not undergo continuous remodelling after mineralization like bone, where remodelling may repair mineralization defects. Developmental defects of teeth can therefore be detected later in life, as in the case of the Seveso accident, when dental defects were observed 25 years after the accident.[121]

In utero and lactational exposure to TCDD was shown to result in wide range of alterations in rats and mice at doses below 1 μg/kg to the dam. They included smaller molar size, delayed eruption, increased susceptibility to caries, altered mineral composition of enamel, increased fluctuating asymmetry of molars and complete arrest of development of the third molars.[91][198][190][199][200] Sensitivity of tooth development to TCDD was also shown in rhesus monkeys, minks, rainbow trout and zebrafish.[201][202][203][204] In tooth development (as well as in the development of several other organs), the target of toxicity seems to be the developing epithelium. Developmental defects are the consequence of impaired epithelial-mesenchymal signalling, and AHR, epidermal growth factor (EGF), transforming growth factor α (TGFα) and perhaps Jun kinases are involved in mediating the effects.[205][206][207][197][208]

Cleft palate is the best-known skeletal effect of dioxins at relatively high maternal doses.[195][196] In utero and lactational exposure to lower doses of TCDD was shown to affect long bones of rats, mice and rhesus monkeys by inducing altered bone geometry, decreased bone mineral density and biomechanical strength and retardation of bone matrix maturation.[209][210][211][212] Further studies indicated that differentiation of bone marrow stem cells to bone forming osteoblasts and bone resorbing osteoclasts is disrupted by TCDD in AHR-dependent manner.[213]

Several studies from different laboratories have indicated a variety of adverse effects on the male reproductive system after in utero or lactational exposure of rats to low doses of TCDD. These include reduction of cauda epididymal sperm counts, daily sperm production, weight of accessory sex organs as well as increased proportion of abnormal sperm and delayed puberty (reviewed by Bell *et al.*).[194] There is remarkable variability among different studies, but the delay in developmental milestones for male reproductive endpoints seems to be the most consistent and sensitive finding. Also decreased male/female sex ratios were reported in the offspring of male mice exposed to TCDD for 12 weeks prior to mating.[214] However, maternal exposure did not affect the sex ratio of rat offspring.[215] The mechanism has been suggested to be reduced fertility of Y-bearing sperm.[57]

Multigenerational and transgenerational effects

Understanding possible effects on next generations is essential for risk assessment, because dioxin concentrations in the environment and human intake have decreased, but effects initiated several decades ago might still linger with us. This was illustrated by the Seveso studies (see above).[122][124] Epigenetically mediated multigenerational or transgenerational effects of TCDD have been found in rats and mice (reviewed by Viluksela and Pohjanvirta).[57] Some of them were paternally mediated or resulted in adult onset disease states. Toxic effects are considered transgenerational if neither the parent nor the offspring is directly exposed (i.e. F3 generation is the first generation without direct exposure).

TCDD has been shown to cause typical epigenetic modifications (e.g. methylation, histone acetylation) in a number of studies.[57] When these occur in gametes they may affect the future generations.

When pregnant rats were exposed to low doses of TCDD several endpoints of toxicity were found in F1-F3 (or F4) generations: primordial follicle loss, polycystic ovaries and early onset of puberty were observed in female F1 and F3 offspring, and histopathological alterations of testis and kidney abnormalities in male F1 and F3 offspring.[216] These changes were associated with differentially methylated DNA regions in F3 generation sperm epigenome.

Relatively high doses of TCDD (10 μg/kg) in female mice indicated robust transgenerational changes in pregnancy outcomes and progesterone receptor density. In the offspring of exposed mice reduced fertility, increased incidence of premature birth and increased uterine sensitivity to inflammation were found in F1-F4 generations.[217][218] Interestingly, infertility and increased incidence of premature birth was also found in unexposed female mice mated with males exposed to TCDD in utero.[219] Premature birth was associated with reduced progesterone receptor expression and inflammation of placenta.

In male mice infertility and increased premature births in unexposed mating partners that persisted to F2 and F3 generations were associated with testicular inflammation and apoptosis of developing spermatocytes.[220] The role of paternal exposure was also studied in male rat offspring (F1) exposed in utero and lactationally to low doses of TCDD and mated with unexposed females to obtain the F2 generation and further the F3 generation.[221] The proportion of implantations per corpus luteum was significantly decreased in all three generations. Thus both maternal and paternal changes can lead to effects in offspring.

Small zebra fish have been extensively used to study the mechanisms of toxicity in fish in the laboratory, especially cardiovascular toxicity, craniofacial malformations, and reproductive toxicity (reviewed by King-Heiden *et al.*).[83] Apart from rats and mice, transgenerationally inherited dioxin-induced effects have also been studied in the zebrafish model.[222][223][224] In zebrafish, TCDD-induced transgenerational and partly paternally-mediated effects include reproductive dysfunction, reduced fertility, skeletal malformations and lowered male/female sex ratio. These effects seem to be phenotypically very similar across these vertebrate classes.

Cancer in laboratory animals

Dioxins are clear multisite carcinogens in animal studies, but are not genotoxic as indicated both by mutagenicity assays and tumour promotion studies. Also the ability of TCDD to inhibit apoptosis and enhance proliferation supports an indirect mechanism of carcinogenicity.

Much of the cancer risk assessment has been based on an early rat study,[225] demonstrating liver tumours in female rats at low doses (10 ng/kg/day TCDD for 2 years). Other studies have confirmed multisite carcinogenicity in several species, but the doses have usually been higher. Toxic hepatitis has also been found in animals with tumours.

Nongenotoxic or promoting mechanisms are favoured, especially inhibition of apoptosis of cancer precursor cells.[226][174] When differently sensitive Long-Evans (Turku/AB) (L-E) and H/W (Kuopio) rat substrains were compared in a 3-month tumour promotion study, there was a difference in effective dose of almost two orders of

magnitude, and in both strains tumour promotion was associated with signs of liver toxicity.[189] Such findings suggest that carcinogenicity may be secondary to organ toxicity.

It has been speculated that induction of oxidative enzymes such as CYP1A1 would produce excessive reactive carcinogenic intermediates and dioxins would thus indirectly increase cancer risk. Oxidation combined with subsequent conjugating reactions is, however, essentially a protective mechanism, and conjugation enzymes are induced simultaneously. Thus, while plausible, this mechanism would require disproportionate induction of oxidation and be likely only at relatively high doses. In tumour promotion studies with two rat strains enzyme induction did not correlate with tumour promoting activity.[189]

Interactions of dioxins with microbes and immune systems

Microbiomes related to the gut, skin and respiratory tract are in frontline of encountering xenobiotics. The microbiome of our intestinal system metabolizes many chemicals in our food, and on the other hand the chemicals may influence the microbes. There are complex interrelationships between chemicals, microbes and our immune systems. The host and microbiome together can even be seen as a "superorganism".[227] AH receptors and therefore dioxins are deeply involved in these interactions. Active research has started to meet the challenge of understanding these phenomena during the last few years, but obviously only the tip of the iceberg has been revealed as yet, and there is limited information about specific microorganisms, enzymes and genes involved.[33]

The simplest part of this issue is the effects of the microbiome on chemicals. Intestinal microbes can metabolize xenobiotics before they are absorbed into the body. This may increase or decrease physicochemical properties and toxicity. As to dioxins, not much is known; dehalogenation is possible,[33] but obviously not very effective. On the other hand, several bacteria are able to metabolize polycyclic aromatic hydrocarbons such as benzo*(a)*pyrene to carcinogenic metabolites prior to absorption.[228]

As to the effect of dioxins on microbes, relatively high doses have been shown to cause remarkable changes in the overall population, and e.g. somewhat ambiguous changes in the *Firmicutes* vs. *Bacteroides* ratio in mice and increases in *Lactobacillaceae* and *Desulfovibrionaceae* have been noticed.[229][230] These changes might be in part responsible for the toxic effects, e.g. liver toxicity. AH receptors seem to sense microbial toxins and stimulate their neutralization by enzyme induction as well as regulating cytokine and chemokine production and leukocyte activation.[71]

An interesting field in these interactions is the highly complex influence of chemicals via the AH receptors on the immune systems.[231][72][5] This is mostly outside the scope of this review, and interested readers are encouraged to read the thorough recent review of Rothhammer and Quintana.[5]

AHR activation seems to be crucial in maintaining intraepithelial lymphocytes in the intestines and skin as a first line of defence against microorganisms.[232] By using several genetically modified mouse models it was shown that high constitutive activity of CYP1A1 depletes natural AHR ligands in the gut and this leads to similar deficiencies in immune defence mechanisms and increased susceptibility to infections as seen in AHR knockout animals. Interestingly this deficiency can be counteracted by increased supply of natural AHR ligands such as 6-formylindolo[3,2-b]carbazole (FICZ) many of which are present e.g. in vegetables.[73] This implies that CYP enzymes act as feedback controls metabolizing more or less of the AHR ligand supply to keep the receptor activity at an optimal level. In fact AHR activity in intestinal epithelial cells, intraepithelial lymphocytes and innate lymphoid cells seems important for tissue homeostasis at the structural and functional level.[5]

Respiratory system is the other important pathway for environmental noxious agents to the body, especially viral infections, and the AHR seems to be intrinsically involved in defence mechanisms.[72][233] An interesting indole derivative is malassezin produced by pathogenic skin yeast *Malassezia furfur*.[234] The question has been how AHR

can mediate protective effects in some contexts and toxicity in others. This is partially an open question, but it may simply include the impact of time and dose. FICZ and other similar ligands are metabolized rapidly, and so their concentrations will never increase very high and persistent. Therefore their toxicity is not apparent.

Microglia are specialized macrophages in the central nervous system, and as such important for immune surveillance, debris removal and defence against microorganisms as well as for the development of immune functions and synapse maturation.[5] AHR expression is upregulated in the CNS traumatic or autoimmune injury, and may control the inflammatory activities. Here AHR ligands produced by microbes may be important and deficits of AHR agonists have been reported in multiple conditions.[5] Thus there may be option of therapeutic development of AHR ligands in autoimmune, neoplastic and degenerative diseases. Although the AHR signalling may be fundamental in neuronal development, overactivation seems harmful.[235][236] Thus the current understanding is limited and active research is needed.

Conclusions

Dioxins are a group of related persistent, bioaccumulating environmental poisons that act via the AHR, an intracellular receptor which also serves to regulate multiple physiological functions. Hence a certain level of activity is important in normal biology, but inappropriate activation leads to a number of deleterious effects. It is essential to understand dioxins as one risk factor among others rather than as a sole causative agent. This means that dose-responses should be appreciated in regulations as with any other chemical, and risk-benefit aspects should be carefully taken into account. Otherwise unwise remedy may turn out to be worse than the disease.

The most sensitive adverse effects of dioxins are developmental consequences in different structures, from teeth and bones to sexual organs. This concerns specifically women in child-bearing age. The safety margins between current environmental exposure levels and the levels required for sensitive adverse effects are presently about an order of magnitude, but the safe level was probably exceeded in the 1970s and 1980s. Transgenerational effects of these historical high exposures are of concern, but are so far poorly known. It is then risk management and political issue to decide how large safety margins are necessary.

Carcinogenicity has caused confusion, because it probably occurs at high industrial or accidental exposure levels, but dioxins are not genotoxic, and there is neither good evidence nor logical reason to assume that dioxins would cause cancer at levels below those causing developmental effects.

In conclusion, strict environmental controls of dioxin emissions are still important and they should be the first priority, rather than limitations of important food items. It is important to avoid measures that would increase competing risks. This danger is obvious when overregulating the levels in food. The benefits of e.g. breast feeding are estimated clearly greater than possible risks of contaminants, and the nutritional benefits of fish consumption also outweigh toxic effects, if any.

Additional information

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Competing interests

It is acknowledged that after writing a textbook chapter on the same topic, it was not possible to avoid some repetition of both style and details (Tuomisto and Viluksela).[237] Otherwise there are no conflicts of interests. There was no funding for writing this article.

Notes

1. I-TEQ (international TEQ for PCDD/Fs) was used before present TEQs were agreed under the auspices of the World Health Organization. The differences are minor. The TEQs used in this text are sometimes called WHO-TEQs.

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