Biological Implications of Dioxins/Furans Bioaccumulation in Ecosystems

14

Jose Gnanaleela Aswin Jeno, Ravichandran Rathna, and Ekambaram Nakkeeran

Abstract

Dioxins and furans are a class of persistent, bioaccumulative and toxic organic pollutants in the environment that have garnered attention within the scientific community. This chapter encompasses the bioaccumulation of dioxins/furans in the ecosystem. Further, information on the source and exposure of dioxins/furans is discussed. In addition, the presence of dioxins/furans in the global environment and its regulatory responses are also presented. Persistent dioxins/furans undergo bioaccumulative and biomagnification in the food chain and led to metabolic transformations in human. A detailed compilation of health effects in humans is also elaborated.

Keywords

Bioaccumulation · Biomagnification · Dioxins/furans · Global environment · Health effects

14.1 Introduction

The continuous expansion of civilizations around the globe has resulted in several scientific developments on one aspect, whereas the other side causes deleterious environmental damages. Rapid urbanization, deforestation, population explosion, industrialization and pollution accelerate the accumulation of persistent organic pollutants in the environment. Persistent organic pollutants (POP) are a peculiar type of pollutants that have garnered huge attention within the scientific community

J. G. A. Jeno · R. Rathna · E. Nakkeeran (✉)
Department of Biotechnology, Sri Venkateswara College of Engineering (Autonomous), Sriperumbudur Tk, Tamil Nadu, India
e-mail: nakkeeran@svce.ac.in

R. Prasad (ed.), *Environmental Pollution and Remediation*, Environmental and Microbial Biotechnology, https://doi.org/10.1007/978-981-15-5499-5_14

owing to their persistency and toxic accumulation in the ecosystem. This class of persistent compounds include polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), benzo(a)-pyrene (BaP), hexachlorobenzene (HCB), polychlorinated naphthalene, octachlorostyrene, 1,1,1-trichloro-2,2-diethane, alkyl-lead pesticides such as mirex, dieldrin, aldrin, chlordane and toxaphene. Of these POPs, PCDDs, PCDFs and PCBs (dioxin-like compounds) are the three prime categories of dioxins and furans that have gained importance in the scientific community.

PCDDs/PCDFs and PCBs are the most dangerous anthropogenic toxicants since these chemicals have a widely reported environmental damage history over the past few decades and also highlighted as "the most toxic man-made chemical" ever made. PCDDs and PCDFs are two classes of planar polycyclic halogenated aromatic hydrocarbons with a total of 410 different compounds, only 30 of which are considered to be significant congeners. The characteristic of the congeners is certain to depend on the nature, position and number of halogen atoms bound to the aromatic carbon rings; one such classic example is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD), chlorine substituted in the 2, 3, 7, and 8 positions of the aromatic benzene ring, which is the most toxic congeners. 2,3,7,8-TCDDs are known for its lowest lethal dose median (LD_{50}) among the dioxin family in male guinea pigs which is nearly 1 μg/kg of body. Dioxins/furans were not produced or created intentionally for market value but were the by-products of several industrial processes and combustion techniques. An example of such a phenomenon is the burning of plastic which contains chlorinated phenolic compounds that release dioxins and are termed to be accidental contaminants. Due to the accumulation of members of dioxins family in the fat tissues and thereby entering the food chain, efforts are being made to minimize the exposure of such chemicals into the environment.

Since the nineteenth century, there has been an incidence of dioxin and furan pollution from industries. German industrial workers were overexposed to 2,3,7,8-TCDD or dioxin that resulted in chloracne, oozing skin lesions. During the Vietnam War (1965–1971), United States (US) military sprayed herbicide dubbed Agent Orange as a defoliant, which was contaminated with 2,3,7,8-TCDD and showed serious health effects. Dioxin pollution and its ill effects came to public attention after the explosion of Industrie Chimiche Meda Societa Anonima (ICMESA) chemical factory in Seveso, Italy, in 1976. Boda et al. (2018) demonstrated the associations of dioxins in breast milk and cord blood sex hormones in Vietnamese newborn infants residing near the former US Air Force base. TCDD has the highest degree of toxicity rated 1 (reference value), while others are less toxic. In 2005, the World Health Organization (WHO) re-evaluated the toxic equivalency factor (TEF) values defined on the 1998 WHO-TEF value for human risk assessment (Van den Berg et al. 2006). According to Ren and Zheng (2009), the differences between dioxin and furan estimation with each unit should not exceed 28%. Reduction in levels of dietary dioxins/furans in food sources between 1998 and 2018 was observed in the general population of Spain (González et al. 2018).

This chapter encompassed the current status of dioxin/furan accumulation and its biological implication in the ecosystem. In addition, detailed information on the sources and exposure risk of dioxins/furans are explained. This chapter also discusses the presence of dioxins and furans in the global environment and related regulatory measures. A detailed compilation of bioaccumulation and biomagnification of dioxins/furans in the food chain and its adverse side effects in human is also elaborated. For brevity, PCDDs/PCDFs are termed as dioxins/furans unless specified in the chapter.

14.2 Nature of Dioxins and Furans

Dioxins/furans are volatile to an extent, slightly soluble in water and readily soluble in lipids. Their lipid solubility aids directly to cross the cell membranes and accumulates in the fat tissues of several organisms. These compounds have high toxic properties causing severe abnormalities, developmental problems and interference with regulatory hormonal functions. These are non-polar, poorly water-soluble, lipophilic compounds generally resistant to chemical breakdown through an acid-base reaction, redox and hydrolysis. The nature of dioxins and furans is summarized in Table 14.1. These physicochemical properties of dioxins and furans favour their long-range transport and have been detected in arctic organisms. In fact, PCDDs/PCDFs are a serious threat to public health due to their persistence in the environment as illustrated by the half-life of 2,3,7,8-TCDD in the soil of 10–12 years (Mukerjee 1998).

14.3 Sources and Exposure of Dioxins/Furans

Dioxins/furans are formed as the result of undesirable by-products from anthropogenic activities including certain industrial applications and process. Figure 14.1 illustrates the various sources of dioxins and furans responsible for its release into the environment.

Table 14.1 Nature of dioxins and furans

Nature	Dioxins	Furans
Chemical formula	$C_4H_4O_2$	C_4H_4O
Physical state and appearance	Solid	Liquid
Molecular weight (g/mol)	321.96	68.07
Melting range (°F)	581–617	−122.8
Boiling range (°F)	789.8–834.8	89.6
Solubility in water (g/L)	Insoluble	Very slightly soluble in cold water
Vapour pressure (at 20 °C)	7.4×10^{-8} mm Hg	493 mm Hg
Specific gravity (water = 1)	1.827	0.94

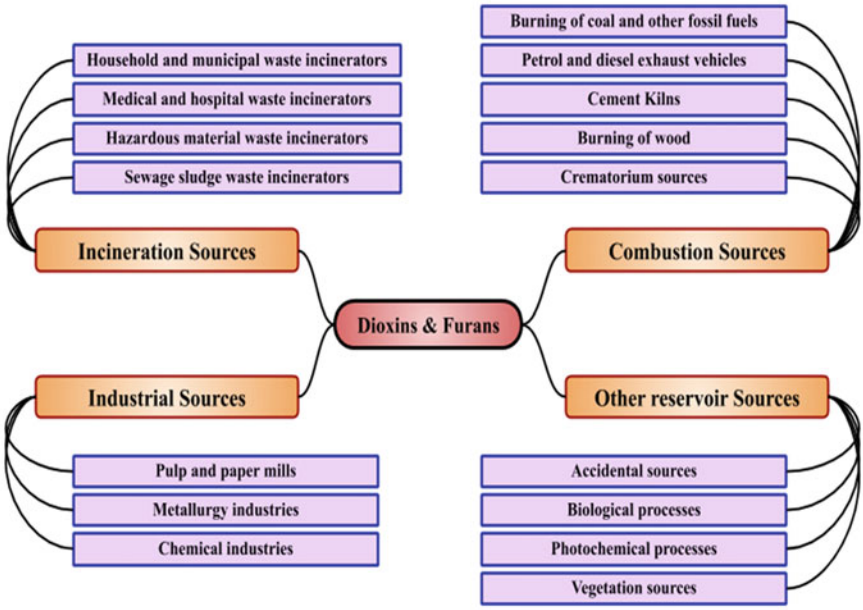

Fig. 14.1 Sources of dioxins and furans

14.3.1 Incineration

Incineration is a thermal waste reduction method that involves combustion process and one of the major anthropogenic sources for the emission dioxins and furans. However, incineration of contaminated wastes in rotary kilns is usual practice in many industrialized countries, as they are best suited to accept solid, pasty or liquid waste. Municipal waste incineration, hazardous waste incineration, medical waste incineration, light-fraction shredder waste incineration, waste wood and waste biomass incineration and sewage sludge incineration are the important waste incineration categories in a nation. The major incineration categories that emit dioxins and furans are municipal waste incineration, hazardous waste incineration and medical waste incineration, while the rest are least studied. Medical waste incinerators in China reported emitting 1.18 kg I-TEQ of PCDDs/PCDFs in the year 2004 (11.5% total PCDD/PCDF emission). In order to minimize the emission of PCDDs/PCDFs from medical waste incinerators, an advanced gas cleaning and stable combustion system should be enforced (Li et al. 2010). Municipal solid waste incinerators contribute to the emission of dioxins, furans and derivatives of dioxins through stack flue gases and ashes (Wang et al. 2010). Therefore, appropriate control strategies should be installed to regulate the emission of dioxins and furans.

In India, municipal waste incineration is absent and around 94% of the municipal solid waste simply dumped, while the rest is either composted (4%) or recycled

(2%). In case of hazardous waste incineration in India, there are around 120 hazardous waste incinerators and 11 hazardous waste landfills and releases 5505.6 g TEQ/a in air and residue. The release of dioxins and furans from medical waste incineration in India is 272.37 g TEQ/a in air and residue. An amount of 14.6 g TEQ/a dioxins and furans is released in Portugal from waste incineration (Quina et al. 2011). In the United States, the annual emission in the year 2000 is less than 12 g TEQ/a dioxins and furans which are released from municipal solid waste (Psomopoulos et al. 2009). The release of dioxins and furans from incineration sources in the developed nation is less than the developing nation due to abatement strategies and sophisticated technologies to limit the release of toxic compounds into the environment. Yang et al. (2019) investigated the effects of small-scale domestic waste incinerators in the emission of dioxins and dioxin-like compounds which has a major impact on the environment and human health.

14.3.2 Combustion

Combustion is an exothermic redox reaction of a substance in the presence of oxygen. Incomplete combustion process release PCDDs/PCDFs and related congeners to the surrounding. The generation of dioxins and furans from combustion sources is lower than the incineration sources. The main categories of combustion sources are cement kilns, firewood combustion, diesel vehicles, crematoria, coal-fired utilities and uncontrolled fires in landfill sites. Karstensen (2008) evaluated more than 2000 PCDDs/PCDFs from cement kiln and reported an emission level of 0.1 ng I-TEQ/m^3 indicating the well-managed and operated modern cement kilns co-processing waste in Australia. Conesa et al. (2016) assessed the emission of persistent dioxin and furan pollutants using a long-term monitoring system from a cement plant. Further, an average of 0.23 ng I-TEQ (equivalent)/ton clinker of PCDDs/PCDFs was found to emit from the plant. Rivera-Austrui et al. (2014) demonstrated the installation of alternate fuels with clinker kiln stack significantly reduced the emission of harmful persistent organic compounds.

In India, total dioxin released to air from cement kilns, lime production, brick manufacturing units and glass production emits 83.64, 7.12, 50.54 and 0.03 g TEQ/a, respectively. Crematoria used for the purposes of burial found to form and release PCDDs/PCDFs from the cadavers containing chlorinated compounds and precursors. From crematoria, a total of 0.56 and 0.14 g TEQ/a dioxins released to air and residue, respectively, in India. The annual release of PCDDs/PCDFs from disposal/landfill in India to water was 1.22 g TEQ/a, to the product 70.16 g TEQ/a and to residue 3.44 g TEQ/a. Vehicle population in developing countries like India is increasing tremendously; the emission of PCDDs/PCDFs into the air by transportation is 9.57 g TEQ/a, especially for diesel engines. During the uncontrolled combustion processes like forest fires, open burning of wastes and accidental fires emitted 45.48 g TEQ/a in air and land in India.

14.3.3 Industrial

Processes in the chemical industry, pulp and paper industry, dry cleaning, brominated flame-retardants manufacturing, metallurgical processes, reactivation processes of granular carbon, etc. are some examples of industrial sources of dioxins and furans. These toxic chemicals are generated as a by-product during the manufacture of chlorinated pesticides, phenoxy herbicides and polyvinyl chloride synthesis. In pulp and paper industries, chemical bleaching of pulp with chlorine produced PCDDs/PCDFs and its congeners like 2,3,7,8-TCDD, 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF) and 1,2,7,8-tetrachlorodibenzofuran (1,2,7,8-TCDF). Wang et al. (2012) reported the average annual emission of concentration PCDDs/PCDFs from Chinese non-wood pulp and paper mills to be 27.59 g I-TEQ. Further, 2,3,7,8-TCDF highly formed during hypochlorite bleaching stage and removed during alkaline digestion, extraction and hydrogen peroxide bleaching. The recycling process of TV plastic materials resulted in the release of a higher amount (ten-fold increase) of dioxins/furans when compared with the original material (Ortuño et al. 2015).

In India, the major dioxin congener from pulp and paper mills was 1,3,6,8-TCDD found before effluent treatment, while 2,5-diphenyl furan congener was found in the secondary sludge of effluent treatment plant. Metallurgy industry is the major contributor to dioxin and furan emission in the atmosphere. Table 14.2 depicts the dioxin and furan emission from metallurgical industries in India. Rezaei et al. (2013) investigated and evaluated the release of dioxins and furans in the Iranian mining and ore processing industries and stated an annual release of 120 g TEQ/a of PCDDs/PCDFs.

Table 14.2 Dioxin and furan emission from metallurgical industries in India

Metallurgical industries	Release (g TEQ/a)		
	Air	Residue	Total
Iron ore sintering	260.06	0.16	260.22
Coke production	24.99	–	24.99
Iron and steel production	116.45	601.42	717.87
Foundries	27.63	1.3	28.93
Secondary copper production	32.12	404.68	436.8
Secondary aluminium production	17.5	200	217.5
Secondary lead production	4.53	2.8	7.33
Secondary zinc production	40.20	–	40.20
Brass and bronze production	0.138	–	0.138
Thermal non-ferrous metal production	16.06	–	16.06

14.3.4 Reservoir

Dioxins and furans are emitted into the atmosphere through redistribution from the accumulated sites such as vegetation, soils and landfills (Kulkarni et al. 2008). During natural calamities like volcanic eruptions, forest fires emit dioxins and furans accidentally into the environment. Over the past decades, the incidental release of dioxins and furans from the contaminated biota is increasing. In 2013, the Food Safety and Inspection Service (FSIS), an agency of the US Department of Agriculture (USDA) determined that the chicken imported to the United States from Chile was exposed to dioxins. In 2007, the European Commission detected the traces of dioxins (a contaminant of pentachlorophenol pesticide – no longer used) in guar gum from India. Pemberthy et al. (2016) showed and evaluated the presence of PCDDs/PCDFs and dioxin-like polychlorinated biphenyls in soybean, olive oil, fish oil, butter and shrimp used for human consumption in Colombia. Many such historical proofs manifest many sources of high-level release of dioxins in the food and threatened the food safety. Researchers reported the release of dioxins and furans by the microbial activity of chlorinated compounds under suitable environmental conditions. Composting, sewage decomposition and photolysis of chlorinated compounds are some typical examples of such sources. Ueno et al. (2005) elucidated the contamination of the marine environment with PCDDs/PCDFs from highly industrialized countries of Northeast Asia.

14.4 Dioxins/Furans in the Global Environment

Over the past few decades, several historical incidents have taken place which led to dioxin and furan contamination, especially during 1920–1970. Industrial activities involving organic/inorganic chloride are the prime source for the release of dioxins and furans to the environment. Dioxin/furan pollution is directly or indirectly linked to the food chain of humans, such as animal and poultry feed and dairy food products. One of the biggest food recalls in the world has happened in Ireland in 2008 because of chemical contamination in pork meat. The government of Ireland had to recall tons of pork and other pork-related products when it found out traces of dioxin over 200 times of the safe limit. Further, the food safety authorities traced back the incident to the contamination of animal feed with dioxins. In 1999, illegally disposed dioxin- and furan-contaminated industrial oils led to the contamination of poultry feed in Belgium. Subsequently, very high levels of dioxins and furans were found in poultry products.

Dioxin and furan contamination is observed in air, soil, water, plants and animals. The global government began to investigate the presence of dioxins and furans contamination in soil, air and water over the course of time to interrogate the severity of damage caused to the environment and humans. Taiwanese elementary school children were reported to be exposed to different persistent organic pollutants through classroom dust at lower than the threshold risk values (Gou et al. 2016). Bruce-Vanderpuije et al. (2019) reported about the epidemiological studies of

Table 14.3 Dioxin contamination levels in soil, water and air in different European countries

Sampling source	Region	Sampling year	PCDD/PCDF (pg TEQ/g)
Soil	Netherlands	1991	2.2–16
	Austria	1989–1993	1.6–14
	Germany	1992	1–5
	Belgium	1992	2
	France	1999	0.02–1
Water	Germany	1994	1–20
	Netherlands	1980–1990	8–21
Air	England	1991–1996	0–810
	Germany	1992	70–350
	Belgium	1993	86–129
	Netherlands	1991–1993	4–99
	Austria	1996	26–314

37 participants from Ghana who had no known accidental or occupational exposure to dioxins/furans but exhibited levels of ~5.3 pg WHO-TEQ/g. However, the data retraining to the levels of dioxins and furans are limited in environmental matrices. Table 14.3 represents the region-wise split up of dioxin and furan contamination in the soil, water and air.

14.4.1 Dioxin and Furan Contamination in Soil

One of the major sources of contamination of dioxins and furans is the soil and soil sediments. In soil, the contamination generally occurs through the deposition of atmospheric particulate contaminants. Interestingly, migration of dioxins and furans into the deep soil is very minimal. Further, ~90% of dioxins and furans are found within the shallow topsoil (10 cm). Similarly, the contaminants once settled in the soil will no longer be evaporated or lost due to decay. The soil contamination levels in Germany and Switzerland were estimated to be around 100 and 200 pg TEQ/g, respectively. Open dumping sites in developing countries like Cambodia, Philippines, India and Vietnam reported a release of 0.12–35 mg TEQ/year of dioxins and furans into the environment (Nguyen et al. 2003). The correlation of population density with soil dioxin-TEQs in Taiwan was reported by Hsu et al. (2018).

14.4.2 Dioxin and Furan Contamination in Water

Dioxins and furans are poorly soluble in water; however, it undergoes surface adsorption with the suspended solid particles which settle at the bottom of the stream substrate. Contamination in water is mainly due to the sewage sludge, paper and pulp industries, fertilizer industries, etc. Water contaminated with dioxins and furans is

the primary source for bioaccumulation and biomagnification. Kumar et al. (2001) reported the presence of dioxins and furans in Ganges River dolphins and fish in India. Recently, surface sediments of rivers in Russia (the Neva River and the Eastern Gulf of Finland), Uruguay (Uruguay River) and Argentina (Gualeguaychú River) reported the presence of dioxins and furans (Metelkova et al. 2019; Matta 2018). The concentration levels of dioxins/furans in egg tissues of two species of salmon in Ontario lake are significantly higher than that of the levels determined by Canadian Council of Ministers of the Environment (Garner and Pagano 2019).

14.4.3 Dioxin and Furan Contamination in the Air

Incineration processes, combustion processes and several natural methods contribute to the dioxin and furan content in the atmosphere of all countries. Until 1990, the standard investigation was not carried out to estimate the toxic chemicals such as dioxins and furans in the atmosphere. Thus, it led to an outbreak of the maximum amount of chemicals in the atmosphere during that decade. Rahman et al. (2014) reported dioxin and furan contamination in ambient air at urban residential areas in Seoul, Korea. An industrial park in China (Tibet–Qinghai Plateau) reported being the source for dioxin/furan and dioxin-like compound pollution in the atmosphere (Hu et al. 2019).

14.5 Regulations

Foreseen, the dangerous effects of dioxins and furans, United States Environmental Protection Agency (USEPA) jumped into action to frame a strong regulatory framework called the "Dioxin Reassessment" and was reviewed by EPA's science advisory board. A strong regulation was framed to minimize the fatal impact of dioxins and furans in the environment as well as humans. The ultimate aim of the regulatory activities is to reduce the release of dioxins/furans into the environment from incinerator waste. Dioxins/furans are not produced in an intentional way for commercial activities or for any other industrial purpose, the key problem for developing guidelines and regulatory activities. Human exposure to dioxins/furans is through the food chain, and thus, regulatory actions must ensure ways to minimize the impact on the human food chain. Maximum Achievable Control Technology (MACT) was introduced by the USEPA in September 1999 for several contamination sources such as cement kilns, incinerators and combustion sources, to adopt this technology within their premises. Table 14.4 represents the Interim MACT Standards for Combustors in the United States (EPA 1999). POPs that are regulated through MACT were lead, cadmium, arsenic, beryllium, carbon monoxide, chromium, hydrocarbons and majorly dioxins and furans. Table 14.5 represents the international environmental standards for dioxins and furans from different sources.

Table 14.4 Interim MACT Standards for Combustors in the United States

Types of pollutants	MACT standards for different sources		
	Domestic and lightweight kilns	Cement kilns	Incinerators
Dioxins and furans (ng TEQ/dscm)	0.20	0.20 or 0.40	0.20
Hydrocarbons or carbon monoxide (ppmv dry)	–	10 or 100	–
Hydrocarbons (ppmv dry)	–	50	–
Hydrocarbons or carbon monoxide (ppmv dry)	20 or 100	20 or 100	10 or 100
Opacity (%)	–	20	–
Particulate matter (mg/dscm)	57	0.15	34
HCl/Cl_2 (ppmv dry)	600	86	21
Low volatile metals (μg/dscm)	110	54	97
Semivolatile metals (μg/dscm)	43	180	120
Mercury (μg/dscm)	120	120	45

Table 14.5 International environmental standards for dioxins and furans from different sources

Country	Sources of dioxins/furans	Standards for dioxin/furan emission
United States	Municipal solid waste incinerator (>35 Ton/day)	13 ng/m^3 (Total mass) about 0.1–0.3 ng I-TEQ/m^3
	Hazardous waste incinerator	0.2 ng I-TEQ/m^3
European Union	Municipal waste and hazardous waste incinerators	0.1 ng I-TEQ/m^3
Japan	Municipal solid waste incinerator (>4 Ton/h)	0.1 ng I-TEQ/m^3
	Municipal solid waste incinerator (2–4 Ton/h)	1.0 ng I-TEQ/m^3
	Municipal solid waste incinerator (<2 Ton/h)	5.0 ng I-TEQ/m^3
Hong Kong	Municipal solid waste incinerator	13 ng/m^3 (Total mass)
	Chemical waste treatment plants	0.1 ng I-TEQ/m^3
Canada	All incinerators	0.08 g I-TEQ/$m^{3.}$

14.6 Bioaccumulation of Dioxins/Furans

Human exposure to both dioxin and furan compounds is mainly through the food chain. The dairy products and aquatic seafood are the major sources of bioaccumulated products that happen to intrude the food chain of humans. The hydrophobic nature of dioxins and furans facilitates to form small particulate matter in both aquatic and other water resources. Dioxins and furans released as unintentional by-products that have an immediate effect on land and water thereby affect the ecosystem and human health.

14.6.1 Terrestrial Ecosystem

Out of all the sources, food exposure becomes the predominant source of toxic elements to humans in the terrestrial ecosystem. The main reason behind this scenario is that the concentration of abundant nutrients in each level of the food pyramid is different. Since both dioxins and furans are highly lipid-soluble, stable and less biodegradable, they reach the topmost part of the pyramid instantly. In terrestrial ecosystems, one of the main concerns is dairy products. Dioxins and furans emitted by incinerators, fly-ash machines, cement kilns, etc. are found to be less than 0.1–100 ng/m^3. Particles of this size are easily deposited on the plants, grass, weed and even soil because of certain climatic conditions such as precipitation and atmospheric currents. In vitro bioaccessibility of dioxins and furans from soil matrix within the human gastrointestinal tract ranged from 34.3% to 62.1% (Roberts et al. 2019). Cockerham and Young (1983) reported that the beach mice (*Peromyscus polionotus*) showed levels of 540–1300 ng/Kg TCDD in liver tissues. Young et al. (1976) studied the contamination levels in a reptile, *Cnemidophorus sexlineatus*, and estimated the levels of dioxins and furans to be around 360 ng/Kg in the visceral mass and 370 ng/Kg in the trunk of the reptile. Hryhorczuk et al. (1981) studied the contamination of dioxins and furans in grazing horse cattle and found levels over 165 ng/Kg in fat tissues and 57 ng/Kg in liver tissues. Cow grazing in an outside environment is directly exposed to such toxic chemicals contaminating their feed such as grass and hay. An amount of 1–50 pg TEQ/g (level of contamination) of dioxins/furans is directly ingested into the system of a higher organism. After ingestion, the gastrointestinal absorption of dioxins and furans by the animal takes place, thus resulting in a very low absorption rate. Generally, half-life times of dioxins and furans in cows are very low because lactation is the only route of excretion; moreover, the distribution of dioxins and furans throughout the body of cows is very high since it directly deposits on the adipose tissues of cows. Piskorska-Pliszczynska et al. (2017) reported that sugar beet pellets are the main source for dioxin and furans contamination in cow's milk. Dioxin and furan contamination has the ability to increase the chromosomal abnormalities and fragility in sheep (Perucatti et al. 2006), cow (Di Meo et al. 2010) and buffalo (Genualdo et al. 2012). Meat outlets in France revealed a detectable range of dioxins and furans to be around <1 pg TEQ/g fat. Similarly, in Austria, the dioxin and furan level goes up to 69 pg TEQ/g fat in cow's milk where the location is very close to a copper smelter. When compared with the bovine fat, the concentration of dioxins and furans in human fat is nearly 10 times higher. In vivo studies of dioxin and furan contamination on buffaloes reported 1,2,3,7,8-PCDD, 2,3,4,7,8-PCDF, 2,3,7,8-TCDD and 1,2,3,6,7,8-HCDD as the major contributors of TEF (Chirollo et al. 2018). Schuhmacher et al. (2019) compared the dioxin TEQs of NATO and WHO with that of the human breast milk TEQ which was significantly independent and moving in a decreased trend. Breast milk of humans has been observed to contain nearly 10–30 pg TEQ/g. From 2008 to 2011, dioxin and furan concentration in human breast milk was found to decrease in Canada (Rawn et al. 2017). Further, dioxin and furan contamination in human breast milk is higher in Europe than in North

Table 14.6 Dioxins and furans in human adipose tissue (ng/Kg wet tissue) in various countries in 1989

Congener	Countries						
	United States	Japan	Germany	Sweden	Canada	North Vietnam	South Vietnam
2,3,7,8-TCDD	7.2	9.0	150.0	3.0	6.4	<2	28.0
1,2,3,7,8-PCDD	11.1	15.0	19.2	10.0	10.0	<2	15.0
1,2,3,6,7,8-HCDD	96	70.0	77.0	15.0	81.0	11	100.0
1,2,3,7,8,9-HCDD	–	12.0	9.4	4.0	–	–	–
1,2,3,4,6,7,8-HCDD	164	77.0	56.0	97.0	135.0	28.0	178.0
Octa-CDD	707	230.0	267.0	414.0	830.0	104.0	1256.0
2,3,7,8-TCDF	–	9.0	0.9	3.9	–	–	–
1,2,3,7,8-PCDF	14.3	25.0	44.0	54.0	15.0	13.0	21.0
1,2,3,4,7,8-HCDF	–	15.0	10.0	6.0	–	–	–
1,2,3,6,7,8-HCDF	31.3	14.0	6.7	5.0	16.0	13.0	58.0
2,3,4,6,7,8-HCDF	–	8.0	3.8	2.0	–	–	–
1,2,3,4,6,7,8-HCDF	16.5	–	19.5	11.0	30.0	7.0	29.0
Octa-CDF	–	–	1.0	4.0	–	–	–

TCDD tetrachlorodibenzo-p-dioxin, *PCDD* polychlorinated dibenzo-p-dioxin, *HCDD* hexachlorodibenzo-p-dioxin, *CDD* chlorinated dibenzo-p-dioxin, *TCDF* tetrachlorodibenzo-p-furan, *PCDF* polychlorinated dibenzo-p-furan, *HCDF* hexachlorodibenzo-p-furan, *CDF*-chlorinated dibenzo-p-furan

America. Few other studies done between 1980 and 1990 show that the adults ingest around 150–300 pg/TEG/day on a median scale of around 2.3 pg TEQ/day, a maximum amount being 4 pg TEQ/Kg/day. The serum dioxin/furan levels among Michigan past and current workers (The Dow Chemical Company) had little or no impact of dioxin- and furan-contaminated sites; however, PCB 126 exhibited significant effect (Burns et al. 2008). Interestingly, a correlation with age and body fat with the workers exposed to dioxins and furans contamination was observed. There is very few information related to dioxin and furan contamination of human tissues mainly because of the complications and difficulties in sample collection and tracing back of source contamination. The ranges of contamination of both dioxins and furans are similar in developing as well as developed countries. The standard values that were recorded in several countries in 1989 in the human adipose tissue are listed in Table 14.6.

This includes several factors such as the number of toxicants present in the environment, bioaccumulation in the food chain, the bioavailability of such toxicants after absorption process metabolic changes that happen within humans. All these factors totally combine to form the bioaccumulation level in human tissues. Notably, once the toxicants get released into the environment, it directly attaches itself to the food sources, thereby entering the food chain of humans, an important mechanism of bioaccumulation in terrestrial ecosystems.

14.6.2 Aquatic Ecosystem

According to the USEPA, even a low concentration of dioxins and furans is highly lethal to aquatic organisms. It is estimated that the aquatic life accumulates such toxic elements in their body near the vicinity of dioxin- and furan-related industries. Edible parts of certain fish varieties such as catfish, yellow perches and suckerfish from Saginaw Bay, Michigan, United States, were estimated for the accumulation of dioxins and furans which was around 4.0–695 ng/Kg. It was reported that a certain type of fish variety called "bottom feeder fish" accumulated more dioxins and furans because it directly feeds on the adsorbed contaminants in water. Dioxins and furans were also targeted several species of crabs. A mean concentration level of 990 pg/g was observed in hepato-pancreas of crabs in Sweden which was due to the effluent discharge from the paper industry. One of the major congeners responsible for contamination of the aquatic ecosystem is later found to be 2,3,7,8– PCDD/PCDF. The acute and chronic levels of concentration are estimated to be 0.01 μg/L and 0.001 μg/L, respectively. Thompson et al. (1992) reported the elevated levels of dioxins and furans in shellfish and fish varieties in Australia. The overall predicted bioaccumulation factor in aquatic life is estimated to be around 3000–900,000, but the measured value was around 390–13,000. Assefa et al. (2019) investigated about the aquatic contamination of dioxins/furans in several species of Atlantic herring fishes using statistical modelling approach and concluded that the thermal sources were the biggest toxicants in herring fishes of the Baltic Sea. Biomagnification of dioxins/furans in lipid content of aquatic fish in China was found to have positive significant correlation on adverse health effects in humans who consume high-fat-content fish varieties (Zhou et al. 2019). Recently, Bartalini et al. (2019) reported inceptive immunosuppression of all sperm whales in the Mediterranean Sea that surpassed the threshold of 210 pg WHO-TEQ/g l.w.

14.7 Health Effects in Humans

High exposure to dioxin/furan compounds can result in various diseases of several effects depending on many factors. These factors include dosage of exposure, sex of the individual, duration of exposure and method of contact with the contaminants. Dioxins/furans enter into the human system by food chain through dairy products such as milk, meat, fish and eggs and are accumulated in the system for a very long

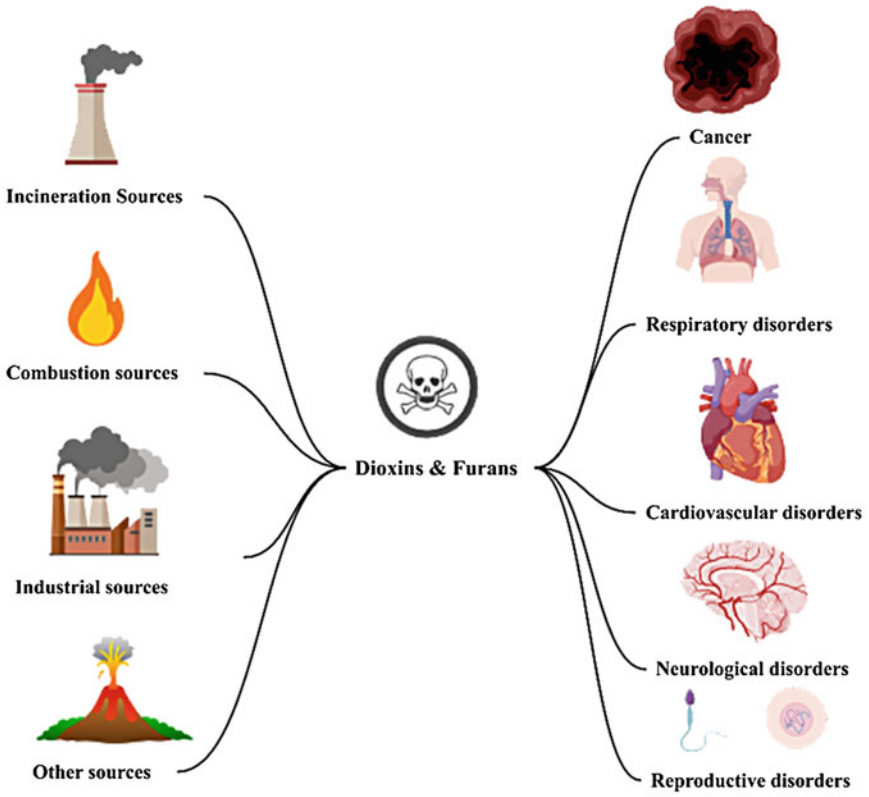

Fig. 14.2 Schematic representation of sources of dioxins/furans and its impact on humans

period. This subsequently leads to several complex diseases in humans in the form of neurodegenerative disorders, weakened immune system, kidney malfunction, skeletal deformities, liver abnormalities, heart disorders, reproductive impairments and sexual disorders. A health report from WHO suggests that more than 90% of the bioaccumulated dioxins/furans come from food ingestion. A schematic representation of the sources of dioxins and furans and possible disorders of such contamination is given in Fig. 14.2.

14.7.1 Cancer

Dioxins and furans are considered to be one among the deadliest carcinogens to humans according to a report from the WHO report. They are classified as level 1 carcinogen ever known to the history of mankind. 2,3,7,8-TCDD is the most studied congener of all compounds known to humans. The USEPA classifies this compound as the "strongest known carcinogen" and also as the "complete

carcinogen" because even a very small dose can induce cancers. The main target organ for this compound is studied to be liver, whereas other tissues such as thyroid, lung and oral cavity were also found to be affected by cancer. The onset of cancer because of dioxins and furans is almost 50% dependent on the sex of the organism. In a standard hepatic carcinogenic study with mice and rats, male mice were most affected by cancer, and on the other hand, female rats were most affected by cancer. There are also several epidemiological case studies which reported the development of cancer because of dioxins and furans contamination. One such study was done with the population of Seveso, Italy, where the people were accidentally exposed to remarkable doses of dioxins and furans in the year 1976. These people were exposed to dioxins and furans nearly 100–1000 times compared with the general population. Several types of cancers such as myeloma, lymphoma, sarcoma and liver cancer were seen to be predominant among the groups of tested people of Seveso. In general population, zero or no cases were seen attributing to dioxins and furans exposure. There are several biochemical receptors in the human body that are majorly affected by dioxins and furans. These include glucose transporter proteins, vitamin C uptake, lipoprotein lipases, low-density lipoprotein receptor and insulin secretion receptor.

The mechanism of action of both dioxins and furans is that they directly change or modify the key protein kinase activity by activating the mitotic signals. This eventually modifies the nuclear transcription factors, thereby altering the primary response genes through receptor-mediated mechanisms. The main role of such nuclear transcription factors includes regulation of nutritional indexes and protection of the hormone-sensitive genes. Besides this, dioxins and furans act on several enzymes in the body such as cytochromes, estrogen receptors, interleukins and cytokines. This leads to cellular oxidative stress and blockage in growth factors. This ultimately leads to apoptosis which thereby results in the death of healthy cells. Estrogen receptor-positive cases of breast cancer were directly associated with the long-term airborne exposure of dioxins/furans (Danjou et al. 2019). Another mechanism by which dioxins and furans cause cancer effects in humans is by inducing both cell proliferation and cell differentiation which leads to hypoplasia, hyperplasia, metaplasia and neoplasia. All these forms of abnormalities are directly linked to several types of cancers including Hodgkin disease, non-Hodgkin disease and sarcoma. Effects of one of the most toxic forms of dioxin, TCDD, were studied on rodents, which showed the development of several forms of tumours in thyroid, skin, liver, lung, oral cavity and other tissues. It directly suppresses the immunity, indirectly causing the carcinogenic effects. Tests conducted on animals are more evident than that of humans that TCDD has the most carcinogenic effect among all congeners of dioxin and furan families.

Xu et al. (2016) provided detailed epidemiological evidence about the carcinogenic effects of TCDD on the human hematopoietic system through several types of cancers. The aryl hydrocarbon receptor mechanism of action by dioxins and furans is the most accepted mechanism by which dioxins and furans cause carcinogenic effects. Similarly, dioxins are known to upregulate the enzymes which regulate the metabolic activity of several drugs which leads to an imbalance in hormone secretion. Wimmerová et al. (2016) assessed the human risk associated with dioxin

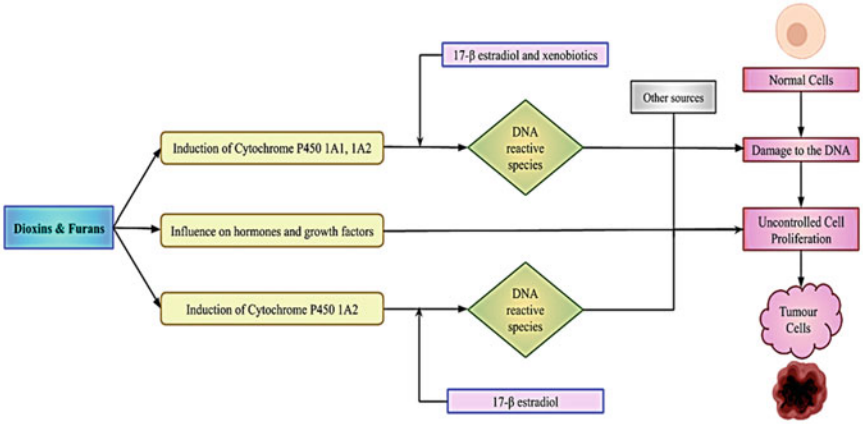

Fig. 14.3 Mechanism of tumour cell generation by dioxins/furans

exposure in terms of thyroid volume, FT4 serum level, cytochrome P450 1A1 and 1B1 expression and derived the relative effect potency in humans. The mechanism of tumour cell generation by toxicants such as dioxins and furans is represented diagrammatically in Fig. 14.3. Recently, Silveira et al. (2019) demonstrated the protective effect of resveratrol, chemoprotective activity, in rats exposed in utero to TCDD.

14.7.2 Respiratory Disorders

Several respiratory diseases are associated with the contamination of both dioxins and furans. Since the main source of contamination is through incineration and combustion of toxic materials, it is to be noted that the fly ash and smoke produced from such sources are the chief causal agents of respiratory ailments. Commonly seen respiratory problems of such smoke- and fly-ash-related sources are an allergy, asthma, nasal congestion, laboured breathing, wheezing, cough and itchy and watery nose. Since the toxic substances in the atmosphere directly reach the human body through respiratory air, the toxicants have the highest chance of reaching the lungs, thereby causing inflammation or damage to the lungs. The toxic substances that enter into the lungs have the capacity to create acute or chronic lung cancer. Kuratsune et al. (1971) studied the accidental exposure to PCB contaminated cooking oil during the late 1960s over 4000 people of Japanese and Taiwanese population. Several patients were reported to suffer from respiratory disorders such as damage in the nasal cavity and lungs along with several oil diseases. Not many studies have been performed on the respiratory system alone to estimate the effects of dioxin and furan contaminations.

14.7.3 Cardiovascular Disorders

Heart and its related organs are some among the main targets of toxic pollutants such as dioxins and furans. Several studies have been performed to estimate the damage it does to the cardiovascular system. Henríquez-Hernández et al. (2017) associated the persistence of cardiovascular diseases to the levels of dioxins/furans through contamination from various dietary sources of food. Kopf and Walker (2009) reported the reduced heart size, reduced blood flow to the heart and reduced contraction rate in the heart in fish model studies. Thinner ventricle walls, extensive cardiac dilation and reduced responsiveness to chronotropic stimuli were observed in the chicken embryo. Cardiocyte proliferation and cardiovascular apoptosis was commonly seen in all animal models exposed to higher levels of dioxins/furans.

Upregulation of several genes such as atrial natriuretic peptide (ANP), myosin heavy chain beta (MHC-β), and endothelin 1 (ET-1) resulted in heart failure as well as cardiac hypertrophy in mice models exposed to high doses of dioxins/furans (Fujisawa et al. 2019). Exposure to dioxins and furans in humans has also resulted in hypertension and cardiovascular diseases. Thackaberry et al. (2005) elaborated about the heart-related ailments in mammals using mice models. The disruption of aryl hydrocarbon receptors (AhR receptors) is the mechanism by which the toxicants cause human congenital heart disorder. The direct correlation between the amounts of exposure to body weight also plays an important role in the onset of several cardiovascular diseases. Studies have also shown that the human embryo is less sensitive to cardiovascular diseases which are induced by both dioxins and furans, but the developmental exposure will result in serious cardiovascular diseases.

14.7.4 Neurological Disorders

Several forms of dioxins and furans have known to cause multiple neurodegenerative disorders in humans as well as wildlife and such diseases, which have been studied over the past two decades. The direct target of dioxin compounds such as 2,3,7,8-TCDD decreases the effect of reactive oxygen species, thereby inhibiting the proliferation of nervous system cells. Because of its extensive usage as pesticides, hydraulic fluids, flame retardants, etc., dioxins and furans become easily accumulated in the food chain and biomagnified easily. During the early 1970s, the first study was carried out to understand the effects of dioxins and furans as a neurotoxic agent since there was acute and chronic exposure of chlorinated pesticides in the environment. After several studies, it is now established that dioxins and furans have adverse effects on attacking the central nervous system and to have neurobehavioral changes.

Fonnum and Mariussen (2009) reported the neurotoxic mechanisms (oxidative stress, calcium homeostasis disturbance and neurotransmitter transport) associated with environmental exposure of dioxins and furans. These chemicals directly target and induce the phospholipase A2 mobilization and induce protein kinase C, thereby creating oxidative stress to the nervous system (Fonnum and Mariussen 2009). They

also change the astroglial intracellular Ca^{2+} and glutathione (GSH) levels, decrease glutamine synthetase immunoreactivity, and thereby, maintenance of the pH is lost. Dioxins and furans also are known to cause peripheral nerve damage by targeting the ROS system by suppressing the basal generation and inhibiting the proliferation of neuronal cells which is being investigated with human neuroblastoma cells. Being a lipophilic agent, TCDD directly accumulates in liver and fat tissues faster than that of the brain and central nervous system. This is in contrast with newborns and infants where the intoxication by TCDD is at a higher rate during lactation and gestation period. During the developmental stages of infant, serious neurotoxic diseases such as reduced neuronal calcium uptake, death of neurons, reduce neurotransmittance and cognitive defects are predominantly seen. This has been studied in extrahepatic tissues of mice and rats through the alteration of redox reaction balances. Even in this study, the ROS induction takes places which thereby leads to an increase in peroxidation reaction of lipid content and decrease in GSH content in several parts of tissues such as testis and liver. This correlates with the effect of TCDD on cell proliferation and reduction in the rate of uptake of thymidine to the cells.

Ames et al. (2019) reported about the association between exposure of dioxins/furans to the neuropsychological functioning of adolescent children and found no significant correlation between the two factors. Dioxins and furans entered into the body cannot be washed out easily by the human body. Women have two different methods of getting rid of it, one being the placental method and the other being lactation. But men, on the other hand, do not have any methods for getting rid of such toxicants, thus leading to bioaccumulation at a much faster rate than women.

14.7.5 Reproductive Disorders

Several animal models have been studied to report the effects of TCDD on both reproductive diseases and developmental studies. The whole dioxin and furan family of compounds has effects on gamete production, size of reproductive organs, number of spermatozoa, fertilization processes, number of ovules produced during the follicular phase of females, etc. The effect of fertility in males has been in fewer studies, but in females, the effect of TCDD has a major impact on fertility during the prenatal stages. The major mechanism by which the dioxin compounds such as TCDD acts on the reproductive and sexual system is that it targets the hypothalamic-pituitary axis, thereby inhibiting the functional signals of the system. Studies were carried out on rodents whose hypothalamus was affected which resulted in the decreased sexual activity. Several developmental delays during the differentiation of trophectoderm were also observed in such rodents. There was also a negative response in the action of several growth factors such as transforming growth factor-beta (TGF-ß) which is majorly responsible for the organogenesis process. The same effect has been seen in human fetal tissue cultures where the signs of organogenesis are absent or delayed. In a different study with the continuous exposure of TCDD on female rhesus monkeys, a serious reproductive disorder, endometriosis, was observed.

High exposure of TCDD can also result in continuous abortions in females which are observed even now in parts of Seveso, Italy. Several conditions based on the production of sperm in males such as oligospermia, asthenospermia and teratozoospermia are still observed in few populations in Seveso, Italy. Breastfeeding is one among the major mechanisms by which an offspring gets exposed to dioxins and furans. One such study was conducted by Finnish group researchers. The mothers were also affected by impaired fertility and endometriosis. Few researchers in the Netherlands and Germany also concluded similar results of that of the Finnish group of researchers. Few epidemiological studies were also conducted based on environmental exposure to the human fetus and found out that even without breastfeeding, the fetus was very vulnerable to both dioxins and furans from the external atmosphere. Gray et al. (1997a, b) and Mably et al. (1992a) reported the effects of TCDD and other such chemicals in the reproductive development of laboratory animals such as mice and rats. The animals showed signs of decreased sperm count; vaginal thread reduced accessory gland weight and delayed puberty.

Hale et al. (2019) assessed the contamination levels of dioxins/furans in American alligator embryos and concluded that the expression of several genes related to embryo–yolk mass ratio and embryo mass was associated with the dioxin/furan exposure. Different studies were performed at different dosage levels of exposure of TCDD and concluded the detection of several types of sexual deformities in both mice and rats. Hamm et al. (2000) reported about the lactation effects and deformities in rats were due to the exposure of about 2.0 g TEQ/kg. The decrease in sperm count in Holtzman rats was observed by Mably et al. (1992b) at a significantly lower dose of about 0.5 g/kg. In contrary, Faqi et al. (1998) reported the increased sperm production on the exposure of about 100 g PCB77/kg along with an increase in the size of testicles. Manikkam et al. (2012) demonstrated TCDD exposure on male Hsd:Sprague Dawley rats promoted transgenerational effects and sperm epimutations on male reproduction. Several reproductive disorders such as decreased fertility, lower daily sperm production, and low testosterone levels were found in Sprague Dawley rats which were exposed to higher doses of furans (Rehman et al. 2019). Foster et al. (2009) demonstrated utero exposure of TCDD induced changes in epididymal sperm; however, spermatogenesis was not affected. Pereg et al. (2001) reported the effects of intermediate reactive compounds that are metabolized from dioxin and furan contamination which rapidly causes secondary sexual deformities. Egeland et al. (1994) reported decreased testosterone and increased gonadotropin levels in several workers of the NIOSH cohort who were associated with the higher concentrations of dioxin compounds such as TCDD. In 1968, women were accidentally exposed to dioxin- and furan-contaminated rice oil in Japan led to reducing the birth weight and hyperpigmentation of Yusho disease (Tsukimori et al. 2012). During the time period 1977–1984, a test was conducted on 239 men and 296 women in Seveso, Italy, and reported that the sex ratio was changed to an excess of females over males. This corresponds to the TCDD contamination in that area during that period. This test was conducted to both parents who were exposed to high doses of TCDD during the exposure. There was also an

increase in the probability of female births (p-value = 0.008) which was associated with the higher concentrations of TCDD in the serum samples of fathers. Though such reports have been made, biological explanation of such occurrences has not yet been made. Michalek et al. (1998) and Rogan et al. (1988) studied a similar type of pattern in other population where the dosage of TCDD exposure was much lower than in Seveso, Italy. A retrospective cohort study from Seveso Women's Health Study on TCDD exposure and reproductive health over past 30 years reported no association of serum TCDD with pregnancy, spontaneous abortion, gestation length and fetal growth (Wesselink et al. 2014). Besides this, there have not been major studies relating to the concentration of dioxin and furan exposure to the time of pregnancy.

14.8 Future Considerations and Conclusions

Dioxins and furans being defined as persistent, possessing characteristics of bioaccumulation, being highly stable and having a very high half-life, with a high range of atmospheric transport, are likely to produce several adverse effects on human health as well as the environment. Keeping in pace with the scientific advancements, it is possible to assess the risk associated with dioxin and furan incorporation into the environment. It is high time that the human associate the regulatory focus of emitted dioxins and furans along with the strategies to limit or stop emissions of such chemicals. A complete understanding and knowledge of formation and mechanism of action of dioxins and furans will help us a long way in battling effects that have on the environment as well as humans. Being identified as POPs, many countries including Hungary, Czech Republic, Ukraine, Slovakia, Slovenia and Croatia have already agreed to limit the total annual emissions of identified POPs, few among them being dioxins and furans. These countries have agreed to take effective measures under the circumstances of abnormal levels of POP emission with a set reference value. The year 1990 is set as a reference value year; the emission levels at any point of time should be less than that of the emissions that happened during the year 1990. Many of the Asian countries including India have taken an extensive measurement in reducing the emission levels of POPs. Such toxic and extremely harmful chemical compounds should be eliminated using existing advanced technologies to provide a healthy and better environment for the future generation.

14.8.1 Better Understanding and Identification of Sources

Over the past few decades, there have been several cases of dioxin and furan contamination into the environment. During the early stages, it was due to the incineration of chlorinated compounds. Later, this contamination was due to the construction of individual household incinerators which led to a rapid increase in the levels of dioxins and furans in the environment. Later during the same period,

control of such constructions as well as metal processing of chlorine compounds have reduced much of the contamination. In view of such a matter, an analysis was performed by a European data agency reporting the creation of herbaria including the sedimentary samples from all the contaminated sites. This would be helpful in estimating the nature of sources over different periods of time and assessing them according to different environmental patterns. The agency also suggested that the government bodies would get access to contaminated samples of historical accidents. This led to the establishment of the Soil Monitoring Agency (SMA) to observe and maintain different sources of contamination of toxic chemicals or POPs including dioxins and furans.

14.8.2 Understanding the Mechanism of Action

Effective understanding of the transfer of dioxins and furans from soil to plants, soil to water and soil to air needs to be done carefully. Several agencies such as The French Institute for Agronomy Research (INRA), The French National Center for Scientific Research (CNRS) and Bureau for Geology and Mining Research (BRGM) have studied the effect of microorganisms in degrading dioxins and furans. Such areas of research should be appreciated and given more importance.

14.8.3 Development of New Techniques to Identify Contamination

Gas chromatography-mass spectroscopy (GC-MS) is a widely used assay method for reference of dioxins and furans. Though being a highly sensitive method, the presence of more than 210 different compounds and maximum variability between different laboratories, it has become extremely difficult to interpret the results with accuracy. The development of new biological and analytical assay methods for identification of dioxins and furans would facilitate the survey methods to be performed easily.

14.8.4 Development of Toxicological and Epidemiological Studies

The dose–response value of each compound of dioxins and furans needs to be understood and studied in order to understand the effects on humans and the environment. Several toxicokinetic and toxicodynamic methods are established by scientific advisory groups to estimate the cut-off limit of each compound. Similarly, epidemiological studies are necessary to assess the relation and distribution pattern of diseases related to dioxin and furan contamination.

With all the scientific advancements and technologies, it becomes easier to study the impact and its effects on humans and the environment. The most important effect is the poisoning of the food chain from the contaminated sites of the food supply. Similarly, animals and other organisms face the threat due to such harmful

chemicals. Every effort should be made to minimize the exposure of such contaminants to the animals and the environment. Several ways of accomplishing this are building a modern scientific process to prevent the release of such contaminants to the outside environment and also biological methods, including the creation of hybrid organisms such as bacteria, fungi and yeast for the elimination of such toxic components. Thus, the development of high throughput technologies in the near future will certainly reduce the effects of such components in the environment.

Acknowledgements Authors thank Prof. M. Sivanandham, Secretary, SVEHT and SVCE Management for their support and encouragement.

References

Ames J, Warner M, Siracusa C, Signorini S, Brambilla P, Mocarelli P, Eskenazi B (2019) Prenatal dioxin exposure and neuropsychological functioning in the Seveso Second Generation Health Study. Int J Hyg Environ Health 222(3):425–433

Assefa A, Tysklind M, Bignert A, Josefsson S, Wiberg K (2019) Sources of polychlorinated dibenzo-p-dioxins and dibenzofurans to Baltic Sea herring. Chemosphere 218:493–500

Bartalini A, Muñoz-Arnanz J, Marsili L, Mazzariol S, Fossi MC, Jiménez B (2019) Evaluation of PCDD/Fs, dioxin-like PCBs and PBDEs in sperm whales from the Mediterranean Sea. Sci Total Environ 653:1417–1425

Boda H, Nghi TN, Nishijo M, Thao PN, Tai PT, Van Luong H, Anh TH, Morikawa Y, Nishino Y, Nishijo H (2018) Prenatal dioxin exposure estimated from dioxins in breast milk and sex hormone levels in umbilical cord blood in Vietnamese newborn infants. Sci Total Environ 615:1312–1318

Bruce-Vanderpuije P, Megson D, Jobst K, Jones GR, Reiner E, Sandau CD, Clarke E, Adu-Kumi S, Gardella JA Jr (2019) Background levels of dioxin-like polychlorinated biphenyls (dlPCBs), polychlorinated, polybrominated and mixed halogenated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs, PBDD/Fs & PXDD/Fs) in sera of pregnant women in Accra, Ghana. Sci Total Environ 673:631–642

Burns CJ, Collins JJ, Budinsky RA, Bodner K, Wilken M, Rowlands JC, Martin GD, Carson ML (2008) Factors related to dioxin and furan body levels among Michigan workers. Environ Res 106(2):250–256

Chirollo C, Ceruso M, Pepe T, Vassallo A, Marrone R, Severino L, Anastasio A (2018) Levels and congeners distribution of dioxins, furans and dioxin-like PCBs in buffaloes adipose tissues sampled in vivo and milk. CyTA-J Food 16(1):1109–1114

Cockerham LG, Young AL (1983) Ultrastructural comparison of liver tissues from field and laboratory TCDD-exposed beach mice. In: Human and environmental risks of chlorinated dioxins and related compounds. Springer, Boston, pp 373–389

Conesa JA, Ortuño N, Abad E, Rivera-Austrui J (2016) Emissions of PCDD/Fs, PBDD/Fs, dioxin like-PCBs and PAHs from a cement plant using a long-term monitoring system. Sci Total Environ 571:435–443

Danjou AMN, Coudon T, Praud D, Lévêque E, Faure E, Salizzoni P, Le Romancer M, Severi G, Mancini FR, Leffondré K, Dossus L (2019) Long-term airborne dioxin exposure and breast cancer risk in a case-control study nested within the French E3N prospective cohort. Environ Int 124:236–248

Di Meo GP, Perucatti A, Genualdo V, Caputi-Jambrenghi A, Rasero R, Nebbia C, Iannuzzi L (2010) Chromosome fragility in dairy cows exposed to dioxins and dioxin-like PCBs. Mutagenesis 26(2):269–272

Egeland GM, Sweeney MH, Fingerhut MA, Wille KK, Schnorr TM, Halperin WE (1994) Total serum testosterone and gonadotropins in workers exposed to dioxin. Am J Epidemiol 139 (3):272–281

EPA US (1999) National air toxics program: the integrated urban strategy. Fed Regist 64:38705–38740

Faqi AS, Dalsenter PR, Merker HJ, Chahoud I (1998) Reproductive toxicity and tissue concentrations of low doses of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in male offspring rats exposed throughout pregnancy and lactation. Toxicol Appl Pharmacol 150(2):383–392

Fonnum F, Mariussen E (2009) Mechanisms involved in the neurotoxic effects of environmental toxicants such as polychlorinated biphenyls and brominated flame retardants. J Neurochem 111 (6):1327–1347

Foster WG, Maharaj-Briceño S, Cyr DG (2009) Dioxin-induced changes in epididymal sperm count and spermatogenesis. Environ Health Perspect 118(4):458–464

Fujisawa N, Tohyama C, Yoshioka W (2019) Cardiotoxicity induced by 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure through lactation in mice. J Toxicol Sci 44 (7):505–513

Garner AJ, Pagano JJ (2019) Trends of polychlorinated dioxins, polychlorinated furans, and dioxin-like polychlorinated biphenyls in Chinook and Coho salmonid eggs from a Great Lakes tributary. Environ Pollut 247:1039–1045

Genualdo V, Perucatti A, Iannuzzi A, Di Meo GP, Spagnuolo SM, Caputi-Jambrenghi A, Coletta A, Vonghia G, Iannuzzi L (2012) Chromosome fragility in river buffalo cows exposed to dioxins. J Appl Genet 53(2):221–226

González N, Marquès M, Nadal M, Domingo JL (2018) Levels of PCDD/Fs in foodstuffs in Tarragona County (Catalonia, Spain): Spectacular decrease in the dietary intake of PCDD/Fs in the last 20 years. Food Chem Toxicol 121:109–114

Gou YY, Que DE, Chuang CY, Chao HR, Shy CG, Hsu YC, Lin CW, Chuang KP, Tsai CC, Tayo LL (2016) Dust levels of polybrominated diphenyl ethers (PBDEs) and polybrominated dibenzo-p-dioxins/furans (PBDD/Fs) in the Taiwanese elementary school classrooms: assessment of the risk to school-age children. Sci Total Environ 572:734–741

Gray LE Jr, Ostby JS, Kelce WR (1997a) A dose–response analysis of the reproductive effects of a single gestational dose of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in male Long Evans Hooded rat offspring. Toxicol Appl Pharmacol 146(1):11–20

Gray LE Jr, Wolf C, Mann P, Ostby JS (1997b) In uteroexposure to low doses of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin alters reproductive development of female Long Evans hooded rat offspring. Toxicol Appl Pharmacol 146(2):237–244

Hale MD, Bertucci EM, Rainwater TR, Wilkinson PM, Parrott BB (2019) The impact of maternally derived dioxins on embryonic development and hepatic AHR signaling in a long-lived apex predator. Chemosphere 229:489–499

Hamm JT, Sparrow BR, Wolf D, Birnbaum LS (2000) In utero and lactational exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin alters postnatal development of seminal vesicle epithelium. Toxicol Sci 54(2):424–430

Henríquez-Hernández LA, Luzardo OP, Zumbado M, Serra-Majem L, Valerón PF, Camacho M, Álvarez-Pérez J, Salas-Salvadó J, Boada LD (2017) Determinants of increasing serum POPs in a population at high risk for cardiovascular disease. Results from the PREDIMED-CANARIAS study. Environ Res 156:477–484

Hryhorczuk DO, Withrow WA, Hesse CS, Beasley VR (1981) A wire reclamation incinerator as a source of environmental contamination with tetrachlorodibenzo-p-dioxins and tetrachlorodibenzofurans. Arch Environ Health Int J 36(5):228–234

Hsu YC, Que DE, Gou YY, Tsou TC, Liu CK, Wang YL, Hou WC, Lin YH, Liu WY, Chao HR, Lee WJ (2018) National surveillance of 2, 3, 7, 8-substituted polychlorinated dibenzo-p-dioxins/furans in soil in Taiwan. Chemosphere 203:239–252

Hu J, Wu J, Xu C, Zha X, Hua Y, Yang L, Jin J (2019) Preliminary investigation of polychlorinated dibenzo-p-dioxin and dibenzofuran, polychlorinated naphthalene, and dioxin-like

polychlorinated biphenyl concentrations in ambient air in an industrial park at the northeastern edge of the Tibet–Qinghai Plateau, China. Sci Total Environ 648:935–942
Karstensen KH (2008) Formation, release and control of dioxins in cement kilns. Chemosphere 70 (4):543–560
Kopf PG, Walker MK (2009) Overview of developmental heart defects by dioxins, PCBs, and pesticides. J Environ Sci Health C 27(4):276–285
Kulkarni PS, Crespo JG, Afonso CA (2008) Dioxins sources and current remediation technologies-a review. Environ Int 34(1):139–153
Kuratsune M, Yoshimura T, Matsuzaka J, Yamaguchi A (1971) Yusho, a poisoning caused by rice oil contaminated with polychlorinated biphenyls. HSMHA Health Rep 86(12):1083
Li XD, Yan M, Chen T, Lu SY, Yan JH, Cen KF (2010) Levels of PCDD/Fs in soil in the vicinity of a medical waste incinerator in China: The temporal variation during 2007–2009. J Hazard Mater 179(1–3):783–789
Mably TA, Bjerke DL, Moore RW, Gendron-Fitzpatrick A, Peterson RE (1992a) In utero and lactational exposure of male rats to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin: 3. Effects on spermatogenesis and reproductive capability. Toxicol Appl Pharmacol 114(1):118–126
Mably TA, Moore RW, Goy RW, Peterson RE (1992b) In utero and lactational exposure of male rats to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin: 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood. Toxicol Appl Pharmacol 114(1):108–117
Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK (2012) Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. PLoS One 7(9):e46249
Matta EJ (2018) Pollution in the Uruguay-Argentina border: critical data analysis from two rivers and the pulp mill effluent. Int J Environ Health 9(1):84–109
Metelkova L, Zhakovskaya Z, Kukhareva G, Rybalko A, Nikiforov V (2019) Occurrence of PCDD/PCDFs, dioxin-like PCBs, and PBDEs in surface sediments from the Neva River and the Eastern Gulf of Finland (Russia). Environ Sci Pollut Res 26(8):7375–7389
Michalek JE, Rahe AJ, Boyle CA (1998) Paternal dioxin, preterm birth, intrauterine growth retardation, and infant death. Epidemiology 9:161–167
Mukerjee D (1998) Health impact of polychlorinated dibenzo-p-dioxins: a critical review. J Air Waste Manage Assoc 48(2):157–165
Nguyen HM, Tu BM, Watanabe M, Kunisue T, Monirith I, Tanabe S, Sakai S, Subramanian A, Sasikumar K, Pham HV, Bui CT (2003) Open dumping site in Asian developing countries: a potential source of polychlorinated dibenz-p-dioxins and polychlorinated dibenzofurans. Environ Sci Technol 37(8):1493–1502
Ortuño N, Lundstedt S, Lundin L (2015) Emissions of PBDD/Fs, PCDD/Fs and PBDEs from flame-retarded high-impact polystyrene under thermal stress. Chemosphere 123:64–70
Pemberthy D, Quintero A, Martrat MG, Parera J, Ábalos M, Abad E, Villa AL (2016) Polychlorinated dibenzo-p-dioxins, dibenzofurans and dioxin-like PCBs in commercialized food products from Colombia. Sci Total Environ 568:1185–1191
Pereg D, Tampal N, Espandiari P, Robertson LW (2001) Distribution and macromolecular binding of benzo [a] pyrene and two polychlorinated biphenyl congeners in female mice. Chem Biol Interact 137(3):243–258
Perucatti A, Di Meo GP, Albarella S, Ciotola F, Incarnato D, Jambrenghi AC, Peretti V, Vonghia G, Iannuzzi L (2006) Increased frequencies of both chromosome abnormalities and SCEs in two sheep flocks exposed to high dioxin levels during pasturage. Mutagenesis 21(1):67–75
Piskorska-Pliszczynska J, Maszewski S, Mikolajczyk S, Pajurek M, Strucinski P, Olszowy M (2017) Elimination of dioxins in milk by dairy cows after the long-term intake of contaminated sugar beet pellets. Food Addit Contam Part A 34(5):842–852
Psomopoulos CS, Bourka A, Themelis NJ (2009) Waste-to-energy: A review of the status and benefits in USA. Waste Manag 29(5):1718–1724

Quina MJ, Bordado JC, Quinta-Ferreira RM (2011) Air pollution control in municipal solid waste incinerators. The impact of air pollution on health, economy, environment and agricultural sources, pp 331–358

Rahman MM, Shon ZH, Ma CJ, Brown RJC, Pandey SK, Park CG, Bae IS, Sohn JR, Yoon HO, Kim KH (2014) Partitioning of dioxins (PCDDs/Fs) in ambient air at urban residential locations. Int J Environ Sci Technol 11(7):1897–1910

Rawn DF, Sadler AR, Casey VA, Breton F, Sun WF, Arbuckle TE, Fraser WD (2017) Dioxins/furans and PCBs in Canadian human milk: 2008–2011. Sci Total Environ 595:269–278

Rehman H, Ullah I, David M, Ullah A, Jahan S (2019) Neonatal exposure to furan alters the development of reproductive systems in adult male Sprague Dawley rats. Food Chem Toxicol 130:231–241

Ren Z, Zheng M (2009) Impacts of human activities on dioxins emissions at national scale. Chemosphere 76(6):853–859

Rezaei E, Farahani A, Buekens A, Chen T, Lu SY, Habibinejad M, Damercheli F, Moghadam SA, Gandomkar M, Bahmani A (2013) Dioxins and furans releases in Iranian mineral industries. Chemosphere 91(6):838–843

Rivera-Austrui J, Martínez K, Marco-Almagro L, Ábalos M, Abad E (2014) Long-term sampling of dioxin-like substances from a clinker kiln stack using alternative fuels. Sci Total Environ 485:528–533

Roberts SM, Lowney YW, Stuchal LD (2019) Bioaccessibility of polychlorinated dioxins and furans in soil from a Superfund site. Chemosphere 214:418–423

Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS, Wu YC, Yang D, Ragan NB, Hsu CC (1988) Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241(4863):334–336

Schuhmacher M, Mari M, Nadal M, Domingo JL (2019) Concentrations of dioxins and furans in breast milk of women living near a hazardous waste incinerator in Catalonia, Spain. Environ Int 125:334–341

Senthil Kumar K, Kannan K, Paramasivan ON, Shanmuga Sundaram VP, Nakanishi J, Masunaga S (2001) Polychlorinated dibenzo-p-dioxins, dibenzofurans, and polychlorinated biphenyls in human tissues, meat, fish, and wildlife samples from India. Environ Sci Technol 35 (17):3448–3455

Silveira LTR, de Mello Santos T, Camora LF, Pinho CF, Anselmo-Franci JA, Domeniconi RF, Justulin LA, Barbisan LF, Scarano WR (2019) Protective effect of resveratrol on urogenital sinus and prostate development in rats exposed in utero to TCDD (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin). Reprod Toxicol 83:82–92

Thackaberry EA, Nunez BA, Ivnitski-Steele ID, Friggins M, Walker MK (2005) Effect of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin on murine heart development: alteration in fetal and postnatal cardiac growth, and postnatal cardiac chronotropy. Toxicol Sci 88(1):242–249

Thompson GB, Chapman JC, Richardson BJ (1992) Disposal of hazardous wastes in Australia: implications for marine pollution. Mar Pollut Bull 25(5–8):155–162

Tsukimori K, Uchi H, Mitoma C, Yasukawa F, Chiba T, Todaka T, Hirata T, Fukushima K, Wake N (2012) Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease. Environ Int 38(1):79–86

Ueno D, Watanabe M, Subramanian A, Tanaka H, Fillmann G, Lam PK, Zheng GJ, Muchtar M, Razak H, Prudente M, Chung KH (2005) Global pollution monitoring of polychlorinated dibenzo-p-dioxins (PCDDs), furans (PCDFs) and coplanar polychlorinated biphenyls (coplanar PCBs) using skipjack tuna as bioindicator. Environ Pollut 136(2):303–313

Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M (2006) The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93(2):223–241

Wang LC, Hsi HC, Wang YF, Lin SL, Chang-Chien GP (2010) Distribution of polybrominated diphenyl ethers (PBDEs) and polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD/Fs) in municipal solid waste incinerators. Environ Pollut 158(5):1595–1602

Wang X, Ni Y, Zhang H, Zhang X, Chen J (2012) Formation and emission of PCDD/Fs in Chinese non-wood pulp and paper mills. Environ Sci Technol 46(21):12234–12240

Wesselink A, Warner M, Samuels S, Parigi A, Brambilla P, Mocarelli P, Eskenazi B (2014) Maternal dioxin exposure and pregnancy outcomes over 30 years of follow-up in Seveso. Environ Int 63:143–148

Wimmerová S, van den Berg M, Chovancová J, Patayová H, Jusko TA, van Duursen MB, Murínová ĽP, Canton RF, van Ede KI, Trnovec T (2016) Relative effect potency estimates of dioxin-like activity for dioxins, furans, and dioxin-like PCBs in adults based on cytochrome P450 1A1 and 1B1 gene expression in blood. Environ Int 96:24–33

Xu J, Ye Y, Huang F, Chen H, Wu H, Huang J, Hu J, Xia D, Wu Y (2016) Association between dioxin and cancer incidence and mortality: a meta-analysis. Sci Rep 6:38012

Yang L, Liu G, Zhu Q, Zheng M (2019) Small-scale waste incinerators in rural China: Potential risks of dioxin and polychlorinated naphthalene emissions. Emerg Contam 5:31–34

Young AL, Thalken CE, Arnold EL, Cupello JM, Cockerham LG (1976) Fate of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) in the environment: summary and decontamination recommendations (No. USAFA-TR-76-18). USAF Academy Colorado Springs

Zhou S, Zhu H, Huang S, Zhou J, Zhang S, Wang C (2019) Biomagnification and risk assessment of polychlorinated biphenyls in food web components from Zhoushan fishing ground, China. Mar Pollut Bull 142:613–619