



LEARNING TOXICOLOGY
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POLYCHLORINATED DIBENZO- *p*-DIOXINS AND POLYCHLORINATED DIBENZOFURANS (PCDD/ PCDF)

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INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/PCDF) are a group of dangerous organic compounds, emitted mostly from anthropogenic sources, that have negative effects on human health. PCDD/PCDF(dioxines/furans), are not produced commercially, they are by-products resulting from the production of other chemicals and have no known use. They have never been produced intentionally (except for pure substances used as references in analytical /and toxicological research, and never served any useful purpose. Dioxines/furans are formed as unwanted by-products in many industrial and combustion processes. They also have been naturally formed in the environment, by forest fires/volcanic eruptions, and also by enzymatically catalysed processes. The natural formation is generally of less importance, compared to the anthropogenic formation. Dioxins/furans may be released into the environment through the production of pesticides and other chlorinated organic compounds. Dioxins/furans are related to incineration reactions, and the synthesis and use of a variety of chemical products. Furans are major contaminants of PCBs. Both dioxins/furans have been detected in emissions from the incineration of coal, peat, wood treated with PCP, hospital waste, municipal waste, pesticide wastes, hazardous waste, etc. Cigarette smoke, some home-heating systems and exhaust from vehicles using leaded/unleaded gasolines, as well as diesel fuels, also produce small amounts of dioxins/furans. (EPA, 2013, Dopico et. al., 2015). Primary sources of environmental contamination with dioxines/furans in the past were the production and use of organic chemicals containing chlorine, pesticides, in high-temperature processes as those from metallurgical industry, waste incineration, home heating and other energy production processes. The factors favourable for the formation of dioxines/furans are high temperatures, alkaline media, the presence both of ultraviolet light, and of radicals in the chemical process

(Fiedler, 2007). A major source of dioxins/furans was the production of pentachlorophenol and the bleaching process in pulp and paper industry. Nowadays, changes in industrial processes determined a reduction of dioxines/furans concentration in products. Whereas in the past, the chemical industry and the pulp and paper industry were the main sources of dioxines and furans formation and of many contaminated sites, today's dioxines/furans pollution is correlated with the thermal processes (Booth et. al. 2013). Dioxins/furans are found also in solid residues from any combustion process such as bottom ash, slag and fly ash. With advanced technology and better burnout of the ashes and slag, the concentrations of dioxines/furans in environment have declined. Since dioxins/furans formation depends on anthropogenic sources, the development of chemical industry between 1920-1970 determined the increasing of dioxins/furans emissions and concentration levels in air, soils, and water correlated with the ignorance of the negative effects of these compounds in living organisms (Hites, 2010). The lack of control and emergency procedures in industrial plants of the time were associated with accidents in different parts of the world and catastrophic environmental effects (Seveso, Italy), dioxins/furans also being present in armed conflicts (Agent Orange gas in the Vietnam War). After the 1970, due to a stricter legislation and introduction of more efficient, green industrial technologies, a reduction in emission and contamination levels of dioxines and furans from industrial sources has been registered (Kulkarni et al., 2008). In present, the principal mechanism in the formation of dioxines and furans is considered "*de novo synthesis*", which consists on the oxidative breakdown and transformation of polymers/macromolecular carbon structures to aromatic compounds. The resulted dioxins/furans from de novo synthesis will remain partially in the solid phase and the other part will desorb to the gas phase and will be carried by off-gas flow. Nowadays, the emissions from nonindustrial sources (such as residential heating and residential waste combustion), remained more or less constant, represent the main source of dioxines/furans proliferation (Booth et al., 2013, Dopico et al., 2015). The annual global

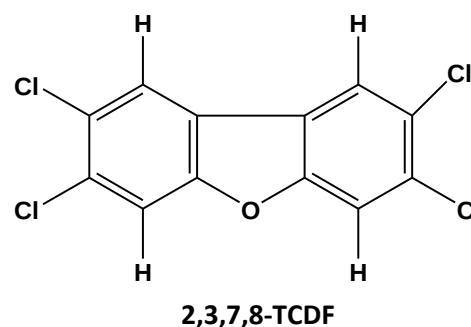
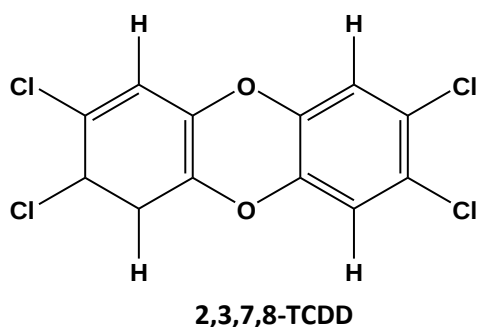
dioxins/furans production is of 17,226 kg. From the total annual emission rate of dioxins into the atmosphere, only 9 kg (3%) remains in the air, the rest, (57%) is deposited to land areas (163 kg) and the remainder (40%), (354 kg/year) is absorbed by ocean waters (Morales et al., 2014). The continent of Europe is one of the main producers of dioxins worldwide. The emissions proceed both from industrial activities and nonindustrial burning processes, and the ambient concentration vary depending on the climate, residential activities, and degree of development and social awareness of the habitants from the respective countries (Dopico et. al., 2015). Dioxins/furans and related compounds are usually released in relatively low concentrations (e.g., parts per trillion or parts per quadrillion), but because they are very persistent, they remain in the environment and can accumulate in the tissues of animals (EPA, 2013).

CHEMICAL STRUCTURE OF DIOXINS AND FURANS

Dioxins/furans are a group of aromatic hydrocarbons, with similar chemical and physical properties, formed by a triple-ring structure of two benzene rings interconnected by a third oxygenated ring. Depending on their structural configuration, especially the positions where chlorine atoms may be attached, different forms and congeners of dioxins/furans can be formed. Theoretically, 75 dioxins and 135 furans congeners are possible, having physical and chemical properties determined by the number of chlorine atoms and their positions on the molecular nucleus. The toxicology of dioxins/furans is controlled by the presence of chlorine atoms in the 2, 3, 7, and 8 positions of the different congeners. There are 7 dioxines and 10 furans with the pattern of the compound 2,3,7,8-tetrachlorodibenzo-p-dioxine (TCDD), the most toxic and important congener of all the dioxin-like class, with a toxic equivalency factor (TEF) of 1.0 (WHO, 2010) classified as a group 1 carcinogen by the IARC (International Agency for Research on Cancer). All the 2,3,7,8-substituted PCDDs (with no chlorine substitution at the *ortho* positions) show the same type of biological and toxic activity. Toxic equivalents (TEQs) are used to describe

the toxicity of 16 other forms relative to 2,3,7,8-TCDD. The differences between the toxic activity of congeners are not higher than 28%. (EPA Dioxine, 2013).

Dioxins and furans formulas



PROPERTIES OF DIOXINS AND FURANS

Dioxines/furans are insoluble in water, lipophilic and very persistent. Because the chemical properties of each of the isomers has not been elucidated, discussion regarding their properties have to take into account the correlation with the number of chlorine atoms present in molecule. In the Table 1. are presented the properties for selected dioxins and furans.

Table 1. Physico-chemical properties for selected dioxins and furans

	TEF	P_L Pa	S mg/m ³ (ng/L)	log K_{ow}	H (Pa m ³ / mol)	log K_{oa}
1-CDD	0	0.075	417	4.75	6.288	7.34
2,3,7,8-TCDD	1	1.18×10^{-4}	0.0193	6.80	3.337	9.67
OCDD	0.001	9.53×10^{-7}	0.000074	8.20	0.684	11.8
2,8-CDF	0	1.46×10^{-2}	14.5	5.44	6.377	8.03
2,3,4,7,8-PCDF	0.5	1.72×10^{-5}	0.236	6.5	0.505	10.2
OCDF	0.001	1.01×10^{-7}	0.00116	8.00	0.191	12.1

Subcooled liquid pressure (p_L), water solubility (S), octanol/water partition coefficient (K_{ow}), Henry-constant (H), Octanol /air partition coefficient (K_{oa} . from Mackay et al. 1991. determined for 25^o C.

Dioxins/furans are characterized by their lipophilicity, semi-volatility and resistance to chemical and biochemical degradation. The photodegradation of particle-bound dioxins/furans in air was found to be negligible and predispose them to long environmental persistence and to long-range transport (LRT). They also are able to bioconcentrate and biomagnify under typical environmental conditions, and potentially achieving toxicologically concentrations (WHO, 2010). The tetra–octa PCDD have lower vapour pressures than PCBs and are therefore not expected to undergo LRT to the same extent, but there is evidence for deposition in Arctic soils and sediments (AMAP, 2014). The toxicity of dioxins/furans can be expressed in different forms (N-TEQ, I-TEQ, and WHO-TEQ) depending on the Toxicity Equivalency Factors (TEF) used for their estimation (EPA, 2013). In order to compare the toxicity of the mixtures of dioxins/furans, the International Toxicity Equivalency Factors (TEFs) have been assigned to individual dioxins/furans, based on a comparison of the toxicity with 2,3,7,8-tetra- chlorodibenzodioxin (2,3,7,8-TCDD), which has been shown to be one-tenth as toxic as 2,3,7,8-TCDD in animal tests, having TEF 0.1. TEFs are regarded as risk management tools and actually they tend to overestimate the toxicity of mixtures. Dioxins/furans are usually released in relatively low concentrations (e.g., parts per trillion or parts per quadrillion), but because they are very persistent, they remain in the environment and can accumulate in the tissues of animals (Dopico et. al. 2015).

PERSISTENCE OF DIOXINS/FURANS IN AIR, WATER, SOIL AND SEDIMENT

Concentrations of dioxins/furans in drinking-water and surface water are very low, because they are poorly soluble in water. The low vapor pressure, low water solubility and strong ability to adhere to particulates, ensure dioxins/furans immobility in soils and sediment and accumulation in fat-containing tissue (EPA, 2013). Dioxins/furans from “*primary sources*” (formed in industrial or combustion processes) are transferred and enter the environment. Dioxins/furans from “*secondary sources*” (*reservoirs in environment*) are already

present in the environment, or as chemical products in landfills, waste dumps, contaminated soils and sediments (Fiedler, 2007, Dopico et. al., 2015) Because of their persistent nature and lipophilicity, once dioxins/furans enter the environment and living organisms, they will remain for a very long time, like many other halogenated aromatic compounds (Booth et al. 2013). The adsorption of dioxins/furans to organic carbon in soils and sediment particles determine their mobilization, by leaching, into deeper layers of soils and groundwater or run-off from topsoil into the environment. During photochemical degradation, the half-life of dioxins/furans in soil are 10-12 years. Highly chlorinated dioxins/furans are more resistant to degradation comparing with those with few chlorine atoms. The air is significant compartment for the environmental distribution of dioxins/furans which can be bound to particles, while the rest will be in the gaseous phase, and can be subject to LRT up to thousands of kilometres. Monitoring concentrations of ambient air represents an important source of information regarding the evolution of pollutants, location, meteorology variables, mechanisms of transportation, deposition, dispersion (EPA, 2013; Gunes, 2014). The concentration of dioxins/furans in ambient air is higher during winter months (AMAP, 2014). In the particulate phase, these processes are of minor importance and the transport range of the particulate phase will primarily depend on the particle size. Dioxins/furans are extremely resistant to chemical oxidation and hydrolysis, and these processes are not significant in the aquatic environment. Photodegradation and microbial transformation are the most important degradation routes in surface water and sediment (Onofrio et al., 2011). For dioxins/furans fraction that is deposited or absorbed in soils and waters, the lowest concentration levels are found in the Antarctic and Oceania, while Europe presents the highest concentrations in soils. On the other hand, the north of the Pacific Ocean and the Mediterranean Sea show the highest levels of dioxins in water (Booth et al., 2013).

BIOACCUMULATION OF DIOXINES AND FURANS

Releases of dioxins/furans to air, from inadequate incineration, and from waste sites, contaminated soil and aquatic sediments, determine their bioaccumulation and bioconcentration through food-chains. The higher chlorinated dioxins/furans and congeners with specific positions of chlorination, persist longer in the environment and show greater bioaccumulation (Booth et al. 2013). Dioxins/furans have low water solubility and high fat solubility, which may lead to higher concentrations in fatty foods, such as dairy products, some fish, meat and shellfish. Most human exposure is through ingestion of contaminated food, and these compounds persist in fatty tissue, with half-lives in humans in excess of 7 years (WHO, 2010; EPA, 2013). The physicochemical properties of dioxins/furans and their metabolites enable these compounds to be absorbed readily by living organisms. The rates of accumulation into living organisms vary with the species, the duration of exposure, the concentration of dioxins/furans and the environmental conditions. The high retention of dioxins/furans and their metabolites, implies that toxic effects can occur in organisms spatially and temporally far distance from the original release (Ding et al., 2013), the half-life in animals are around 1 year in monkeys and 7–10 years in humans. The levels of dioxins in birds eggs, expressed as TEQ, decreased from 3.3 ng/g lipids to around 1 ng/g between 1969 and 1990, the same trend being observed for hering fish.

EXPOSURE AT DIOXINS/FURANS

At present, the major source of dioxins/furans exposure in the general environment, seems to be the redistribution of previously introduced compounds. Dioxins/furans are today found in almost all compartments of the global ecosystem, in at least trace amounts. They are present in soil, sediments and air. Excluding occupational or accidental exposures, most human background exposure to dioxins/furans occur through the diet with food of animal origin being the major source, as they are persistent in the environment

and accumulate in animal fat (Dopico et. al. 2015). The past and present human exposure to dioxins/furans results primarily from their transfer along the pathway: *atmospheric emissions* → *air* → *deposition* → *terrestrial/aquatic food chain* → *human diet*. Data from food surveys in industrialized countries indicate a daily intake of dioxins/furans of 50–200 pg y for a 60-kg adult (WHO, 2010). Recent studies from countries that started to implement measures to reduce dioxins/furans emissions show the decreasing dioxins/ furans levels in food and, consequently, a lower dietary intake of these compounds within the past 10 years. The level dioxins/furans accumulate in human adipose tissue, reflects the history of intake (Srogi, 2006). Breast-milk represents the most useful matrix for evaluating time trends of dioxins/furans and other POPs. Factors affecting the dioxins/furans content of human breast-milk are the mothers age, the duration of breast-feeding and the fat content of the milk. Studies from 21 countries established that the population is mainly exposed to dioxins/furans through fatty food of animal origin, meat, certain fish and diary products and shellfish. In the body, dioxins/ furans accumulate in fatty tissues and are slowly released. Lactation or weight loss increases the release of the substances into the blood. Dioxins/furans can cross the placenta from mother to fetus, and are excreted into the breast-milk, determining concentrations in human milk usually higher than in cow's milk or other infant foods. As a result, breastfed infants undergo higher dietary exposure than those who are not breastfed, particularly for infants of womens whose diet is based on fish from highly contaminated rivers and lakes (such as the Great Lakes and the Baltic Sea). Dioxins/furans concentrations in human milk have decreased significantly in countries that have taken measures against these substances (EPA, 2013, WHO, 2010).

HUMAN HEALTH EFFECTS

The main risk of dioxins/furans for human health is that they can alter the development of many cells and can be the cause of illnesses like cancer,



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disruption of the endocrine system, or reproductive and development problems (Srogi, 2008; Booth et al., 2013).

Short-term exposure to high levels of dioxins/furans in occupational settings or following industrial accidents may cause skin lesions known as chloracne, which is persistent.

Longer-term environmental exposure causes immunotoxicity, developmental and neurodevelopmental effects, and effects on thyroid and steroid hormones and reproductive function. The most sensitive life stage is considered to be the fetus or neonate. Epidemiological studies in animals and occupational settings indicate human carcinogenicity at multiple sites. The International Agency for Research on Cancer (IARC) classified dioxins/furans in Group 1 (*carcinogenic to humans*) and some other dioxins in Group 3 (*not classifiable as to their carcinogenicity to humans*). IARC recently classified 2,3,4,7,8-pentachlorodibenzofuran and 3,3',4,4',5-pentachlorobiphenyl in Group 1. Many countries and intergovernmental organizations have taken measures to prevent the formation and release of dioxins/furans, also have interdicted/restricted the production, use, handling, transport and disposal of dioxins/furans. As result, the release of dioxines/furans into the environment has decreased in many developed countries. However, analysis of food and breast-milk show that they are still present, but in levels lower than those measured in the 1960s and 1970s (EPA, 2013, WHO, 2010).

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