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REVIEW ARTICLE

Influence of dioxin intoxication on the human system and possibilities of limiting its negative effects on the environment and living organisms

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Abstract

Introduction and objective. Despite the restrictive legal regulations related to the reduction of dioxins emission, their concentration in the environment is still too high. Mainly, this is related to the illegal utilisation of electronic equipment and combustion of wastes, and also to intensified activity and maintenance of ships, especially in developing countries. The most important remaining source in Europe is the metal industry. Studies on the mechanism of impact of dioxins are still being carried out. This review points at new possibilities for limiting the molecular mechanisms of dioxins activity, *inter alia,* through the application of high doses of tocopherol and acetylsalicylic acid while treating dioxins intoxication.

Brief description of the state of knowledge. Apart from the knowledge of dioxins affinity to the aryl hydrocarbon receptor (AhR), the multi-stage radical-form actions and the pro-inflammatory mechanism associated with cyclooxygenase-II enzyme (COX-2) are under intense investigation at the moment. Due to the high affinity of dioxins to animals adipose tissue and their ability to accumulate in it, they can enter the food chain. Furthermore, high dioxin doses can cause poisoning manifested as advanced clinical symptoms, whereas in smaller doses, when cumulated, can cause metabolic changes which are often difficult to associate with their presence. Recently, some serious food contaminations by dioxins have been demonstrated. Sea fish and products from contaminated aqueducts still constitute potential sources of dioxins pollution.

Conclusion. According to recent studies, dioxins are present in different concentrations in the environment and cause specific and long-time effects. These effects could be limited by the use of tocopherol and acetylsalicylic acid.

Key words

aryl hydrocarbon receptor (AhR), dioxin, inflammatory, persistent organic pollutants, 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), tocopherol

INTRODUCTION

Dioxins organic pollutants belong to the group of persistent organic pollutants (POPs), the emission of which into the environment has been associated for many years with ecological and health problems. Although POPs are characterized by specific and known chemical and physical properties and are easily detected, their analysis (in both the environment and food) is still difficult and requires sophisticated equipment. Currently, their emission into the environment is limited by the provisions of The Stockholm Convention on Persistent Organic Pollutants of 22 May 2001, and the national legislation established by the regulatory authorities, agencies, or international organizations, such as the World Health Organization (WHO), United States Environmental Protection Agency (EPA), the European Food Safe Authority (EFSA) or the European Chemicals Agency (ECHA). Despite the rigorous limits in POPs emission established in legislation documents, some sources of POPs emission into the environment are still a huge problem, e.g. private waste combustion. Usually, they pollute soil and seas.

Although the impact of dioxins on the organism is inevitable, it can be limited. Unfortunately, people are not aware that dioxins are produced while grilling, backyard barrel burning, or using some central heating systems, and how harmful these may be for the environment and every living organism. The economic and energy crisis also has a stimulating effect on this production.

Objective. This review focuses on determination of the influence of dioxins toxicity on the biochemical changes in the organism, and demonstrates the possibilities for reducing the negative effects of exposure to dioxin.

DESCRIPTION OF THE STATE OF KNOWLEDGE

The threat of dioxin poisoning. The organic pollutants group of POPs is divided into 12 groups of chemicals. One of them is polychlorinated dibenzo-*p*-dioxin (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) (Fig. 1). Polychlorinated dibenzo-*p*-dioxin (PCDDs), determined as dioxins, are a group of 75 compounds which contain benzene rings with varying numbers of chlorine atoms (Clx, Cly) in different positions of these rings. They can form congeners with varying numbers and localizations of chlorine atoms in the benzene frame. The 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the standard compound of PCDDs.

According to epidemiological studies, dioxins are considered as cancerogenic factors, [2], defined by the

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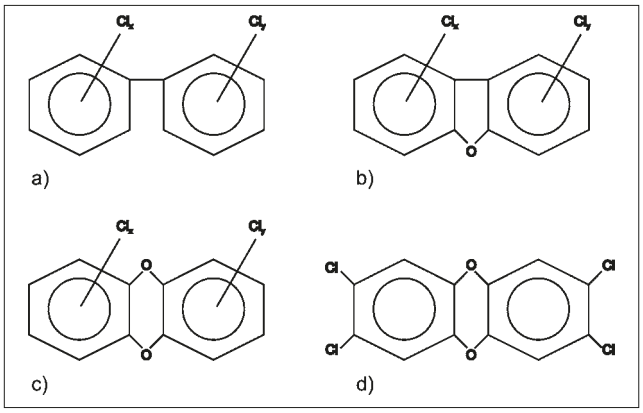

Figure 1. Structure of the individual groups POP representatives a) polychlorinatedbiphenyls (PCB), b) polychlorinateddibenzofurans (PCDF), c) polychlorinateddibenzodioxins (PCDD), d) 2,3,7,8- tetrachlorodibenzo-*p*-dioxin (TCDD). On the basis of [82]

International Agency for Research on Cancer (IARC) as a group 1 cancerogenic compound of group 1, and their activity is still being investigated by experiments on animals [1]. Nevertheless, there are some reports that criticize the IRAC classification of dioxins as proven human carcinogens [3].

The main dioxin and the best-examined compound is the TCDD which has a very high toxicity; it is therefore considered to be a reference for determining the toxicity of other toxic compounds of this group [4, 5]. The toxic equivalent factor determines TCDD toxicity and has a value of 1 [6]. The Total Toxic Equivalent (TEQ) presents an estimated value of 2,3,7,8-tetrachlorinedibenzo-*p*-dioxin (TCDD)-like activity of the mixture by the sum of the individual PCDDs and PCDFs congeners in the sample, multiplied by the corresponding toxic equivalent factors (TEF). TEQ and TEF value indices were established and then systematically re-evaluated by the WHO to uniformity at the international level and provide recommendations for particular countries [7].

Indeed, the limitation of POPs emission that includes PCDD/PCDF (present in different proportions and having different toxicity) is regulated by the provisions of The Stockholm Convention on Persistent Organic Pollutants. According to this report, the main sources of POPs emissions are: open waste burning, including the burning of landfill sites and thermal processes in the metallurgical industry, specific chemical production processes releasing unintentionally formed persistent organic pollutants, and most of all, the production of chlorophenols and chloranil [8].

Dioxins are formed in every thermal process and are characterized by the presence of the organic matter, chlorine, high temperature (200–900 °C) and low concentration of oxygen. Dioxins are emitted not only during combustions and waste utilization, but also in various technological processes, such as textile and leather dyeing, oil refineries wastes, destruction of animal carcasses and products of the pesticide industry [8, 9]. It is noteworthy that dioxins may be converted from polychlorinated biphenyls (PCBs) or may be a result of sunshine interaction with plastic waste. Dioxins and PCBs are chemically similar and belong to the same group of POPs [10, 11]. Moreover, conflagrations are considered as one of the essential sources of PCBs and PCDD congeners emissions. The measurements in the conflagration region of World Trade Center (WTC) after the terrorist attack in 2001, showed a high concentration of polycyclic aromatic hydrocarbon, not only in the ground zero zone, but also at a significant distance from it [12, 13, 14]. These observations have led to the conclusion that the risk of the tumour morbidity as a long-term effect of dioxin exposition in the population living near the WTC is high [14].

Interestingly, the research carried out on areas where, 30 years earlier, military operations using dioxins and herbicides were conducted, have shown a high elevation of PCDF concentration in the soil. These observations are important for indicating the correlation between food production in areas contaminated by polycyclic aromatic hydrocarbon and the capacity to deposition of these compounds in the food chain [15] (Fig. 2). It has been reported that dioxins are considered as xenobiotics with a hormone-like action. Their concentration, as a result of the utilization processes and individual heat production, is significant, especially in the urban environment [15, 16, 17].

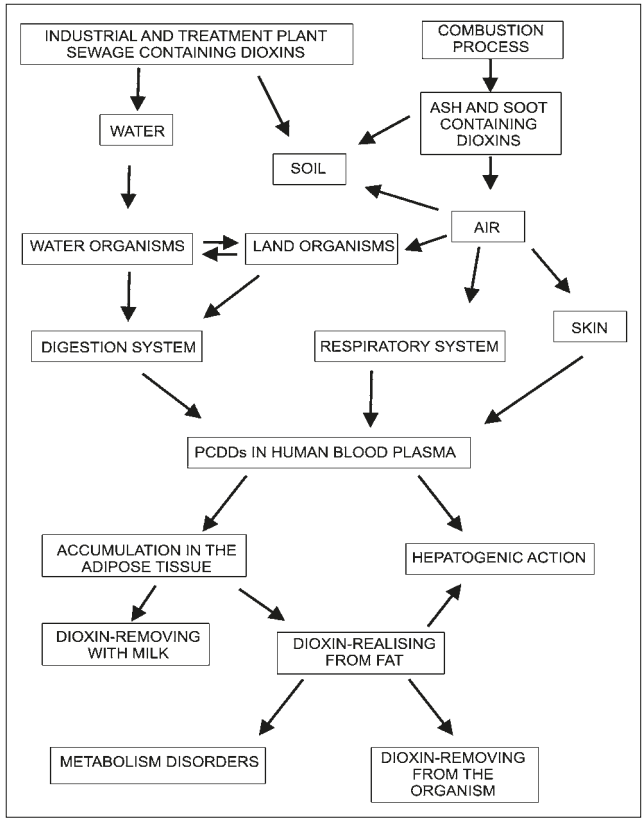

Figure 2. Circulation of dioxins in food chain [83]

It is worth highlighting that prolonged, strong, biological actions of dioxins can be manifested in the second generation, even though only the first generation was exposed to this activity [18, 19].

Dioxin absorption. The important routes of dioxin entry into the organism include the digestion system, respiratory system and the skin. Dioxins have a high affinity to fats and can dissolve in them; thus, they can be delivered and stored in the organism in a simple way [5, 20].

Almost 90% of human exposure to dioxins is from food. These toxins appear in different food chains (Fig. 2) and are absorbed into the organism by the digestion system. For instance, dioxin accumulated in seals could be transferred to the Eskimos from Canada and Greenland, who eat these mammals. Moreover, studies of the metabolism of seals

living near the coast of Greenland have shown a correlation between the age of these mammals and dioxins concentration in their bodies [20]. What is more, a significantly higher concentration of PCDD/PCDF is present in the milk of Norwegian bears than in the milk of seals living in this area, suggesting that the amount of dioxins in the adipose tissue of the final consumers is directly proportional to the lifespan in the dioxins contaminated environment [21]. Additionally, consumption of high-fat foods containing dioxins results in dioxin accumulation in adipose tissue [1, 16, 20].

Although the air is contaminated by xenobiotic absorbing smokes and dusts, the absorption of dioxin by the organism through the respiratory system is insignificant (ca. 8%) and the absorption of dioxins by the skin lipids is even lower (ca. 2%). It should be noted that many different factors, for polluted air, such as soot are absorbed by the respiratory system and skin lipids, and they cause a significant rise of the dioxin level in an organism [17]. The knowledge of dioxin emission sources may help to distinguish occupational groups, such as chimney sweeps, firefighters, soldiers, members of Special Forces and anti-terrorist squads, for whom the risk of exposure to PCDD/PCDF is the greatest. It should be emphasized that the urea of chimney sweeps contains aromatic polychlorinated compounds, which are derivates of POPs [22, 23].

Furthermore, employees of certain industries, as well as residents of industrialized zones, are also exposed to dioxins. The contamination of the population of Seveso in Italy is a prime example of this problem [24, 25, 26, 27].

Dioxin sensitivity. Due to their physical properties, i.e. no taste or smell and solubility in fats, dioxins may easily enter the digestion system. Because of these organoleptic features and the fact that the clinical symptoms of intoxication occur even after a long-time period, dioxins were considered as a potential chemical weapon. Studies conducted 20 and 30 years after the first exposure to these compounds have shown that their concentration in plasma lipids increases with age, since these compounds accumulate when the exposure is continuous. On the basis ofthese results, it was suggested that dioxin concentration is correlated with the body mass index (BMI). Due to the emerging dominance of catabolic processes in the body that appear with ageing or starvation, and because dioxin half-life is long, these compounds accumulated in the adipose tissue can be released into the plasma a long time after the first exposure [22, 24, 25].

So far, research on dioxins has been conducted only on a few animal models. The species most sensitive to TCDD activity, determined by the LD50 value, is the guinea pig (*Cavia porcellus*) [28]. Interestingly, rats and monkeys are 45 times more resistant to TCDD activity than the guinea pig. This species specificity is a result of changes in the regulation of gene expression, especially those responsible for the lipid metabolism [29].

The sensitivity to dioxins activity depends on gender, e.g. female rats are more sensitive to them than the male. The TCDD toxicity determined by LD50 for the female is between 22–50 μg/kg b.w., and for male rats it oscillates between 45–50 μg/kg b.w [30, 31]. Recent studies have shown that administration of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin at a dose of 25 μg/kg b.w in Buffalo strain rat females, causes their death on the third day after TCDD application, accompanied by liver damage and blood extravasation into the bowel. Reducing the dose by half did not cause have these effects [32]. In connection with these studies, the need for the correction of toxicity studies in different animal species has been highlighted [31].

Reducing dioxin activity. Dioxins are transported from the external environment to the adipose tissue or liver through the plasma lipids, and TCDD binds to the aryl hydrocarbon receptor (AhR) in cytosol of hepatocytes [33–36].

The active dioxin-receptor complex is translocated to the cell nucleus and binds to the dioxin response element on DNA (dioxin responsive element, DRE). This complex is a signal for transcription of cytochromes P 450 and P 448 (aryl hydrocarbon hydroxylase – AHH) genes [37, 38]. The highest concentration of AHH, the enzyme responsible for dioxin conversions, occurs in endoplasmic reticulum of hepatocyte. In the initial phase, the hydrolytic degradation of dioxins by monooxygenase occurs and then the products of this reaction are conjugated with glucuronic acid or the glutathione molecule (GSH). After that, these complexes are released from organisms with urea or bile. Dioxins are metabolized more slowly than other high affinity AhR agonists, e.g. 6-formylindolo[3,2-b]carbazole (FICZ). For this reason, their action is much more prolonged in time and is not self-limited [39]. Nevertheless, it should be mentioned that AhR activation by FICZ (via IL-22) inhibited the experimental inflammation and colitis in the gastrointestinal tract of mice [40].

It was reported that certain cytokines play a significant role during dioxin elimination. Moreover, the AhR activation by IL-4 causes the expression of CYP1A1 gene, which is responsible for metabolism of xenobiotics such as TCDD [41, 42]. The AhR receptor inhibition by tocopherol as a possible therapeutic option has been recently described (Fig. 3). The inflammatory effects of dioxin can be also limited by reducing the level of TNF. Furthermore, the application of acetylsalicylic acid blocks cyclooxygenase-II enzyme (COX-2) and deactivates the AhR receptor [43].

The differences in dioxin intoxication effect depend on the type of tissue, subcutaneous adipose or liver tissue in which these compounds are accumulated. After binding to the AhR receptor, dioxins affect DNA stimulating mRNA cyclooxygenase synthesis (CYP 1 and CYP2) and influencing protein metabolism in hepathocytes and haematopoiesis. Accumulation of dioxins in the liver could modify the metabolism of cholesterol and hormones and is directly related to the synthesis of plasma proteins, thereby dioxins are able to change the peripheral blood picture and influence the biochemical response to an inflammatory reaction [44]. Studies have shown that changes in the smooth endoplasmic reticulum of hepatocyte occur between the 5th and 9th day after application of TCDD at a dose 5–25 μg/kg b.w. [45, 46]. The administered doses caused a decrease in bile secretion and an increase of the coproporphyrin concentration [47].

In the murine model, application of 100 μg/kg b.w. of TCDD caused an increase in liver mass during the first 72 hours, and a rise in lanine transaminase (ALT) activity in serum [48]. After this period, no histopathological changes in the liver were observed, whereas the macroscopic and histopathological changes in rat hepatocytes, such as hepatosteatosis and high cholesterol level in serum, were noticed after the 3rd week of TCDD application at a dose of 5 μg/kg b.w. [49]. This indicates that mice manifest a higher

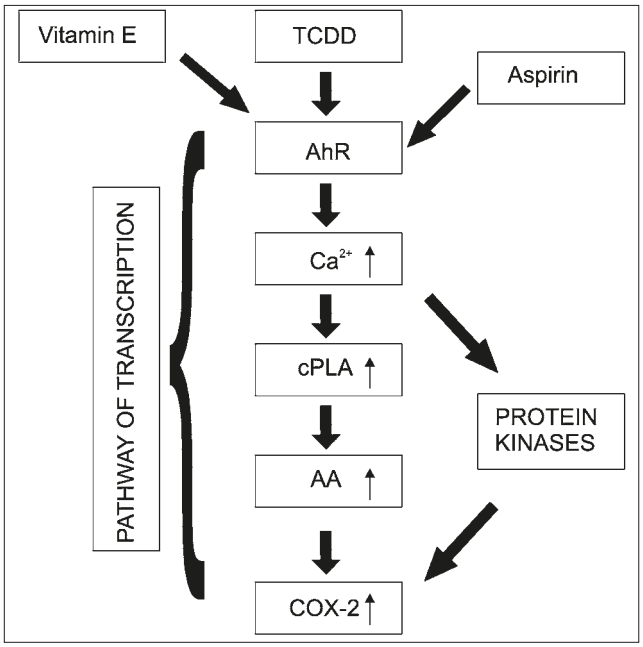

Figure 3. Inflammatory mechanism of dioxin action by stimulation of COX-2 dual-receptor block by tocopherol and acetylsalicylic acid.
Abbreviations: TCDD – 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin; AhR – Aryl hydrocarbon receptor; Ca^{2+}– calcium ions; cPLA– cytosolic phospholipase A2; AA – arachidonic acid; COX-2 – Cyclooxygenase-II enzyme. On the basis of [82]

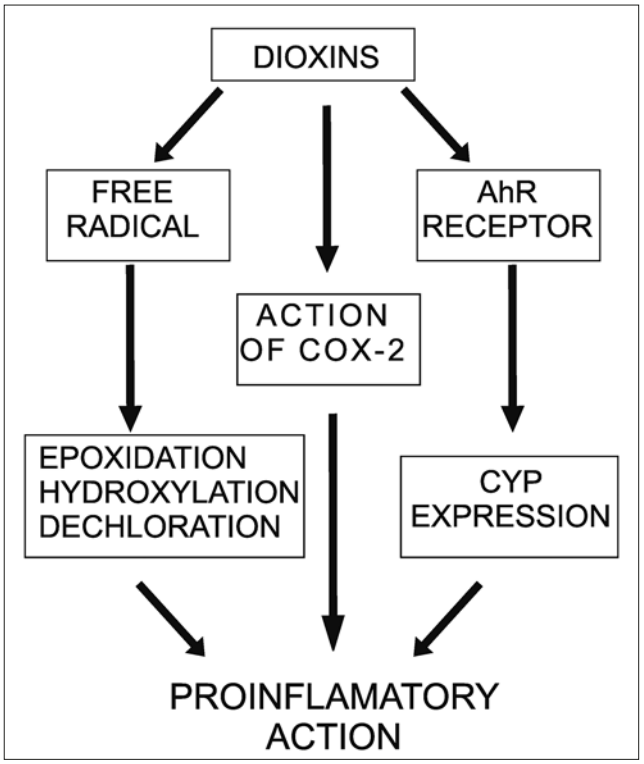

Figure 4. Mechanism of proinflammatory action of dioxins.
Abbreviations: COX-2 – Cyclooxygenase-II enzyme; AhR – Aryl hydrocarbon receptor;
CYP – Cytochrome P450.

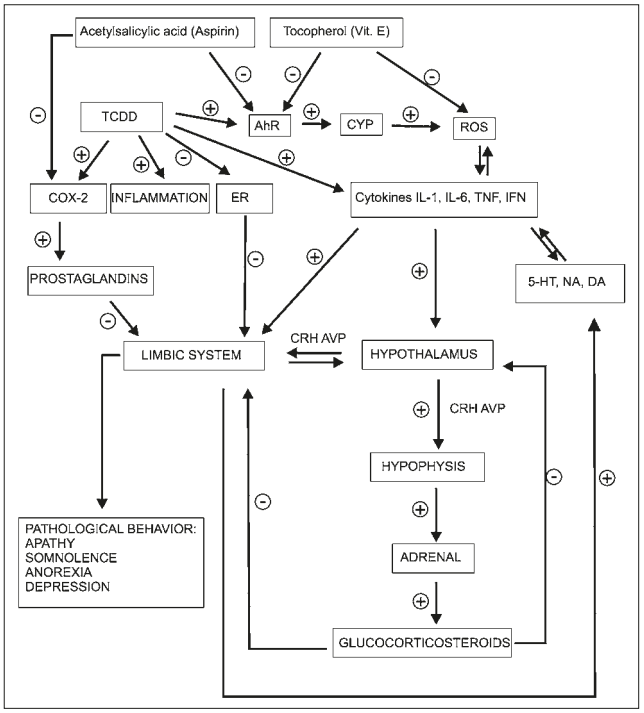

Figure 5. Mechanism of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin, tocopherol and acetylsalicylic acid and their role in the development of pathological behavior.
Abbreviations: TCDD – 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin; COX-2 – Cyclooxygenase-II enzyme; AhR – Aryl hydrocarbon receptor; ER – Estrogen receptor alpha; ROS – Reactive Oxygen Species; CYP – Cytochrome P450; CRH – Corticoliberin; AVP – Arginine vasopressin; IL-1 – Interleukin-1; IL-6 – Interleukin-6; TNF – Tumor Necrosis Factor alpha; INF – Interferon-gamma; 5-HT – Serotonin; NA – Noradrenaline; DA – Dopamine

resistance to dioxin. Moreover, the studies of TCDD activity in monkeys and mice show the rise of lamine A concentration and intensive ALT activity in the liver [48, 50].

Pro-inflammatory character of dioxins. Currently, experiments designed to determine the effect of different doses of dioxins on the central nervous system (CNS) and cardiac muscle of animals are being conducted. These studies indicate the pro-inflammatory character of dioxins, which could be also correlated with oxidative stress and cardiotoxic interactions responsible for the proliferation of connective tissue compounds (Fig. 4) [51, 52].

The mechanisms of dioxin activity include processes related to the distribution of free radicals (hydroxylation, epoxidation), the appearance of free oxygen atoms that cause the formation of hypochlorites. A recently established mechanism is the stimulation of COX-2, which generates synthesis of prostaglandins (PGE 2) [53]. Furthermore, the effects of the AhR receptor contribute indirectly to the increased synthesis of monooxygenase (CYP1), which enhances the inflammatory processes. Recent studies have shown that inflammation generated in one of the organs – for example, the pleura – contributes, through increased pro-inflammatory interleukins and generation of free radicals, to the formation of destructive changes in the structures of the hippocampus. The observed changes are intensified in animals exposed to TCDD action. The mechanism of this process is related to the generation of free radicals by TCDD. These molecules enhance the existing inflammation by affecting AhR receptor, as well as contributing to the stimulation of COX-2. It has been reported recently that administration of high doses of tocopherol and acetylsalicylic acid, which could block the AhR receptor, contributes to the reduction of the changes in the hippocampus caused by administration of TCDD [54] (Fig. 5). One hypothesis states that this mechanism can have an influence on the uncontrollable emotional states observed in humans and animals, manifested as inexplicable aggression or depression [55].

The biochemical parameters and morphology of peripheral blood, as well as the character of inflammatory response in rats treated with dioxin, have also been analysed. Two routes of dioxin action for the change of the nature and dynamics of the inflammatory process have been shown. In the first route, the impact of dioxin on the synthesis of acute phase proteins in the liver and on the increases of catabolism, results in a change in biochemical parameters, whereas the second path of dioxin action in the inflammatory reaction is associated with change in the neutrophil cellular response of lymphocyte response. This observation has important diagnostic value due to indication of liver function in the regulation of inflammation [46, 56].

Dioxins can disturb the secretion of TSH and thyroid hormones (T3, T4) by increasing the metabolism of T4 by induction of glucuronidation, thus the concentration of TSH in blood increases and T4 decreases [57]. They also cause changes in the regularity of sex steroids secretion [57, 58, 59, 60], such as disorders in the menstrual cycle [61]. Moreover, it has been stated that dioxins are responsible for sequential loss of mass of genitalia and sex glands in polar bears (*Ursus maritimus*). Dioxins could cause disorders during spermato- and oogenesis and could lead to intersexuality, miscarriages or perinatal mortality [19, 20]. Active dioxins may be released in milk during lactation [21, 27]. The offspring of bears fed on toxic milk have low survivability because their immunity is disrupted. These anomalies in the reproductive system and behavioural disorders in youthful individuals have also been observed in rats [61].

The suppressive action of dioxins on the estrogen gene transcription is the potential reason of changes in hormonal regulation [62]. Recent studies have shown that a single administration of TCDD contributes to a significant reduction of estrogen receptor (ERα) in the hippocampus, which is also related to the behaviour shown in the prolonged reaction time, as well as being the cause of apathy and depression in test animals [32].

Dioxins influence the immune system and are the main reason for chloracne disease [22, 25, 63]. It is noteworthy that POPs can affect the extracellular matrix (EM), which is a site of repair processes, such as connective tissue growth or destruction processes, and it is essential in the inflammatory reaction. Dioxins could cause oxidative stress, which is important during expression of liver gene responsible for collagen synthesis [64]. TCDD inhibits type 1 collagen synthesis, osteopontins and bones sialoproteins, and deactivates the alkaline phospatate in osseous tissue culture [65]. Furthermore, POPs cause thymus involution [44], the rise of corticosteroids concentration and changes in the composition of plasma protein – the α- and β-globulins level increases and the immune response is weakened [66].

The interaction of dioxins with AhR contributes to the production of cytokines that influence blood cells development. TCDD inhibits mRNA IL-6 expression in the presence of lipopolysaccharides (LPS) and interacts with haematopoietic cells and lymphocytes B; it also decreases globulins synthesis [27, 44]. After administration of TCDD to lymphocytes B culture stimulated by LPS and IL-4, the secretion of immunoglobins, such as IgG1, IgE and IgM, was inhibited [67]. Other reports have shown that TCDD does not cause the increase of IgE synthesis by transformed lymphocytes B. Furthermore, POPs cause long-time immunosuppression of prolymphocytes B in the medulla, which is connected with the stimulation of apoptosis [46]. The studies indicate that the AhR activation interacts with the haematopoiesis of immature lymphocytes as a result of low POPs doses action [68]. These immunosuppressive effects decrease the survivability of youthful individuals [69]. The experiments performed on monkeys (*Callithrix jacchus*) have shown the reduction of absolute and relative lymphocytes numbers with reference to general lymphocytes numbers three weeks after TCDD administration at a dose of 300 ng/kg b.w. Moreover, the reduction of 20% of lymphocytes CD4 was observed. These changes were the result of interaction of TCDD with the thymus [51]. Studies have shown that TCDD increase in the dose dependent manner the TGF-β and integrins concentration [51]. In the murine model immunization by SRBC and application of TCDD at dose of 5μg/kg b.w. has indicated the reduction of CD4 and CD8 lymphocytes in comparison to a control group in which these amount was increased [70]. The exposure to TCDD action causes changes in the innate and acquired immunity in the humoral and cell-mediated immune response. The behaviour of the immune system after dioxin application is a specific indicator of the adaptation of an organism to harmful conditions [69].

CONCLUSIONS

Dioxins are considered as pro-inflammatory environmental factors causing oxidative stress [71]. TCDD also inhibits the regeneration of destroyed fins in ray-finned fish *Archocentrus nigrofasciatus,* which contain connective tissue. These compounds interact with AhR and influence matrix creation [72]. TCDD administered hypodermically has shown cardiotoxic activity in monkeys [50, 52]. Moreover, the distinct character of the dioxins action in the heart has been shown, manifested by the growth in value of collagen, fibronectin and lamins. Dioxins influence prostaglandin and thromboxin synthesis, appearing in the first stage of the inflammatory reaction, and they have an influence on the second stage of the acute phase protein synthesis and may cause changes in the blood picture [73]. TCDD induces oxidative stress in which active forms of oxygen are released and the expression of antioxidant enzymes, e.g. superoxide dismutase, catalase, glutathione reductase and glutathione peroxidise, is decreased [74].

Symptoms of dioxins intoxication are divided, depending on their presence in early and late intoxication stages. The early symptoms occur few days after exposure to dioxin and include:

1. long-lasting Chloracne disease [25];
2. mental disorder (depression, apathy, long-time tiredness) [75];
3. emaciation, anorexia [76];
4. ascites [75];
5. often and long-lasting inflammatory reactions of airways [46];
6. atypical inflammatory reactions [77];
7. hypochromic anaemia – disorders in erythropoiesis [78];
8. susceptibility to infection – immunosuppression action (high mortality in young polar bears) [21];
9. long-lasting bleeding from the digestion system – disorders in thrombopoiesis and fibrinogen synthesis [56]
10. disorder in menstrual cycle, miscarriage, high mortality of infants, disorders in youthful individuals development [79]

Late symptoms appear many years after exposure to dioxin and may include:

1. embriotoxic actions (miscarriage) and teratogenic (cleft palate and backbone, acephalie) [80];
2. cancerogenic action – different cancers (especially in connective tissue) [81];
3. interaction on the hard tissue – disorders in glaze and teeth [7];

According to recent studies, dioxins are present in different concentrations in the environment and cause specific and long-time effects. They influence the main and multistage immune response, for instance, inflammatory reactions responsible for the oxidative stress.

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