Review

DIOXINS AND HUMAN TOXICITY

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The term dioxins usually refers to polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs). As 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) has the highest toxic potential, the toxic potentials of other PCDDs and PCDFs are defined in comparison with it. Human exposure to dioxins can be environmental (background), occupational, or accidental pollution. In the human body, dioxins are in part metabolised and eliminated, and the rest is stored in body fat. People vary in their capacity to eliminate TCDD, but it is also dose-dependent; the elimination rate is much faster at higher than lower levels. The liver microsomal P4501A1 enzyme oxygenates lipophilic chemicals such as dioxins. It is encoded by the CYP1A1 gene. Cytosolic aryl hydrocarbon receptor (AhR) mediates their carcinogenic action. It binds to dioxin, translocates to nucleus and together with hydrocarbon nuclear translocator (ARNT) and xenobiotic responsive element (XRE) increases the expression of CYP1A1.
Dioxins are classified as known human carcinogens, but they also cause noncancerous effects like atherosclerosis, hypertension, and diabetes. Long-term exposures to dioxins cause disruption of the nervous, immune, reproductive, and endocrine system. Short-term exposure to high levels impairs the liver function and causes chloracne. The most sensitive population to dioxin exposure are the foetuses and infants.
A large number of health effects have been documented in the scientific literature, and they all place dioxins among the most toxic chemicals known to man.

KEY WORDS: *aryl hydrocarbon receptor, CYP1A1, health effects, hydrocarbon nuclear translocator, liver, P4501A1*, PCDDs, PCDFs *TCDD*

Dioxins are a group of chlorinated organic chemicals, and the term usually includes polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs). Some of them have harmful characteristics depending on the number and structural position of chlorine atoms.

PCDDs and PCDFs are formed of two benzene rings bonded via oxygen atoms. In PCDDs, two rings are joined by two oxygen bridges and in PCDFs by a carbon bond and one oxygen bridge. Chlorine atoms can be attached to eight different places on the molecule, numbered from 1 to 8 (Figure 1). Of 210 dioxin and dibenzofuran congeners, only 17 are toxic. 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD,

TCDD), a molecule with four chlorine atoms, is the best known and the most toxic dioxin (Figure 2) (1). It has the highest toxic potential (toxic equivalent factor), the toxic potentials of other 16 PCDDs and PCDFs are defined in comparison to it (2). Only 7 of 75 PCDDs and 10 out 135 PCDFs are determined in laboratories (3, 4).

Dioxins have no use. The only natural sources of dioxins are forest fires and volcano activities. Most are formed and released as by-products of human activities, especially of industrial processes and incomplete combustion processes like waste incineration. Other sources of dioxins in air include emissions from oil- or coal-fired power plants, and burning of chlorinated
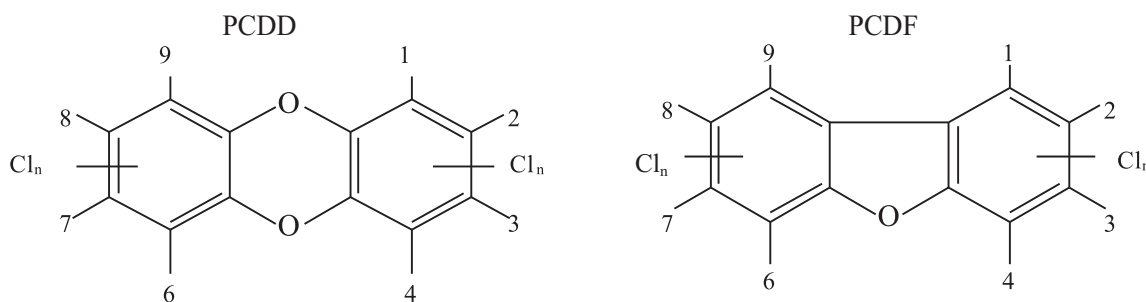
PCDD

PCDF

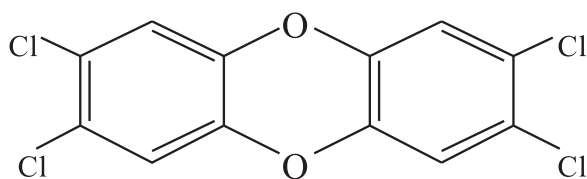**Figure 1** *Chemical structure of PCDD and PCDF*

Figure 2 *Chemical structure of 2,3,7,8-TCDD*

compounds such as polychlorinated biphenyls (PCBs). They contaminate various chlorinated pesticides and herbicides. Dioxins are released in waste waters from pulp and paper mills which use chlorine or chlorine-containing chemicals in the bleaching process (5). However, the main industrial emission sources of dioxins which contribute 45 % of total emissions are waste incinerators, ferrous, and non-ferrous metal production and power generation, and heating while about 40 % of the total emission is released by uncontrolled combustion processes (6).

In pure form, dioxins are colourless solids or crystals, but they enter the environment as mixtures containing a variety of individual components and impurities. Dioxins formed by combustion are bound to particles such as ash. Small particles can be transported to much longer distances from the emission source. Dioxins are hydrophobic and strongly lipophilic, and their solubility in organic solvents increases with chlorine content. As they are not soluble in water, in aquatic environment most of them attach strongly to any material with high organic content, especially to microscopic plants and animals (plankton) which are eaten by larger animals. This is how they circulate and accumulate at each step of the food chain. This process is called biomagnification.

Considering that dioxins are found in mixtures with other dioxins and structurally related compounds (PCBs), it is very difficult to calculate their toxicity. Toxic Equivalency Factor (TEF) of 2,3,7,8-TCDD is 1. All other TEFs are expressed

in relation to this reference, and show the relative toxicity of other dioxins. The toxic potency of a mixture is a sum of each compound's TEF, multiplied with its concentration. This value is known as Toxic Equivalent (TEQ) (5, 7).

Dioxins have raised a number of issues in relation to municipal solid waste, medical waste, and industrial incinerators. While incineration minimizes the quantity of waste and destroys some hazardous components within the waste, it also produces other harmful substances, including dioxins. The amount of dioxins produced during incineration depends on chamber temperature, O_2 and CO_2 concentrations, and especially on the chlorine content of waste. Temperatures from 200 °C to 400 °C favour PCDD formation, while temperatures over 800 °C destroy PCDDs (2). Pyrolysis, a process occurring in the absence of oxygen, at temperatures higher than 700 °C causes 99 % destruction of all PCBs and dioxins. However, this is an expensive technology and is rarely used. Shibamoto et al. (8) showed that the same samples of waste incinerated at different temperatures yielded different TEQ values; low temperatures yielded higher TEQs than higher temperatures. However, recent technological advances and the use of filters have reduced the dioxin emissions (9, 10). Nevertheless, Zhu et al. (11) have estimated that dioxin emission is actually increasing because the sources of dioxin emission are also increasing without significant improvement in reduction technologies.

Data about dioxin emission at country levels or industry monitoring data in different countries are scarce. A study which included 51 countries and their national dioxin emission inventories showed that the TEQ of dioxins released into the environment from 2000 to 2007 was about 36 kg per year (6). In addition, it identified ferrous and non-ferrous metal production, power generation and heating and waste incineration as the main emission sources of dioxins, which contribute to 45 % of total emissions, while about 40 % is released by uncontrolled combustion.

HISTORY

The 20th century has seen a number of dioxin-related accidents. One of the most notorious is the US Monsanto chemical company accident (12). The company manufactured industrial chemicals, PCBs, pesticides, herbicides, and other chemicals which contained high levels of dioxins and dioxin-like substances. In the 1930s, it was already evident that these substances posed serious health hazard to chemical workers, who developed skin rashes, chloracne (a long-lasting skin disease causing skin lesions), and a wide range of other symptoms (12, 13). Many products manufactured by Monsanto were contaminated with dioxins, including the widely used household disinfectant Lysol, and the known defoliant Agent Orange, used in the Vietnam War. Although Agent Orange was not produced exclusively by Monsanto Company, its products contained the highest levels of dioxins. Agent Orange was a herbicide and a defoliant used by the US army in the Vietnam War from 1961 to 1971 to destroy forest cover for the enemy and their food supplies. It was the most used herbicide within the US army programme. Estimations go as high as 72 million litres of herbicide sprayed over Vietnam, Cambodia, Thailand, and Laos. Severe consequences were seen in Vietnam veterans as a result of exposure to high levels of Agent Orange (14). There were numerous lawsuits in the US courts, which US veterans filed against companies which produced Agent Orange. The aggregate claim amount reached a total of 180 million $, and many cases are still in courts.

Another accident occurred in the 1970s at Times Beach, Missouri, USA. Oil used for spraying streets for dust control had been highly contaminated with dioxins. When the contamination was discovered by the Environmental Protection Agency (EPA), the US government ordered the town to be evacuated and the area cleaned. During the process, more than 265,000 t of dioxin-contaminated soil was incinerated and the waste ash buried on site. Today, that place is a state park commemorating the famous road Route 66 (15, 16).

In 1976, an explosion occurred in a 2,4,5-trichlorophenol reactor of the ICMESA chemical plant in Seveso (25 km north from Milan), Italy. Several thousands of people were exposed to substantial quantities of 2,3,7,8-TCDD (17).

In 1999, a severe crisis emerged in Belgium when 500 t of fodder was contaminated with 50 kg of PCBs and 1 g of dioxins, which were distributed to animal farms mostly in Belgium, but also in the Netherlands, France, and Germany. After a few months, the first signs of toxicity started to appear at chicken farms. Health crisis broke out in Belgium following toxicological analysis. Instantly, all poultry and derived products were removed from the market and most of them were destroyed (18). Health studies showed that the body burden was tripled in people exposed to contaminated food. However, no signs of acute health effects were reported (18).

The best known case was dioxin poisoning of the Ukrainian president Viktor Yushchenko in 2004 (19, 20). His blood serum level was 108,000 pg g^{-1} lipid weight, which is 50,000 times the level in general population. Viktor Yuschenko's TCDD levels were monitored using high-resolution mass spectrometry and gas chromatography at the Geneva University Hospital, Switzerland (21). Mr Yuschenko suffered severe health consequences and disfiguration of the face typical for the chloracne (19-21).

EXPOSURE PATHWAYS

Human exposure to dioxins can be environmental, occupational, or accidental pollution (as described above). General population is mostly exposed to background environmental levels. Most exposures involve secondary pathways such as food of animal origin or other products containing dioxins. According to the World Health Organization (WHO) (22), animal products such as meat, fish, and eggs are the major source of dioxin in humans (22). Exposure can also occur through inhalation, drinking water, soil ingestion, and skin absorption.

Once dioxins enter the human body, a part is metabolised and eliminated and the other part is stored in body fat (bioaccumulation). To be eliminated from the body, dioxins first have to convert to polar derivatives. Biological half-life differs between congeners; 2,3,7,8-TCDD half-life is between five and ten years (23), arguably seven to 11 years (24). Elimination depends on dose, age, and quantity of body fat. Aylward et al. (25) have shown a certain variability in individual capacity to eliminate TCDD; elimination was quicker in men and younger people than in women and older people. In addition, recent studies have shown dose-dependent elimination of TCDD; elimination rate was much greater with higher than with lower levels (25, 26).

WHO has set standards for the tolerable daily intake (TDI) of dioxins at TEQ=(1 to 4) pg kg^{-1} body

weight per day. At those exposures no toxic effects have been noticed (27). As dioxins accumulate in body fat, the total amount of dioxin uptake equals its body burden (average dioxin human tissue level at a given point in time) and TEQ can be expressed in pg kg^{-1} of body weight or in pg g^{-1} of serum lipid. The WHO reported that the standard TDI of TEQ=(1 to 4) pg kg^{-1} body weight results in body burden of TEQ=(2 to 6) ng kg^{-1} body weight or (10 to 30) pg g^{-1} serum lipid. Table 1 compares body burdens of different exposures to dioxins (of people exposed to different amounts of dioxins) (1, 27).

MOLECULAR MECHANISM OF DIOXIN ACTION

Dioxins accumulated in the adipose tissue are expressed as body burden. They can be metabolised and eliminated by biochemical mechanisms such as enzyme complex of cytochrome P450. The cytochrome P450 superfamily plays a critical role in the oxygenation of xenobiotics (including drugs and environmental and occupational pollutants such as dioxins) (28, 29). Oxygenation is the first step in their conversion to polar substrates, which can be excreted from the body. The liver microsomal P450 enzymes involved in xenobiotic biotransformation belong to three main P450 gene families: CYP1, CYP2, and CYP3. P4501A1 (encoded by CYP1A1 gene) oxygenates lipophilic chemicals such as dioxins. Induction of P4501A1 is a result of increased transcription of the CYP1A1 gene (29). The most potent inducers of the CYP1A1 expression are indolo(2,3-b)carbazole (polycyclic aromatic hydrocarbon, PAH), and 2,3,7,8-TCDD (29, 30). It is known that CYP1A1 detoxifies carcinogens like

PAHs and related compounds, but can also bioactivate them into reactive toxic metabolites (31). However, Hu and Bunce (32) have shown that the metabolism of PCDDs, PCDFs, and PCBs represents detoxification prior to bioactivation.

Over the years, many studies have given an insight into the molecular mechanisms of CYP1A1 induction, especially into the transcription through aryl hydrocarbon receptor (AhR) action (31, 33, 34).

AhR is a cytosolic receptor that binds to different environmental pollutants, including dioxins, and mediates their carcinogenic action (31, 33, 34). It is a ligand-activated nuclear transcription factor which mediates cellular response in terms of expression regulation of a large number of genes. AhR upregulates a number of xenobiotic metabolising enzymes such as cytochrome P4501A1 (CYP1A1), P4501A2 (CYP1A2), and P4501B1 (CYP1B1) as well as the phase II enzymes, glutathione S-transferase A1 (GST-A1) and UDP-glucuronosyltransferases (UGT1-06) (35, 36). However, CYP1A1 is the most potently induced gene following AhR activation (31).

After TCDD exposure, AhR binds to a ligand, then translocates into the nucleus, where it forms an active heterodimer with aromatic hydrocarbon nuclear translocator (ARNT). This AhR/Arnt heterodimer binds to a specific xenobiotic responsive element (XRE) located upstream in the promoter region of the target gene, resulting in increased expression of the gene (37-39). A study which investigated the effects of PAHs and dioxins on 1152 genes in waste incineration workers occupationally exposed to dioxin reported upregulation of five genes involved in oxidative stress, including GSTA1 (40).

Activated AhR also interacts with other signalling proteins involved in the regulation of the cell cycle and apoptosis. It can alter cell function such as growth and differentiation. In addition, dioxins can induce

Table 1 *Body burden at different dioxin exposures (1, 27)*

		Body burden (average human tissue levels of dioxins) I-TEQ / pg kg^{-1} b.w.
TDI		2,000 to 6,000
Industrialized countries (background exposure)		2,000 to 6,000
Cases of acute dioxin poisoning	Seveso chemical factory workers	20,000 to 100,000
	US Vietnam veterans	10,000

TDI = tolerable daily intake [TEQ=(1 to 4) pg kg^{-1} b.w.]
I-TEQ = international toxic equivalent

responses caused by other signalling pathways (41). Although AhR signalling is the first step of dioxin toxicity, there can be a variety of biochemical and toxicological responses to dioxin exposure. However, Poellinger (42) has allowed that there may also be an AhR-independent pathway of dioxin-induced toxicity.

HEALTH EFFECTS

Humans are not equally exposed to dioxins or equally sensitive to dioxin exposure. Developing foetuses and newborn babies are the most sensitive group, especially those exposed to high levels of dioxins through mothers' milk. Some people are exposed to higher amounts of dioxins than the TDI because of their specific dietary habits (large seafood consumers like the Inuit) or occupation (workers in pesticide industry or incinerators of hazardous waste).

Short-term exposure to high levels of dioxins is known to damage liver function and cause chloracne, a chronic inflammatory skin condition characterised by keratinous plugs with cysts and dark acnes. They mostly appear on the face, but in case of severe poisoning also on shoulders, back, chest, and the abdomen (21).

Long-term exposure is associated with disturbances in the nervous, immune, reproductive, and endocrine system. TCDD's persistence in the body can cause atherosclerosis, hypertension, diabetes, and nervous system damage (43). The International Agency for Research on Cancer (IARC) and the WHO classified TCDD as a "known human carcinogen", based on many human and animal epidemiology data (44).

After the Seveso incident, many scientific activities and investigations were performed, especially those concerning the health effects of acute exposure to dioxins. Bertazzi et al. (45) reported that Seveso population had increased incidence of the gastrointestinal, lymphatic, and hematopoietic cancer and of the soft-tissue sarcoma. A number of studies were conducted 10 to 20 years after the accident (45-47). Their aim was to biomonitor the affected population and track their cancer and non-cancer mortality. They all found increased death rate from all cancer types, especially in the male population. Moreover, a significant increase in lymphohaemopoietic neoplasms was found in both sexes, as well as in non-Hodgkin's lymphoma (NHL)

and myeloid leukaemia. Mortality due to diabetes mellitus was substantial in women, while chronic circulatory and respiratory diseases were slightly higher than in general population (46, 47).

Over the last few decades waste incinerators have been the subject of great controversies. Many studies have evaluated there effects on populations living in their vicinity (48-53). Most studies assess the health impact of dioxins. Zambon et al. (48) found a significant association between the sarcoma risk in general population and dioxin emissions from incinerators and industrial plants. A Portuguese study (49) showed statistically significant differences in PCDD and PCDF blood levels between exposed and non-exposed individuals. A French study (50) of non-Hodgin's lymphoma (NHL) patients in the 1990s showed a statistical association between living in the vicinity of incinerators and increased risk of NHL. Nadal et al. (51) compared their 2007 with 1998 and 2002 results of PCDDs and PCDFs levels in adipose tissue in people living near a hazardous waste incinerator in Catalonia, Spain. They found a 64 % drop from 1998 to 2007, but also a 47 % increase between 2002 and 2007, which was not directly connected to emissions from the incineration facility. These findings were supported by two studies of dioxin exposure with human milk and plasma as bioindicators (52, 53). The results also show that plasma and milk levels of dioxins are much better indicators of current exposure. Through the years, dioxins tend to accumulate in the adipose tissue and can not reliably show the extent of current exposure, especially in older people, because the body burden increases with age.

Direct inhalation seems to be a minor contributor of dioxin exposure in comparison with other sources, especially with food (54-56). This may also be related to significant technological advancement of incineration facilities in emission treatment systems and maintenance (57).

There is a number of studies of health effects in populations occupationally exposed to much higher levels of dioxins than typical for background exposure of the general population (58-60). A German retrospective cohort study included 1189 male workers in an herbicide plant in Hamburg occupationally exposed to TCDD, PCDDs, and PCDFs (58). It established that cancer and ischemic heart disease mortality were in a dose-dependent relationship with TCDD, PCDD, and PCDF levels; workers exposed to the highest levels of PCDDs and PCDFs ran the

highest risk of cancer development and ischemic heart disease. Ott and Zober (59) evaluated long-term effects in workers accidentally exposed to high levels of dioxins. They found a dose-dependent relationship between TCDD and gastrointestinal carcinoma, as well as increase in total cancer mortality. An international cohort study of workers exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries reported a small increase in overall cancer and in the risk for specific cancers (soft-tissue sarcoma, malignant neoplasms, non-Hodgkin's lymphoma, and lung cancer) (60).

Some epidemiological studies investigated the relationship between dioxin exposure and breast cancer risk (61-63). A study which included women from Seveso found a significantly increased risk of breast cancer associated with increased TCDD in serum (61). A study from Russia reported higher risk of breast cancer among women living in the area of a chemical plant which contaminated the surrounding environment with dioxins (62). However, Viel et al. (63) did not find an association between breast cancer risk in younger women and exposure to dioxins emitted from a local incinerator. Moreover, the study showed a decreased risk in older women who lived in the area, which was highly polluted with dioxins.

Not only is TCDD carcinogenic, but it is also toxic for the development, endocrinological, immunological, and reproductive system in experimental animals (64-66). Gestational exposure to TCDD produces foetotoxic responses in most laboratory mammals such as decreased foetal growth, prenatal mortality, nervous system changes (67).

Increased metabolism in pregnant women and mobilisation of accumulated dioxins in fat tissue present a threat to foetuses and infants. Dioxins can pass through the placenta and reach the foetus and exposure continues in infants through breastfeeding. Brouwer et al. (68) suggest that prenatal exposure could be even more relevant than postnatal exposure. The WHO reports that breastfeeding accounts for 10 % to 12 % of lifetime human exposure (69). Kreuzer et al. (70) reported higher levels of TCDD in breastfed compared to non-breastfed infants. However, TCDD body burden decreases a few years after the breastfeeding has stopped and is no different from the levels found in non-breastfed children. For these and many other reasons breast feeding remains recommended by the WHO.

CONCLUSION

Many accidents related to dioxin overexposure occurred in the last century. They have shown us how toxic and dangerous dioxins really are. There is evidence that problems with high emissions of dioxins in incineration processes are being taken care of. Moreover, WHO reports a decrease in environmental concentrations and a decline in general population's exposure to PCDDs and PCDFs (27). However, many countries have not introduced dioxin monitoring into routine practice, mainly because technology is expensive.

Studies assessing the threat to populations exposed to high dioxin levels in their living or working environment were relevant for establishing reference values for dioxins such as TDI. Today, research has focused on toxicogenomics and changes in gene expression, which provides answers about genetic variations and individual differences in susceptibility to dioxin and other toxins.

A large number of health effects have been documented in research literature and even though many are still inconsistent, they all agree that dioxins are among the most toxic chemicals known to man. These studies have certainly helped us to understand the importance of proper hazardous substances management and the need to minimize their release in the environment at all times to protect human health.

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Sažetak

DIOKSINI I NJIHOVA TOKSIČNOST ZA LJUDE

Dioksini su skupina kemijskih spojeva koji obuhvaćaju poliklorirane dibenzo-dioksine (PCDD) i poliklorirane dibenzo-furane (PCDF). Najveći toksični potencijal (faktor ekvivalentne toksičnosti) ima 2,3,7,8-TCDD, dok su toksični potencijali drugih PCDD i PCDF određeni u odnosu na njega. Izloženost dioksinima može biti izravna: izloženost dioksinima emitiranim u okoliš kao posljedica nesreće, profesionalna izloženost te neizravna, tzv. pozadinska. Nakon ulaska u ljudski organizam dioksini se djelomično metaboliziraju i eliminiraju, a ostatak se pohranjuje u adipozno tkivo. Postoji određena varijabilnost između ljudi u kapacitetu eliminacije TCDD. Eliminacija TCDD ovisna je o dozi – kod veće izloženosti (izloženost višim koncentracijama) brzina eliminacije je viša nego kod manje izloženosti (izloženost nižim koncentracijama). Enzim P4501A1 najvažniji je u oksigenaciji lipofilnih supstrata poput dioksina. Kodiran je genom CYP1A1.

AhR je stanični receptor koji djeluje kao transkripcijski faktor koji posreduje u njihovu karcinogenom učinku. AhR veže dioksin te se premješta u jezgru gdje zajedno s ARNT (engl. *aryl hydrocarbon nuclear translocator*) i XRE (engl. *xenobiotic responsive element*), smještenim u promotorskoj regiji gena za CYP1A1, uzrokuje povećani izražaj CYP1A1.

Dioksini su karcinogeni spojevi, ali imaju i nekarcinogene učinke poput ateroskleroze, hipertenzije, dijabetesa, poremećaj živčanog, imunosnog, reproduktivnog i endokrinog sustava, posebice kod kronične izloženosti. Akutna izloženost uzrokuje oštećenja jetre i klorakne. Najosjetljivija skupina izloženosti dioksinu je dojenčad u prenatalnom i postnatalnom razdoblju. U znanstvenoj i stručnoj literaturi dokumentirani su brojni zdravstveni učinci kao posljedice izloženosti dioksinima te ih svi ističu kao jedne od najtoksičnijih kemijskih spojeva.

KLJUČNE RIJEČI: *ARNT, CYP1A1, jetra, P4501A1, PCDD, PCDF, receptor arilnih ugljikovodika, TCDD, zdravstveni učinci*

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