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ENVIROMENTAL CONTAMINANTS-DIOXINS AND THEIR HEALTH EFFECTS

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ABSTRACT
Polychlorinated dibenzo dioxins (PCDDs) are group of chlorinated organic compounds widely known as dioxins and their toxicity is depending on the position and the number of chlorine atoms. 17 out of 210 which are known today, are toxic. 2,3,7,8-TCDD (tetrachlorodibenzo-para-dioxin) is the best known and most toxic dioxin. In daily life, human exposure to toxins can be enviromental, occupational or accidental. Most dioxins are produced and released by human activities such as industrial processes and incomplete combustion. General population is exposed to background or enviromental dioxins through food or other products containing dioxins. 2,3,7,8-TCDD was evaluated as carcinogenic to humans by IARC in 1998. This was based on most recent epidemiologic data on exposed human population (accidental exposure) and there is a strong evidence of increased risk for all cancers combined. Experimental data in laboratory animals show sufficient evidence of carcinogenity of 2,3,7,8-TCDD who was shown to act through mechanism involving aryl hydrocarbon receptor (AhR). This receptor is evolutionary conserved and function in the same way in humans as well as in animals. On the other side, there is inadequate evidence for the carcinogenity of other polychlorinated dibenzo dioxins.
Keywords: dioxins, TCDD, ArH receptor, toxic effects, cancer (10 pt, Bold)

1. INTRODUCTION
Polychlorinated dibenzo dioxins (PCDDs) are group of chlorinated organic compounds widely known as dioxins. Their toxicity is depending on the position and the number of chlorine atoms. 17 out of 210 which are known today, are toxic. It is important to known their physical and chemical properties in order to understand their toxicological behaviour. Toxins are hydrophobic substances with water solubility of 1.93×10^{-5} mg/l at 25°C for the best studied 2,3,7,8-TCDD. Their solubility in organic solvents increases with number of chlorine atoms attached. Pure dioxins are colorless solids or crystals, but they exist in nature as mixtures.
The concept of toxic equivalency factors (TEF) has been developed and is used in the evaluation of the risk of exposure to different dioxins. Since 2,3,7,8-TCDD is the most potent and best studied dioxin, TEF value assigned to it is 1, and TEF values for other dioxins are derived by estimating their potency relative to that of 2,3,7,8-TCDD [1]. World Health Organization has established a tolerable TCDD daily intake of 1–4 pg/kg body weight (ppq). The average lipid-adjusted body burden of TCDD in people living in North America and Europe is 2 ppt [2].
Over the past two centuries, human activity has been primarily responsible for the production of these chemicals and dioxins have been extensively studied due to their toxicological potency and their varied effects on human health.

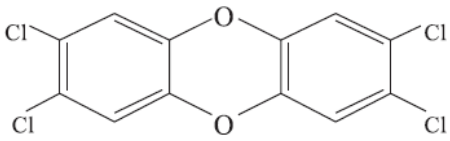

Figure 1. Structure of 2,3,7,8-TCDD

2. DIOXINS AND THEIR OCCURENCE

In daily life, human exposure to toxins can be enviromental, occupational or accidental. Natural sources of dioxins are consider to be forest fires and volcano activities, but most dioxins are produced and released by human activities such as industrial processes and incomplete combustion. Largely general population is exposed to background or enviromental dioxins through food or other products containing dioxins. It is estimated that intake from food consumption accounts for well over 90% of the body-burden of PCDDs and PCDFs (polychlorinated dibenzo furans) in the general human population [3,4].

Meat, milk, fish and eggs are found to be major source of dioxins in humans. On the contrary, PCDD levels in the fruit and vegetables are found to be very small. Apart from food, also drinking water and inhalation are considered to be sources of environmental exposure to dioxins. Data collected during the last 15 years from 10 different countries show increased levels of dioxins in the air. Trace levels of dioxins are detectable in emissions from motor vehicles using leaded gasoline or diesel fuel.

Occupational exposure to dioxins occurs during chemical manufacturing such as production of herbicides and polychlorinated phenols (TCP), but also emission of dioxins in the air from oil- and coal-fired power plants affects workers at these places. About 45% of total emission comes from the waste incinerators and metal production. Workers in paper and pulp mills, steel mills are also exposed to greater amounts of dioxins than others. Vietnam veterans are the group of soldiers which was exposed to large amounts of dioxins from the herbicide Agent Orange, when ca. 72 mill of this herbiced was sprayed in Vietnam, Kambodia, Tailand and Laos.

Accidental exposures mostly due to industrial accidents were quite common during the last century. In 1976 in Seveso, Italy, explosion in the chemical plant happened after which thousands of people were exposed to substantial levels of 2,3,7,8-TCDD [5]. Another accident happened in 1999 in Belgium, when 500 t of fodder was contaminated with dioxins and distributed to animal farms in several European countries [6]. These are only some examples of accidental exposure, but maybe the most notices case of dioxin poisoning was the one in 2004 when the Ukrainian president was poisoned with TCDD[7].

2.1. Aryl hydrocarbon receptor

Aryl hydrocarbon receptor (AhR) is a cytosolic receptor that binds to different enviromental pollutans, such as polycyclic aromatic hydrocarbons (PAHs), including dioxins. It is a ligand-activated basic helix-loop-helix cytosolic transcription factor. In resting state it is bound to co-chaperons which dissociate after ligand binding. After TCDD exposure, TCDD enters the cell via diffusion and binds to an AhR, then translocates into the nucleus, where it forms active heterodimer with aromatic hydrocarbon nuclear translocator (ARNT). The activated AhR/ARNT heterodimer complex is then capable of either directly and indirectly interacting with DNA by binding to recognition sequences located in the 5'- regulatory region of dioxin-responsive genes. The activated receptor exerts two major types of functions: enhance the transcription of target genes and activates tyrosine kinases. Activated AhR also interacts with other signalling proteins involved in the regulation of the cell cycle and apoptosis. It can alter cell functions such as growth and differentiation. This receptor is evolutionary conserved and function in the same way in humans as well as in animals. The fundamental role of the AhR for the toxicity of 2,3,7,8-TCDD was demonstrated by Poland and Glover [8].

2.2. Metabolism of polychlorinated dibenzo-p-dioxins

The cytochrome P450 superfamily (officially abbreviated as CYP) is a large and diverse group of enzymes. CYP enzymes present in most tissues of the body play important roles in hormone synthesis and breakdown, cholesterol synthesis, and vitamin D metabolism, but also function to metabolize potentially toxic compounds.

When in the body, dioxins are either partly metabolized and eliminated from the body, or stored in body fat. In order to be eliminated from the body, dioxins have to be converted to polar substrates. The metabolism contained multiple reactions such as hydroxylation at an unsubstituted position, hydroxylation with migration of a chloride substituent, and hydroxylation with elimination of a chloride substituent. In one study, 12 different forms of human CYP enzymes were examined using recombinant yeast microsomes [9]. According to this study, no major CYPs in human liver showed significant metabolism toward PCDDs. However, CYP1A1 and CYP1A2 showed high catalytic activity toward DD and mono-, di-, and trichloroDDs, while none of the CYPs showed any activity toward 2,3,7,8-TCDD. This strongly suggests that the long half-life (7.1 years) of 2,3,7,8-TCDD in humans was due to an extremely low activity of CYPs toward 2,3,7,8-TCDD in addition to its chemical stability.

3. DIOXINS AND THEIR EFFECTS ON HUMAN HEALTH

For the last 50 years, scientists have been interested in the effects observed in animals following TCDD exposure. This exposure caused wide spectra of effects depending on the dose of TCDD. At low doses reproductive and developmental effects, hepatocarcinogenesis, tumor promotion, and immune suppression are observed, while the high doses caused slow death. Toxicity associated with the TCDD exposure is mediated through activation and binding to AhR. TCDD is different from other ligands of AhR because it doesn't induce its own metabolism. On the contrary, it is resistant to enzymes induced by activation of AhR which contribute to its toxicity through persistent activation of the AhR.

Humans appear to be affected by dioxins in a similar manner to that of laboratory and wildlife animals. The effects of dioxins on humans have been well studied following accidental releases of dioxins into human enviroment and food supplies. Short exposure to high doses of dioxins is known to damage liver function by causing alterations in liver enzyme levels. It also cause chloracne, which are chronic inflammatory skin condition. Health effects of long-term dioxin exposure can be numerous, some of them beeing cardiovascular disease, diabetes, cancer, porphyria, early menopause, reduced testosteron and thyroid hormones, altered immunological response, altered growth factor signaling and altered metabolism [10].

After the Seveso incident, many scientific investigation were performed in order to investigate health effects of accute exposure of dioxins, but also numerous studies were conducted 10,20 or ever 30 years after the accident. One of these studies showed that thyroid-stimulated hormone was elevated in infants born from mothers with presently elevated plasma dioxin levels because prenatal exposure is more relevant than postnatal [11]. Other study showed reduced sperm count and motility at men who were exposed to dioxins prior to puberty, while the opposite was the case for the men who were exposed during adolescence [12].

As for cardiovascular diseases, studies show that the mammalian embryo is less sensitive to cardiovascular defects by dioxin and dioxin-like compounds, but developmental exposure increases the risk of cardiovascular disease later in life. Also recent animal research has confirmed human epidemiology studies that dioxin exposure in adulthood is associated with hypertension and cardiovascular disease [13].

PCDDs cause suppresion of both cellular and humoral immunity. Since TCDD is considered to be one of the most potently immunosuppressive chemicals known it has been extensively studied. Some of the reported effects of TCDD include thymic involution, decreased host resistance to pathogens and tumors, suppressed fetal lymphocyte development and maturation, and suppressed adaptive immune responses, including antibody production, cytotoxic T lymphocyte (CTL) activity, and delayed hypersensitivity responses [14].

In order to draw best conclusion for the carcinogenity of PDCCs, studies were chosen in which the highest exposure to the dioxins have occured. Based on the results of 4 studies of herbicide producers in which exposure to dioxins was highest, there is an evidence for the carcinogenity of TCDD for all

cancers combined rather than for any cancer at specific site [15]. Also, increased risk for lung cancer is detected, but smoking in addition to dioxin exposure could explain a part of this risk. On the other side, there is inadequate evidence for the carcinogenity of other polychlorinated dibenzo dioxins.

4. REFERENCES

[1] Ahborg, V.G., Brouwer, A., Fingerhut, M.A., Jacobson, J.L., Jacobson, S.W., Kennedy, S.W., Kettrp, A.AF., Koeman, J.H., Poiger, H., Rappe, c., Safe, S.H., Seegal, R.F., Tuomisto, 1. & van den Berg, M.:Impact of polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. Europ. J. PharmcoL.-environ. ToxicoL. PharmcoL. Sect., 228: 179-199, 1992

[2] Aylward, L.L. & S.M. Hays.. Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels. J. Expo. Anal. Environ Epidemiol 12: 319–328, 2002

[3] Gilan, A., Newhook, R & Birgham, B. An updated assessment of the exposure of Canadians to dioxins and furans. Chemosphere, 23: 1661-1667, 1991

[4] Travis, C.e. & Hattemer-Frey, H.A. : Human exposure to dioxin. Sei. total Environ., 104: 97-127, 1991

[5] De Marchi B, Funtowicz S, Ravetz J. : Seveso: A paradoxical classic disaster. In: Mitchell JK, editor. The long road to recovery: Community response to industrial disasters. Tokyo: United Nations University Press; 1996.

[6] Larabeke N., Hens L., Schepens P., Covaci A., Baeyens J., Everaert K., Bernheim J., Vlietinck R., Poorters G. : The Belgian PCB and dioxin incident of January-June 1999: exposure data and potential impact on health. Environ Health Perspect;109:265-73, 2001

[7] Sterling B., Hanke W.: Dioxin toxicity and chloracne in the Ukraine. J Drugs Dermatol;4:148-50, 2005

[8] Poland, A. & Glover, E. : 2,3,7,8-Tetrachlorodibenzo-p-dioxin: segregation of toxicity with the Ah locus. MoL. Pharmcol., 17: 86-94, 1979

[9] Kuniyo Inouye, Raku Shinkyo, Teisuke Takita, Miho Ohta, Toshiyuki Sakaki: Metabolism of polychlorinated dibenzo-p-dioxins (PCDDs) by human cytochrome P450-dependent monooxygenase systems. Journal of Agricultural and Food Chemistry ; 50: 5496-5502, 2002

[10] U.S. EPA: Dioxin reassessment: draft exposure and human health reassessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Part II: health assessment of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Washington, DC: U.S. Enviromental Protection Agency, 2003

[11] Baccarelli A., Giacomini S.M., Corbetta C., Landi M.T., Bonzini M., Consonni D., Grillo P., Patterson D.G., Pesatori A.C., Bertazzi P.A.: Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. PLoS Med.;5 (7):e161, 2008

[12] Mocarelli P., Gerthoux P.M., Patterson D.G., Jr, Milani S., Limonta G., Bertona M., Signorini S., Tramacere P., Colombo L., Crespi C., Brambilla P., Sarto C., Carreri V., Sampson E.J., Turner W.E., Needham L.L.: Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect.;116 (1):70–7, 2008

[13] Phillip G. Kopf1 and Mary K. Walker: Overview of Developmental Heart Defects by Dioxins, PCBs, and Pesticides. Journal of Environmental Science and Health Part C, 27:276–285, 2009

[14] Nikki B., Marshall I. and Nancy I. Kerkvliet: Dioxin and immune regulation: Emerging role of aryl hydrocarbon receptor in the generation of regulatory T cells. Ann. N.Y. Acad. Sci. 1183 : 25–37, 2010

[15] McGregor D. B., Pertensky C., Wilbourn J. and Rice J.:. An IARC evaluation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis. Enviromental Health Perspectives:106:755-760, 1998