Environment International 139 (2020) 105731

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Severe dioxin-like compound (DLC) contamination in e-waste recycling areas: An under-recognized threat to local health

Qingyuan Dai[a], Xijin Xu[b], Brenda Eskenazi[c], Kwadwo Ansong Asante[d], Aimin Chen[e], Julius Fobil[f], Åke Bergman[g,h,i], Lesley Brennan[j], Peter D. Sly[k], Innocent Chidi Nnorom[l], Antonio Pascale[m], Qihua Wang[a], Eddy Y. Zeng[a], Zhijun Zeng[b], Philip J. Landrigan[n], Marie-Noel Bruné Drisse[o], Xia Huo[a,*]

[a] Guangdong Key Laboratory of Environmental Pollution and Health, School of Environment, Jinan University, China
[b] Laboratory of Environmental Medicine and Developmental Toxicology, Shantou University Medical College, China
[c] School of Public Health, University of California, Berkeley, USA
[d] CSIR Water Research Institute, Accra, Ghana
[e] Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, USA
[f] School of Public Health, University of Ghana, Ghana
[g] Department of Environmental Science, Stockholm University, Sweden
[h] Department of Science and Technology, Örebro University, Sweden
[i] College of Environmental Science and Engineering, Tongji University, China
[j] Department of Obstetrics and Gynaecology, University of Alberta, Canada
[k] Child Health Research Centre, University of Queensland, Australia
[l] Department of Pure and Industrial Chemistry, Abia State University, Nigeria
[m] Department of Toxicology, University of the Republic, Uruguay
[n] Department of Biology, Boston College, USA
[o] Department of Environment, Climate Change and Health, World Health Organization, Geneva, Switzerland

ARTICLE INFO

Handlng Editor: Adrian Covaci

Keywords:
Dioxin-like compound
Toxicity
E-waste recycling site
Human exposure
Health risk

ABSTRACT

Electrical and electronic waste (e-waste) burning and recycling activities have become one of the main emission sources of dioxin-like compounds (DLCs). Workers involved in e-waste recycling operations and residents living near e-waste recycling sites (EWRS) are exposed to high levels of DLCs. Epidemiological and experimental *in vivo* studies have reported a range of interconnected responses in multiple systems with DLC exposure. However, due to the compositional complexity of DLCs and difficulties in assessing mixture effects of the complex mixture of e-waste-related contaminants, there are few studies concerning human health outcomes related to DLC exposure at informal EWRS. In this paper, we have reviewed the environmental levels and body burdens of DLCs at EWRS and compared them with the levels reported to be associated with observable adverse effects to assess the health risks of DLC exposure at EWRS. In general, DLC concentrations at EWRS of many countries have been decreasing in recent years due to stricter regulations on e-waste recycling activities, but the contamination status is still severe. Comparison with available data from industrial sites and well-known highly DLC contaminated areas shows that high levels of DLCs derived from crude e-waste recycling processes lead to elevated body burdens. The DLC levels in human blood and breast milk at EWRS are higher than those reported in some epidemiological studies that are related to various health impacts. The estimated total daily intakes of DLCs for people in EWRS far exceed the WHO recommended total daily intake limit. It can be inferred that people living in EWRS with high DLC contamination have higher health risks. Therefore, more well-designed epidemiological studies are urgently needed to focus on the health effects of DLC pollution in EWRS. Continuous monitoring of the temporal trends of DLC levels in EWRS after actions is of highest importance.

Abbreviations: DLC, dioxin-like compound; e-waste, electrical and electronic waste; EWRS, e-waste recycling site; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; DL-PCB, dioxin-like polychlorinated biphenyl; PBDD/F, polybrominated dibenzo-*p*-dioxin and dibenzofuran; PXDD/F, mixed halogenated dibenzo-*p*-dioxin and dibenzofuran.; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; AhR, aryl-hydrocarbon receptor; TEQ, toxic equivalent; TEF, toxic equivalency factor; dw, dry weight; PeCDF, pentachlorodibenzofuran; bw, body weight; SWHS, Seveso Women's Health Study; TSH, thyroid stimulating hormone; T_4, thyroxine; T_3, triiodothyronine; BMI, body mass index

* Corresponding author at: Laboratory of Environmental Medicine and Developmental Toxicology, School of Environment, Jinan University, Guangzhou 511443, China.
E-mail address: xhuo@jnu.edu.cn (X. Huo).

https://doi.org/10.1016/j.envint.2020.105731
Received 22 November 2019; Received in revised form 7 April 2020; Accepted 7 April 2020
Available online 18 April 2020

1. Introduction

With the rapid development of the economy and technology, the replacement cycle of electronic products is getting shorter, which has resulted in electrical and electronic waste (e-waste) growing at an alarming rate, threatening the environment and human health (Heacock et al., 2016; Awasthi et al., 2018; Kumar et al., 2017; Bakhiyi et al., 2018; Parajuly et al., 2019; Pascale et al., 2018; Xu et al., 2015). The Global E-waste Monitor 2017 shows that the total amount of the world's e-waste generation in 2016 reached 44.7 million tons, on average 6.1 kg per inhabitant (Balde et al., 2017). It is reported that 80% of e-waste generated globally has been treated informally (Balde et al., 2017), especially in developing countries of Asia and Africa (Breivik et al., 2014), including the cities of Guiyu, Qingyuan, and Taizhou, China (Chan et al., 2007; Leung et al., 2006; Wen et al., 2009; Zhang et al., 2017b); Accra, Ghana (Tue et al., 2019; Wittsiepe et al., 2015); Bengaluru and Delhi, India (Chakraborty et al., 2018; Karri et al., 2008); Lagos, Nigeria (Iwegbue et al., 2019); and Trang Minh and Bui Dau, Vietnam (Kincaid, 2019; Tue et al., 2010) (Fig. 1). China once received the largest share of e-waste from around the world (Zhang et al., 2012a), and has surpassed the United States to become the world's largest producer of e-waste (Zeng et al., 2016). After the ban on the import of foreign solid waste effective 1st January 2018 (Fu et al., 2018), predominant sources of e-waste in China have changed to domestic generation. This move leaves a potential for the South Asian and African regions, especially India, to receive and recycle e-waste (Asante et al., 2019; Garg and Adhana, 2019).

Primitive crude recycling processes in informal e-waste recycling sites (EWRS) (unregulated, unregistered, and low-technology units) result in the environmental release of dioxin-like compounds (DLCs) (Ni et al., 2010; Liu et al., 2008; Vaccari et al., 2019; Leung, 2019). The term "DLCs" is a general name for structurally and chemically related planar aromatic hydrocarbons with the capability of binding to the aryl-hydrocarbon receptor (AhR) and dioxin-like toxicity (van den Berg et al., 2006, 2013). The most toxic DLCs include 17 congeners of 2,3,7,8-polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) and 12 dioxin-like polychlorinated biphenyls (DL-PCBs) (WHO, 2016; van den Berg et al., 2006). 2,3,7,8-Substituted polybrominated and mixed halogenated dibenzo-*p*-dioxins and dibenzofurans (PBDD/Fs and PXDD/Fs) have chemical structures similar to PCDD/Fs and have been recommended to be included in the WHO toxic equivalency factor (TEF) scheme (van den Berg et al., 2013; WHO, 1998a). TEFs are assigned based on the relative potency of each dioxin congener to induce AhR activation compared to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic of these DLCs, for which TEF value is fixed to 1.0 (van den Berg et al., 2006). Total toxicity of such a complex mixture mediated by the aggregate activation of AhR receptors is expressed as TCDD toxic equivalent (TEQ) which is calculated by summing the multiplication products of congener concentrations with congener-specific TEFs (van den Berg et al., 1998, 2006). Many studies reported that PBDD/Fs contribute larger dioxin TEQs than PCDD/Fs and DL-PCBs in EWRS (Xiao et al., 2016; Tue et al., 2016, 2019; Ma et al., 2009). However, they are less studied because of the complexity of analytical procedures and paucity of analytical reference standards (Zhang et al., 2016a).

Dioxin-like compounds are released as unintentional byproducts in low-tech e-waste recycling operations including manual disassembly, shredding/comminution, roasting circuit boards, acid-stripping metals, and open burning of e-waste containing chlorinated polymers and/or brominated additives such as polyvinyl chlorides and brominated flame retardants (Wong et al., 2007; Li et al., 2007; Leung et at., 2006b; Xiao et al., 2016; Duan et al., 2011; Zennegg et al., 2014). PBDD/Fs on the other hand can be generated from chemical reaction, photochemical degradation and thermolysis of plastics containing brominated flame retardants (Weber and Kuch, 2003; Ebert and Bahadir, 2003; Kajiwara et al., 2008; Kannan et al., 2012). DL-PCBs are also found in dielectric fluids, lubricants and coolants in generators, capacitors and transformers (WHO/IPCS, 1992). Furthermore, the production of chlorinated chemicals such as pesticides, herbicides, insecticides, and processes like metal smelting, paper production, petroleum refining, and incomplete combustion of municipal, medical and industrial waste can unintentionally produce PCDD/Fs and DL-PCBs (Kulkarni et al., 2008; Ssebugere et al., 2019; Zhu et al., 2008; Zheng et al., 2008; Trinh et al., 2018). PCDD/Fs and DL-PCBs persist widely in the environment and

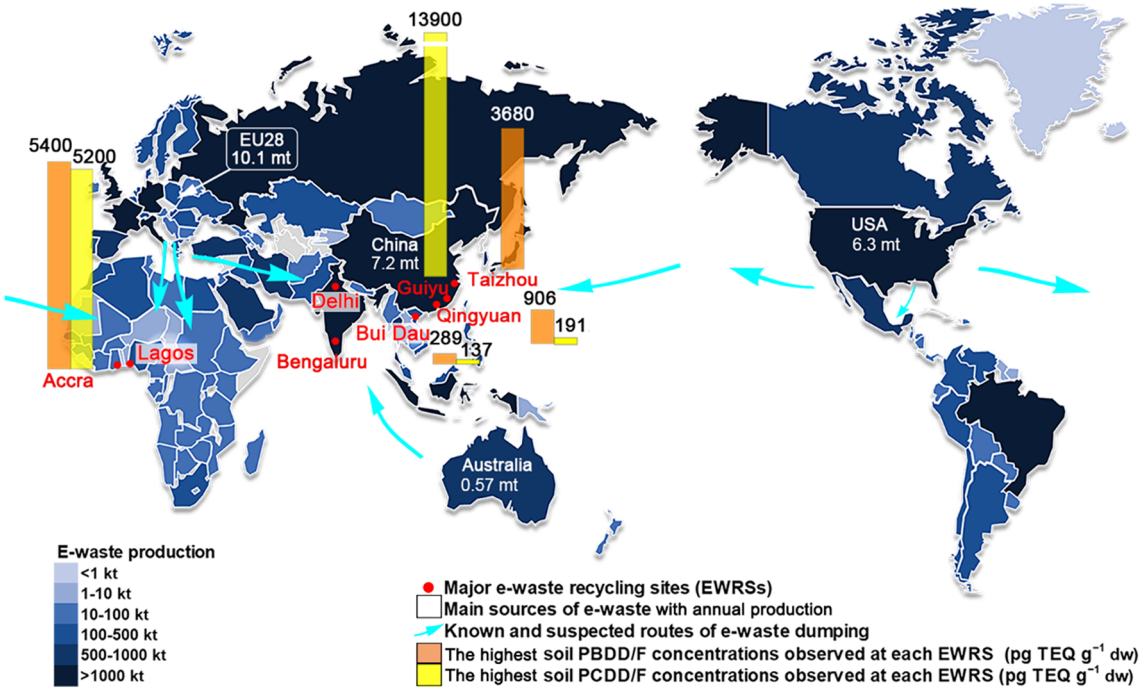

Fig. 1. E-waste production, flows, and recycling sites with the highest soil PCDD/F and PBDD/F concentrations reported (Chen et al., 2011; Balde et al., 2017; Eurostat Statistics Explained, 2019; Pascale et al., 2018).

bioaccumulate through the food chain because they are lipophilic and resistant to biological and chemical degradation (Sadler and Connell, 2012). The half-life of PCDD/Fs and DL-PCBs in the body is estimated to be 7–11 years (WHO, 2016). PBDD/Fs are more lipophilic and more sensitive to UV degradation, and appear to be less persistent in the environment (WHO, 1998a). However, bioaccessibility of PBDD/Fs and PXDD/Fs and their persistence in the human body are still undetermined (Piskorska-Pliszczynska and Maszewski, 2014).

Many epidemiological studies have reported health effects of PCDD/F and DL-PCB exposure, such as skin diseases, reproductive and developmental abnormalities, nervous system disorders, immune deficiency, cancer promotion, and endocrine disruption (Kogevinas, 2001; Marinkovic et al., 2010; Schecter, 2013; World Health Organization WHO, 2010). Although there are limited data on toxicity of PBDD/Fs to human health, comparable biological and toxic effects as their chlorinated analogues (PCDD/Fs) have been found in mammalian and fish models (van den Berg et al., 2013; WHO, 1998a; Mennear and Lee, 1994; Birnbaum et al., 2003). The follow-up studies include occupational or accidental high PCDD/F and DL-PCB exposure cohorts in Seveso, Italy (Bertazzi et al., 1998; Consonni et al., 2008; Eskenazi et al., 2018; Slama et al., 2019; Warner et al., 2013b, 2019), Japan (Kondo et al., 2018; Nagayama et al., 2001; Tsukimori et al., 2008), Germany (BASF Study) (Ott et al., 1993, 1994, Zober et al., 1994, 1997), the Netherlands (McBride et al., 2009, 2018; Mannetje et al., 2018; Mannetje et al., 2005), the Ranch Hand Vietnam Veterans (The Air Force Health Study) (Buffler et al., 2011; Knafl, 2018; Wolfe et al., 1990, 1995), and the US (National Institute for Occupational Safety and Health) (Calvert et al., 1999; Ruder and Yiin, 2011; Sweeney et al., 1997). Background exposed general population cohorts have also been studied in Norway (Caspersen et al., 2016a, 2016b), Germany (the Duisburg birth cohort study) (Neugebauer et al., 2015; Wilhelm et al., 2008; Nowack et al., 2015; Winneke et al., 2014), Japan (the Hokkaido Study on Environment and Children's health) (Kishi et al., 2010, 2013; Miyashita et al., 2018a; Nakajima et al., 2006, 2017), and Taiwan, China (Su et al., 2010, 2012; Wang et al., 2005). Chloracne and cancer are the only TCDD-induced effects established with certainty (Warner et al., 2013a; Mannetje et al., 2018). The possible mechanisms of DLC-induced health hazards may include excessive oxidative stress and oxidatively generated damage to DNA and lipids (Zhang et al., 2019). People working or living in EWRS show evidence of greater DNA damage (Wang et al., 2018; He et al., 2015; Grant et al., 2013; Wen et al., 2008).

Due to the ubiquity of DLCs and their high toxicity, humans potentially have chronic exposure through the environment throughout their entire life which may pose a serious threat to public health (Berry et al., 1993). In addition, accidental and/or occupational exposure may occur (Hens et al., 2016). Even a small daily exposure can accumulate to yield detectable amounts over time. It can be inferred that people living in EWRS with heavy DLC contamination are at higher health risks. There have been several reviews on DLC levels in EWRS (Tue et al., 2013; Chan and Wong, 2013) and many studies on the health effects of DLC exposure. However, partly due to the huge toxicological data gap for the possible mixture effects of a large number of e-waste-related contaminants and limited techniques and finances in developing countries, current data on DLCs in EWRS provide very limited information regarding body burdens and health impacts on e-waste workers and local residents (Wang et al., 2019; Zhang et al., 2010; Xu et al., 2014), especially the vulnerable populations of pregnant women and developing children. Therefore, it is critical to assess the DLC exposure and health risk of people in EWRS. In this context, we identified and reviewed the published literature available online up to November 2019, by using PubMed, Web of Science, Google Scholar, and Medline to search the combined keywords “dioxins” and “health effects,” “e-waste recycling site” for health effects of DLCs and their exposure levels at EWRS. We compare the DLC body burdens at EWRS with the levels reported to be associated with observable adverse effects to help better understand the contamination status and human health risks of DLCs at EWRS.

2. Health hazards of DLCs

Dioxin-like compounds interrupt multiple systems and organ functions of the body (nervous, endocrine, immune, and reproductive systems), mediated through an interaction with the AhR (National Research Council, 2006; Schecter, 2013; Lundqvist et al., 2008; Mandal, 2005). It induces inappropriate modulation of gene expression and an inflammatory response which represent the initial steps in a succession of biochemical reactions, cellular and tissue changes that lead to the observed toxicity and health effects (Fig. 2) (Lindén et al., 2010; Tuomisto, 2019; Mandal, 2005). Epidemiological studies indicate that

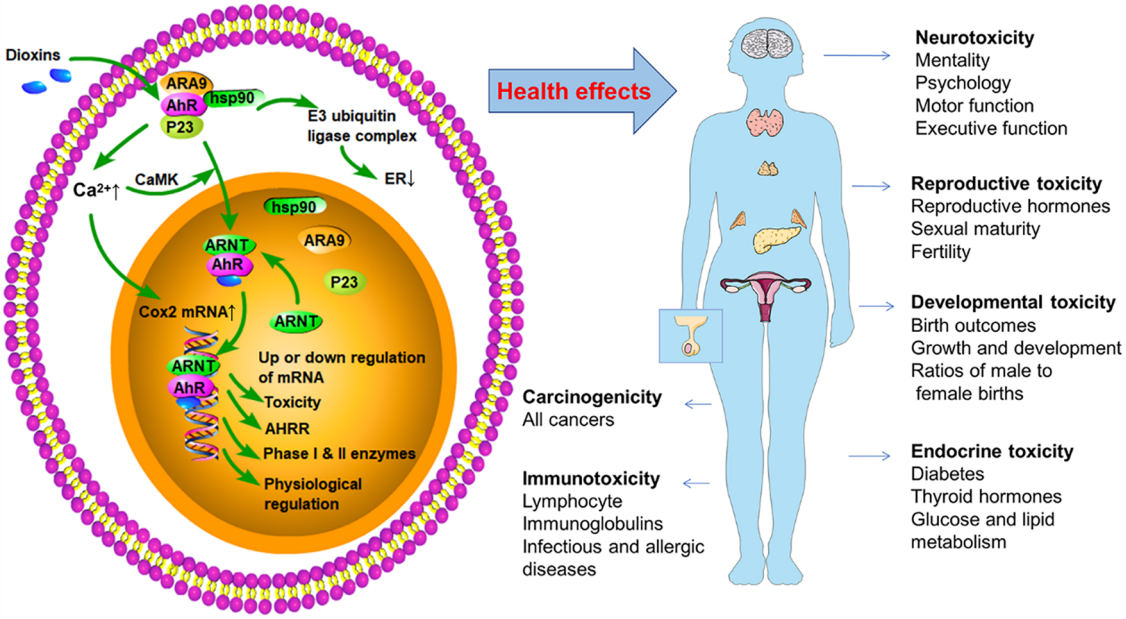

Fig. 2. Toxicity mechanism and health effects of PCDD/Fs and DL-PCBs (Lindén et al., 2010; Tuomisto, 2019).

Table 1
Epidemiological studies examining the effects of PCDD/F and DL-PCB exposure.

Country	Population	Exposure level	Health effect	Reference
Neurotoxicity (children)				
Japan	42 mother-neonates pairs	Breast milk (mean) 0.5[a]; 8.6[b]	↓ Newborn head circumference, $r = 0.424$, $p < 0.01$	(Nishijo et al., 2007b)
Japan	134 mother-infant pairs	Maternal blood (mean) 11.9[b]; 18.8[c]	6 m, PCDD/Fs ↓ Mental development, $\beta = -0.22$, $p = 0.014$; DLCs ↔ Mental and motor development	(Nakajima et al., 2006)
Japan	191 (6 m) and 122 (8 m) mother-infant pairs	Maternal blood (mean) 9.8[b]; 15.1[c]	6 m, DLCs ↓ Motor developmental, $p < 0.05$; 18 m, Six DLC isomers ↑ Mental developmental in female, $p < 0.05$	(Nakajima et al., 2017)
Da Nang, Vietnam	216 mother-infant pairs	Breast milk (mean) 12.5[b]	4 m ↓ Cognitive scores, $p = 0.009$; 1 y ↓ Social–emotional scores, $p = 0.049$; 3 y ↓ Expressive communication scores in boys, $p = 0.03$; 5 y ↓ Total test and balance scores in boys, $p < 0.05$	(Pham et al., 2015; Tai et al., 2013, 2016; Tran et al., 2016)
Norway	44,092 (3 y) and 1024 (3.5 y) mother–child pairs	Maternal dietary intake (median) 0.6[c1]	3 y ↑ Language delay in girls, OR = 2.9 (1.1–7.1); 3.5 y ↔ IQ scores; Executive functions; Attention Deficit/ Hyperactivity Disorder	(Caspersen et al., 2016a, 2016b)
Germany	100 (9–10 y) and 117 (8.5 y) mother–child pairs	Maternal blood (median) 12.9[b]; 13.2[b]	9–10 y ↓ Social Responsiveness Scale scores, $\beta = -6.66$, $p < 0.05$; 8.5 y ↑ Omission errors in the subtest Divided Attention, exp (β) = 1.47 (1.08–2.00), $p < 0.05$	(Nowack et al., 2015; Neugebauer et al., 2015)
Seveso, Italy	161 children of 120 mothers	Maternal serum (median) 1976 74.6[a]; Pregnancy 4.5[a]	7–17 y ↔ Reverse learning; Memory; Attention/Impulsivity; Non-verbal intelligence	(Ames et al., 2019)
Neurotoxicity (adults)				
Seveso, Italy	154 women for physical functioning and 459 for working memory	Serum (median) 1976 45.2[a]; 60.1[a]	↓ Grip strength, inverted U-shaped association; ↔ Walking speed, upper body mobility, manual dexterity, working memory	(Ames et al., 2018a)
Goto, Japan	140 Yusho patients	Blood 2,3,4,7,8-PeCDF	≥ 72.27 pg/g lipid ↑ Pittsburgh Sleep Quality Index global score ≥ 8, OR = 4.84 (1.10–21.25)	(Kondo et al., 2018)
Reproductive toxicity (males)				
Japan	183 mother–child pairs	Maternal blood (median) 14.5[c]	↓ Testosterone/estradiol ratio, sex hormone-binding globulin, and inhibin B levels in male; ↑ Adrenal androgen/glucocorticoid ratios, follicle-stimulating hormone, and dehydroepiandrosterone levels in male	(Miyashita et al., 2018a)
Seveso, Italy	39 exposed mother-son pairs vs 58 reference pairs	Maternal serum (median) 1976 51.7[a] vs 10.0[a]; Conception 26[a] vs 10.0[a]	↓ Sperm concentration, progressive motility, total motile count, inhibin B, $p < 0.05$; ↑ Follicle-stimulating hormone	(Mocarelli et al., 2011)
Seveso, Italy	71 male (1–9 y); 44 (10–17 y); 20 (18–26 y)	Serum (median) 1976 210.0[a]; 164.0[a]; 123.0[a];	1–9 y in 1976 ↓ Sperm concentration, motile sperm, and estradiol; ↑ FSH; 10–17 y in 1976 ↑ Sperm concentration, motile sperm, and FSH; ↓ Estradiol; ↔ 17–26 y in 1976	(Mocarelli et al., 2008)
Chapaevsk, Russia	473 boys (8–9 y); 315 (17–18 y)	Serum (median) 21.1[c]	↓ Pubertal onset [testicular volume = 11.6 months (3.8–19.4) and genitalia = 10.1 months (1.4–18.8)]; ↓ Sexual maturity [testicular volume = 11.6 months (5.7–17.6); genitalia = 9.7 months (3.1–16.2)]	(Burns et al., 2016)
Bien Hoa, Vietnam	42 male residents	Blood (mean) 37.8[c]	↑ Prolactin levels; ↓ Testosterone levels; ↔ Follicle-stimulating hormone luteinizing hormone, or progesterone levels	(Van Luong et al., 2018)
Reproductive toxicity (females)				
Bien Hoa, Vietnam	162 mother-infant pairs	Breast milk (mean) 8.8[b]	↓ Testosterone in girls, $\beta = -0.23$, $p < 0.05$; ↔ Estradiol	(Boda et al., 2018)
Seveso, Italy	310 women; 616; 278; 601	Serum (median) 1976 67.5[a]; 43.7[a]; 50.0[a]; 54.9[a]	↑ Menstrual cycle, 0.93 days in women who were premenarchal in 1976; ↑ Early menopause, 20.1–100 ppt; ↑ Time to pregnancy, 25%; ↑ Infertility, OR = 1.9 (1.14–3.22); ↑ Endometriosis, ≥ 100 ppt	(Eskenazi et al., 2002a, 2002b, 2005, 2010)
Taiwan, China	56 mother–child pairs	Placenta (median) 14.8[c]	8 y ↓ Estradiol, $p = 0.003$; ↓ Fundi and uteri lengths in girls, $p = 0.016$	(Su et al., 2012)
Developmental toxicity				
Norway	50,651 mother–child pairs	Maternal dietary intake (median) 0.6[c1]	↓ Birth weight, 62 g (−73, −50); ↓ Birth length, 0.26 cm (−0.31, −0.20); ↓ Head circumference, 0.10 cm (−0.14, −0.06); ↓ Male proportion, 0.483 (0.46, 0.51); ↑ Spontaneous stillbirth, RR = 2.16 (1.58–2.97)	(Papadopoulou et al., 2013)
Japan	10,959 residents	PCBs + PeCDFs	1968–1977 ↑ Spontaneous stillbirth rates ratio, 2.16 (1.58–2.97); ↓ Sex ratio (male proportion), 0.483 (0.457–0.508); 1978–1987 ↑ Spontaneous stillbirth rates ratio, 1.8 (1.25–2.60)	(Yorifuji et al., 2013)
Japan	214 Yusho women	Blood at delivery PCBs + PeCDFs	1968–1977 ↑ Induced abortion and preterm delivery, $p = 0.03$; 1968–1977 ↑ Spontaneous abortion, $p = 0.11$; pregnancy loss, $p = 0.08$; ↔ 1978–2003	(Tsukimori et al., 2008)
Seveso, Italy	510 women (1996–1998) and 611 (2008–2009)	Serum (median) in 1976 and estimated at pregnancy 1996–1998 46.6[a]; 2008–2009 55.0[a]; 9.9[a]	1996–1998 ↔ Spontaneous abortions, birth weight, births small for gestational age; ↓ Gestational age, 1.0–1.3 day; ↑ Preterm delivery, 20–50%; 2008–2009 ↔ Spontaneous abortion, fetal growth, or gestational length; ↓ Birthweight, $\beta = -22.8$ (−80.1, −34.6)	(Eskenazi et al., 2003; Wesselink et al., 2014)

(*continued on next page*)

Table 1 (*continued*)

Country	Population	Exposure level	Health effect	Reference
Seveso, Italy	239 men and 296 women	Serum (median) 1976 Fathers 96.5[a], mothers 62.8[a]	↓ Sex ratio in fathers < 19 years in 1976 and TCDD > 15 ppt, 0.38 (0.30–0.47); ↔ Sex ratio in fathers ≥ 19 years in 1976 and TCDD > 15 ppt	(Mocarelli et al., 2000)
Seveso, Italy	611 children of 402 mothers	Maternal serum (median) 1976 63.2[a]	2–39 y ↓ BMI in daughters; ↔ In sons	(Warner et al., 2019)
Belgian, Norway, Slovak	367 infant for growth (0–24 m); 251 for BMI (7 y)	Cord blood or breast milk (mean) 18.2[c2]	0–24 m ↑ Growth, β = 0.07 (−0.01, 0.14); 7 y ↑ BMI in girls but not in boys, β = 0.49 (0.07, 0.91); ↑ Overweight in girls, 54% (−6%, 151%)	(Iszatt et al., 2016)
Taizhou	50 exposed mother–child pairs vs 50 reference pairs	Breast milk (mean) 12.9[b] vs 4.3[b]	6 m ↔ Height; 3 y ↑ Height in girls, $p = 0.001$; ↓ Height in boys, $p = 0.046$	(Wang et al., 2019)
Endocrine toxicity				
12 countries (1939–1992)	21,863 workers	Blood TCDD and highly-chlorinated dioxins	↑ Diabetes, RR = 2.25 (0.53–9.50)	(Vena et al., 1998)
New Zealand	245 workers	Serum (mean) 15.2[a]	↑ Diabetes, workers worked in TCDD exposed jobs, OR = 4.0 (1.0–15.4); TCDD ≥ 10 pg/g, OR = 3.1 (0.9–10.7); ↓ FT_4 < 12.8 pmol/l, OR = 4.5 (1.4–14.4)	('t Mannetje et al., 2018)
Seveso, Italy	981 women	Serum (median) 1976 55.9[a]	↔ Diabetes, HR = 0.76 (0.45–1.28); ↑ Metabolic syndrome in women ≤ 12 y in 1976, OR = 2.03 (1.25–3.29), $p = 0.01$	(Warner et al., 2013b)
Nurses' Health Study II	756 diabetes and 766 control	Blood PCB-105, 118, 156, 157, and 167	OR = 1.78 (1.14–2.76), $p = 0.006$	(Zong et al., 2018)
Seveso, Italy	51 mother–child pairs	Extrapolated pregnancy (median) 18.9[a]; 44.8[c]	↑ b-TSH, $p < 0.01$	(Baccarelli et al., 2008)
Seveso, Italy (2008–2009)	909 women	Serum (median) 1976 60.2[a]; 1996 7.0[a], 25.6[c]	1996 ↓ TT_4, β = −0.27 (−0.49, −0.05); ↔ TSH, FT_3, FT_4; 2008 ↓ TT_4, β = −0.11 (−0.32, 0.12); ↔ TSH, FT_3, FT_4 in 2008	(Chevrier et al., 2014)
Taiwan, China	118 (0 m) and 92 (2 y) mother-newborn pairs	Placenta (median) 16.3[c]	Newborns, non-ortho PCBs ↓ FT_4 × TSH, r = −0.2, $p < 0.05$; 2 y, PCDD/Fs ↑ FT_4 × TSH; ↔ 5 y	(Su et al., 2010; Wang et al., 2005)
Immunotoxicity				
Japan	239 mother-infant pairs (0 m); 364 (18 m); 327 (3.5 y); 264 (7 y)	Maternal blood (median) during pregnancy 14.0[c]; 13.9[c]; 14.2[c]; 15.0[c]	Newborns ↓ IgE in boys, −0.87 (−1.68, −0.06); 18 m, PCDFs ↑ Otitis media, OR = 2.5 (1.1–5.9); 3.5 y ↓ Frequency of wheezing in boys, OR = 0.03 (0.00–0.94); 7 y ↑ Frequency of wheezing, OR = 7.81 (1.42–42.9)	(Kishi et al., 2013; Miyashita et al., 2011, 2018b)
Netherlands	207 mother-infant pairs	Maternal and cord plasma, human milk PCBs and PCDD/Fs	Prenatal PCB ↑ T-cell lymphocyte population; ↓ Antibody levels to mumps and measles, and shortness of breath with wheeze, chickenpox; Postnatal PCB ↑ Middle-ear infections, chicken pox; ↓ Allergic reactions; Postnatal DLCs ↑ Coughing, chest congestion, and phlegm	(Weisglas-Kuperus et al., 2000, 2004)
Seveso, Italy	676 children of 438 mothers	Maternal serum (median) 1976 64.7[a]; Pregnancy 11.2[a]	1976 TCDD ↓ Eczema; ↔ Asthma, hay fever; Pregnancy TCDD ↔ Eczema, asthma, and hay fever	(Ye et al., 2018)
Japan	2264 participants	Blood (median) 16.0[c]	Significant inverse dose–response ↓ Atopic dermatitis, OR = 0.26 (0.08–0.70)	(Nakamoto et al., 2013)
Carcinogenic teratogenicity				
Seveso, Italy	278,108 residents; 981 women	Serum (median) 1976 447.0[a] vs 94.0[a]; 71.8[a] vs 51.1[a]	↑ Lymphatic-hematopoietic cancer; ↑ Breast cancer, HR = 2.1 (1.0–4.6)	(Consonni et al., 2008; Warner et al., 2002)
French	429 breast cancer cases vs 716 controls	Air (mean) 0.14[b1] vs 0.12[b1]	↔ Breast cancer	(Danjou et al., 2019)

TCDD, [a]pg g^{-1}; PCDD/Fs, [b]pg WHO-TEQ g^{-1} lipid, [b1]μg-TEQ m^{-2}; DLCs, [c]pg WHO-TEQ g^{-1} lipid, [c1]pg TEQ kg^{-1} bw day^{-1}, [c2]pg CALUX TEQ g^{-1} lipid; CALUX, chemical-activated luciferase expression; TT_4, total thyroxine; FT_4, free thyroxine; HR, hazard ratio; RR, rate ratio; OR, odd ratio; (95% confidence interval).

PCDD/F and DL-PCB exposure is associated with numerous adverse health outcomes (Table 1). The magnitude of effects varies depending on sex, sources and routes of exposure, and timing of cumulative exposure at different life stages (Sexton and Hattis, 2007). There is almost no data on the health effects of PBDD/Fs on people possibly due to limited evidence for general population exposure. However, high PBDD/F concentrations have been found in environmental matrices (Xiao et al., 2016; Ma et al., 2009) and human tissues in EWRS (Bruce-Vanderpuije et al., 2019; Tue et al., 2014), as well as high PCDD/F and DL-PCB levels. Thus, investigations on DLC exposure and the combined human health effects in EWRS is urgent.

2.1. Neurotoxicity

In experimental animal studies, exposure to TCDD during the critical period of brain development has been shown to disrupt expression of key developmentally regulated genes (Hill et al., 2003), alter neurogenesis (Williamson et al., 2005), and induce premature senescence and apoptosis in neuronal cells (Parng et al., 2007; Wan et al., 2014). AhR-mediated dioxin neurotoxicity produces sex-specific disruptions in behavioral and cognitive functions of learning, memory, emotion and motor development in mice (Haijima et al., 2010; Nishijo et al., 2007a; Seo et al., 1999). The toxins that induce neurotoxicity in zebrafish and rodents may cause similar neurotoxicity in humans (Wan et al., 2014; Parng et al., 2007).

Epidemiological studies indicate that perinatal PCDD/F and DL-PCB exposure can interfere with the brain development of fetuses and infants and adversely affect a variety of neuropsychological functions which may last into childhood, including cognition, memory, learning, attention, language, motor function, executive function, and behavior (Neugebauer et al., 2015; Nishijo et al., 2007b; Pham et al., 2015; Tai et al., 2013, 2016). However, in some studies only weak associations were found in subgroups (Ames et al., 2019; Caspersen et al., 2016a). Sex-specific differences in the effect of prenatal PCDD/F and DL-PCB exposure (15.1 pg WHO-TEQ g^{-1} lipid) on mental and motor development were found in some Japanese infants aged 6–18 months. The effect may be stronger in male infants and be attenuated or disappear at later stages of infancy (Nakajima et al., 2006, 2017; Kishi et al., 2013). Some studies demonstrated that poorer cognitive and motor abilities in 42-month-old Dutch children were negatively associated with prenatal but not postnatal PCDD/F and DL-PCB exposure (Patandin et al., 1999), which indicates a more dominant role of *in utero* exposure than lactational exposure (van den Berg et al., 2017). In Norwegian 3–4 year old children, higher odds for language delay was significantly associated with high maternal dietary PCDD/F and DL-PCB exposure, but only in girls (Caspersen et al., 2016b). The sex-specific associations may occur because girls are more vulnerable to endocrine active effects of DLCs in terms of language development (Caspersen et al., 2016b). In general, boys tend to develop language skills later than girls and catch up before school age (Rice et al., 2008; Koenigsknecht and Friedman, 1976). No associations were found with Attention-Deficit/Hyperactivity Disorder, verbal/non-verbal intelligence, or executive functions (Caspersen et al., 2016b). The methodological limitation of dietary PCDD/F and DL-PCB exposure measurement from food frequency questionnaires should be taken into consideration. High prenatal PCDD/F and DL-PCB exposure is also found to increase autistic traits of 8–10 year-old children (Guo et al., 2018; Nishijo et al., 2014; Nowack et al., 2015), particularly in boys (Tran et al., 2016). However, in older Seveso children aged 7–17 years who were born after the industrial accident in 1976, which resulted in one of the highest levels of residential TCDD contamination known, no association between *in utero* TCDD exposure and their neuropsychological function was found, except for subtle deficits among sensitive subgroups of boys and children with shorter lactation histories (Ames et al., 2019). The evidence supports the view that neurodevelopmental decrements associated with *in utero* PCDD/F and DL-PCB exposure may be compensated in later infancy by breastfeeding and a more advantageous parental and home environment (Vreugdenhil et al., 2002; Patandin et al., 1999). Although DLCs can be transferred to infants through breastfeeding, the advantages of breastfeeding far outweigh the potential adverse effects (van den Berg et al., 2017). Infant DLC exposure should be lowered by reducing maternal exposure rather than discouraging breastfeeding.

Adults accidently exposed to a highly TCDD-contaminated environment also show effects on their peripheral and central nervous systems (Urban et al., 2007; Pelcl et al., 2018), especially the biological clock and sleep/wake systems. Frequent symptoms of insomnia and lower subjective sleep quality were associated with higher blood concentrations of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) in Yusho patients (Japan), following ingestion of rice bran oil contaminated with PCBs. Blood 2,3,4,7,8-PeCDF concentrations were high among patients with depression or schizophrenia (Kondo et al., 2018). Some studies also suggest that workers exposed to any TCDD-contained phenoxyacid herbicide or chlorophenol have higher rates of psychological disorders, including fatigue, headache, and suicide (Pelclova et al., 2009, 2018; Vena et al., 1998). However, the Seveso Women's Health Study (SWHS) on women who were in their 30s at the time of the explosion does not indicate an adverse effect on neuropsychological and physical functioning except for grip strength twenty and thirty years after exposure, possibly since the exposure time was not a critical period of brain development and the cohort is not yet old enough for age-related susceptibility to dioxin neurotoxicity to manifest (Ames et al., 2018a). The heterogeneity in exposure time and methods, and neurological assessment measures, limits drawing definite conclusions on health outcomes of neuropsychological function associated with PCDD/F and DL-PCB exposure in children and adults.

2.2. Reproductive toxicity

The reproductive toxicity of PCDD/Fs and DL/PCBs in humans is mainly seen as influencing the reproductive hormones (Egeland et al., 1994), sexual maturation (Burns et al., 2016; Den Hond et al., 2002), and fertility (Eskenazi et al., 2010; Hsu et al., 2003). Except for decreased serum testosterone levels (Sweeney et al., 1997; Gupta et al., 2006; Sun et al., 2020), studies on TCDD's effects on luteinizing, estradiol and follicle-stimulating hormones of highly exposed cohorts have yielded inconsistent results. Significant positive associations with luteinizing hormone and follicle-stimulating hormone were found in chemical plant workers (Egeland et al., 1994), and decreased estradiol and increased follicle-stimulating hormone in Seveso males who were infants and adolescents at exposure, however, not in adults (Mocarelli et al., 2008), nor in residents of dioxin hotspots in the Vietnam war (Van Luong et al., 2018). The age and dose of exposure may account for the inconsistent results. TCDD exposure in infancy was negatively related to sperm concentration and motility, but an opposite association was found with exposure during puberty, which may reflect the differences in the hormonal regulation of Sertoli cells with age (Mocarelli et al., 2008). Pilsner et al. (2017) found that DLCs may induce epigenomic reprogramming in male germ cells of adults during spermatogenesis, causing an increase in the incidence of birth defects in their offspring. TCDD exposure may affect ovarian function of exposed women, which is more sensitive during maturation such as when exposure occurs before menarche, as evidenced by early onset of menopause (Eskenazi et al., 2005), prolonged menstrual cycle (Eskenazi et al., 2002b), endometriosis (Cano-Sancho et al., 2019; Eskenazi et al., 2002a; Koninckx et al., 1994; Martínez-Zamora et al., 2015; Mayani et al., 1997), and infertility (Eskenazi et al., 2010). This may be because TCDD compromises the hypothalamic–pituitary–gonadal regulatory axis, making women less sensitive to estrogen, as well as decreasing ovarian weight and the number of follicles (Schmidt, 2017), although this was not confirmed in the Seveso cohort (Warner et al., 2007).

Prenatal exposure to relatively low PCDD/F and DL-PCB doses, below those that induce overt maternal toxicity, may affect steroid

hormone levels (e.g. lower estradiol and testosterone) (Boda et al., 2018; Miyashita et al., 2018a), behavioral sexual dimorphism (Winneke et al., 2014) and pubertal onset (e.g. shorter penile length and delayed initiation of breast development) of offspring (Leijs et al., 2008; Guo et al., 2004), the consequence of which differ between boys and girls, presumably by interacting with the hypothalamic–pituitary–gonadal axis (Bergman et al., 2013). It suppresses the male secretion of inhibin B and follicle-stimulating hormone which influences the testicular function, including decreased spermatogenic capacity and sperm quality (Mocarelli et al., 2011). Lower estradiol levels in 8-year-old Taiwan children and shorter fundi and uteri lengths in girls were also found to be associated with *in utero* background PCDD/F and DL-PCB exposure (14.8 pg WHO-TEQ g^{-1} lipid) (Su et al., 2012). However, no reproductive developmental effects in boys were found, probably because they were too young at the time of examination to have any signs of reproductive maturation. The evidence indicates that *in utero* DLC exposure may impact the reproductive development of offspring.

2.3. Developmental toxicity

Prenatal and perinatal period, infancy, childhood, and puberty are considered to be the most sensitive exposure windows in terms of growth and development (Beszterda and Franski, 2018; Rice and Barone, 2000), during which exposure to PCDD/Fs and DL-PCBs is associated with poor birth outcomes (Revich et al., 2001), decreased male to female birth ratio (Mocarelli et al., 1996, 2000; Pesatori et al., 2003), and child growth retardation (Guo et al., 2004; Rogan et al., 1988). Studies on Vietnam veterans and residents exposed to dioxin-containing Agent Orange reported a higher incidence of poor birth outcomes, such as miscarriage, preterm birth, stillbirth risk (Le and Johansson, 2001), congenital birth defects (Kang et al., 2000; Knafl, 2018; Ngo et al., 2006), and developmental enamel defects (Ngoc et al., 2019). Among Japanese severely affected by PCB- and PCDF-contaminated rice oil, the incidences of spontaneous abortion and stillbirth, pregnancy loss, and preterm delivery increased, and the ratio of male to female births decreased, but the associations diminished over time (Yorifuji et al., 2013; Tsukimori et al., 2008). Higher maternal blood PCDD/F and DL-PCB levels in Yusho women were associated with lower birth weight, especially in male infants (Tsukimori et al., 2012). The mechanism may be the genetic variation across the maternal AhR gene that increases the susceptibility to low birth weight in newborns prenatally exposed to DLCs (Ames et al., 2018b). Male infants are more susceptible than females to growth restriction induced by prenatal DLC exposure (Tsukimori et al., 2012). The SWHS reported that initial maternal TCDD levels in 1976 were non-significantly associated with low birthweight and increased incidents of preterm delivery. However, no association between maternal TCDD levels at pregnancy and spontaneous abortions or gestational age was found (Eskenazi et al., 2003; Wesselink et al., 2014). The findings suggest that, in epidemiologic studies of pregnancy outcomes associated with dioxin exposure, the highest dose may be more relevant than pregnancy dose. Prenatal and perinatal PCDD/F and DL-PCB exposure is adversely associated with fetal growth and positively associated with infant growth (Papadopoulou et al., 2013; Iszatt et al., 2016). The association exhibit gender-specific differences in 3-year-old children, with a negative effect in boys but a positive effect in girls (Wang et al., 2019; Tai et al., 2016). Studies on European birth cohorts found that perinatal PCDD/F and DL-PCB exposure was associated with increased body mass index (BMI) and risk of overweight in 7-year-old girls (Iszatt et al., 2016). However, the Seveso Second Generation Study found an inverse association between initial maternal TCDD levels in 1976 and BMI of their 2–39 year-old daughters (Warner et al., 2019). The wide age range of the cohort likely increased the variability of the results. These studies on populations worldwide have described the inconsistent effects of DLC exposure on birth and growth outcomes at various ages, for which limited sample size, various exposure assessments, and lack of a standardized measurement of child growth may account.

2.4. Endocrine toxicity

Dioxin-like compounds are known to induce hormone and growth dysregulation and therefore act as environmental endocrine disruptors. When incorporated into the body, they may interfere with the normal functioning of the endocrine system, which is responsible for regulating hormone balance, growth, reproduction, and behavior (Colborn et al., 1993; Bergman et al., 2013; Damstra et al., 2002). Dioxins can alter the metabolic levels of thyroid hormones and insulin, and lower insulin levels or insulin receptors, resulting in glucose metabolic disorders, and ultimately diabetes (Calvert et al., 1999; Remillard and Bunce, 2002; Henriksen et al., 1997; Kern et al., 2004; Lee et al., 2014) and its underlying conditions such as modified glucose metabolism, insulin resistance, impaired insulin secretion and metabolic syndrome (Jaacks and Staimez, 2015; Kokichi, 2018; Uemura et al., 2009; Warner et al., 2013b, 2019). The US Department of Veterans Affairs added type 2 diabetes to the list of presumptive diseases associated with exposure to Agent Orange (Department of Veterans Affairs, 2001).

Epidemiological and experimental *in vivo* studies have revealed that DLC exposure may induce diabetes through insulin resistance and the destruction of beta cell function (Alonso-Magdalena et al., 2011; Chang et al., 2010, 2011; Cranmer et al., 2000; Kim et al., 2019; Lee et al., 2017; Lim et al., 2010). The most informative human data on this association come from studies of high PCDD/F and DL-PCB exposed cohorts, involving Vietnam War veterans (Henriksen et al., 1997; Kang et al., 2006; Kim et al., 2003; Michalek and Pavuk, 2008), occupationally exposed workers in Czech Republic (Pelcl et al., 2018), New Zealand ('t Mannetje et al., 2018), the United States (Calvert et al., 1999), and the International Agency for Research on Cancer multicentric mortality study comprising 36 cohorts from 12 countries (Vena et al., 1998), and residents of contaminated communities in the United States (Klein et al., 2011), Taiwan (Chen et al., 2006; Huang et al., 2015; Wang et al., 2008) and Seveso (Bertazzi et al., 2001; Consonni et al., 2008). Chronic low-level exposures to DLCs of the general population in Japan (Nakamoto et al., 2013; Uemura et al., 2008), Belgium (Fierens et al., 2003), and the National Health and Nutrition Examination Survey from the US (Dzierlenga et al., 2019; Everett et al., 2007; Lee et al., 2006a, 2006b), the Nurses' Health Study II (Zong et al., 2018), and a pregnancy cohort in Crete, Greece (Vafeiadi et al., 2017), are also linked with an increased risk of diabetes (Kokichi, 2018). A systematic review and meta-analysis concluded that there is sufficient evidence of a significant association between serum PCDD/F and PCB concentrations and the risk of type 2 diabetes (Song et al., 2016). However, Goodman et al. (2015) found that a positive dose-response relationship is present only in cross-sectional studies of populations with current TCDD levels less than 10 pg g^{-1} lipid. The cause-effect relationships and detailed molecular mechanisms between DLC body burdens and diabetes remain to be elucidated.

Thyroid hormones play a crucial role in human growth and development, and in the maintenance of normal physiological status. Any deficiency or increase of thyroid hormones during critical periods of brain development may result in irreversible impairment, morphological and cytoarchitecture abnormalities, disorganization, maldevelopment, and physical retardation (Ahmed et al., 2008). DLCs interact strongly with transthyretins and thyroid hormone receptors, which accelerate thyroid hormone clearance (McKinney et al., 1985; Ishihara et al., 2003). *In utero* and lactational exposure to PCDD/Fs and PCBs may have different effects on thyroid hormone levels [thyroid stimulating hormone (TSH), thyroxine (T_4), triiodothyronine (T_3)] and thyroid function in neonates and children (Koopman-Esseboom et al., 1994; Wang et al., 2005; Baccarelli et al., 2008), and may diminish or disappear over time (Su et al., 2010; Pluim et al., 1993). Once again the thyroid hormone metabolism may be influenced by current background exposure to DL-PCBs during adolescence (Leijs et al., 2012). Systematic

reviews of epidemiological studies on the association between perinatal TCDD exposure and thyroid function of children showed inconsistent results, despite some evidence of sub-clinical hypothyroidism found to be induced by dioxin exposure within three months of birth (Giacomini et al., 2006). Epidemiological studies on highly exposed cohorts of Vietnam Air Force Veterans during 1982–1992 found that serum TCDD levels were positively correlated with TSH but not thyroid disease (Pavuk et al., 2003). The SWHS found that initial TCDD exposure before girls' menarche may permanently alter total T_4 (but not free T_4, free T_3, or TSH levels), which tends to be more influential than later TCDD body burden (Chevrier et al., 2014). However, no associations with T_3, T_4, and TSH were found in Yusho patients (Nagayama et al., 2001). Between-studies discrepancies in thyroid levels may not only reflect complex time-specific actions of mixed DLC exposure, but also differences in laboratory methodology, age and sample size (Giacomini et al., 2006; Khoa et al., 2015). The toxicological mechanism of the effect of dioxin exposure on the thyroid gland needs to be further explored.

2.5. Immunotoxicity

The immune system is one of the most sensitive targets for dioxins. The immune response of mammals exposed to DLCs during their maturation stage is more severe and persistent than that caused by adult exposure (Nowak et al., 2019; Dietert, 2009). A broad range of immunotoxicity of DLCs has been observed in animal studies (Gehrs et al., 1997; O'Driscoll et al., 2019; Vorderstrasse et al., 2003), including thymic atrophy, immunosuppression of both humoral and cell-mediated immune responses (Fine et al., 1989; Kerkvliet, 2002; Vos et al., 1973; Camacho et al., 2004). In humans, prenatal background exposure to DLCs may cause postnatal immune dysfunctions and increased susceptibility to infectious and allergic diseases in infancy which persist into childhood (Miyashita et al., 2011; Stølevik et al., 2013; Guo et al., 2004). Common infectious diseases acquired in early life may affect the maturation of the immune system and may thereby prevent the development of allergic diseases (Weisglas-Kuperus et al., 2004). Breastfeeding for 4 months or more can counteract the negative effect of perinatal exposure and prevent children from developing allergic and infectious diseases (Pluim et al., 1994; Ten et al., 2003; Ip et al., 2007; van den Berg et al., 2017). The findings of the Seveso Second Generation Health Study (Ye et al., 2018), the Hokkaido Study on Environment and Children's Health (Kishi et al., 2013; Miyashita et al., 2011, 2018b), and a Dutch birth cohort study (Weisglas-Kuperus et al., 1995, 2000, 2004) support the conclusion that prenatal TCDD exposure may increase the development of infectious diseases and decrease allergic conditions.

Adult exposure to dioxins also adversely affects the immune system function, altering T-lymphocyte subpopulations and immunoglobulins levels (Kim et al., 2018), and increasing susceptibility to infectious diseases (Zober et al., 1994). Increased TCDD levels of Seveso inhabitants were found to be inversely associated with only plasma IgG but not with IgM, IgA, C3, or C4 levels, which indicates that TCDD may play a role in suppressing antibody production (Baccarelli et al., 2002, 2004). A large sample-size cross-sectional study on background dioxin exposure of the general Japanese residents found that low-level DLC exposure (16.0 pg WHO-TEQ g^{-1} lipid) is associated with reduced risk of atopic dermatitis (Nakamoto et al., 2013). However, no immune response (immunoglobulins, autoantibodies, and lymphocyte subsets) was found in 83 adult Yusho patients with relatively high blood PCDD/F and DL-PCB levels, possibly due to the rather small-scale sample size (Nagayama et al., 2001). Therefore, in order to obtain more conclusive results concerning the effects of DLCs on immune response systems, further uniform large-scale investigations with standard exposure assessment methods are needed.

2.6. Carcinogenicity

The International Agency for Research on Cancer classified TCDD, 2,3,4,7,8-PeCDF, PCBs and DL-PCBs as multi-site carcinogens (group 1) (IARC, 1997, 2012, 2016). Overall, human and animal studies indicate that the carcinogenicity of TCDD is for all cancers combined rather than for any specific site (IARC, 1997; Warner et al., 2011; Xu et al., 2016). Excess risks have been observed in TCDD-exposed subjects for all cancers (Manuwald et al., 2012), such as lymphomas (Viel et al., 2008), multiple myeloma (Consonni et al., 2008), soft-tissue sarcoma (Pesatori et al., 2003), lung (Steenland et al., 1999) and liver (Kogevinas et al., 1997) cancers. Mortality and morbidity findings of the Seveso population exposed to TCDD showed increased risk from lympho-hemopoietic neoplasms, digestive system, and respiratory system cancers, and also thyroid gland cancer (Pesatori et al., 2003). An increased prevalence of reproductive cancers (breast, cervical, testicular, endometrial cancer) has been found in high TCDD exposed cohorts (Revich et al., 2001; Warner et al., 2002; Kogevinas, 2001). However, in a recent French case-control study, no increased risk of breast cancer was found for higher airborne PCDD/F levels but an increased risk in estrogen receptor-positive breast cancer with low PCDD/F exposure was observed (Danjou et al., 2019). The findings might be consistent with a non-monotonic dose-response effect of dioxins on breast cancer. The cancer-induced effects found in high DLC-exposed cohorts are still inconsistent, for which specific study limitations (e.g. sample sizes and adjustments for confounders) and the differences in study population and methodology (e.g. exposure assessment) may partially explain (Xu et al., 2016). The impact of temporal variation in exposure should be taken into consideration (Rodgers et al., 2018).

Since DLCs are not directly genotoxic, their carcinogenicity is likely mediated via activation of the AhR leading to tumor promotion. The tumor promoting action of TCDD is reflected in facilitating the growth rate and clonal expansion of initiated cells (Baccarelli et al., 2006; Knerr and Schrenk, 2006), inhibiting the apoptosis of tumor precursor cells, and increasing oxidative stress (Schwarz and Appel, 2005). The dose-response relationship and the mechanisms of action between DLC exposure and cancer needs to be clarified, of which inter-individual variability and susceptibility in response are key determinants (Guyton et al., 2009). Careful consideration should be taken when formulating the maximum tolerated dose of long-term environmental DLC exposure and the cancer potency threshold for TCDD.

3. Environmental levels and human exposure in EWRS

E-waste recycling is a significant source of DLC contamination in China and some other developing countries (Lei et al., 2020; Prithiviraj et al., 2019). High levels of DLCs were detected in environmental (air, particulate, soil, dust, and sediment) and biological (hair, blood, breast milk, placenta, and meconium) samples in well-known EWRS (Chan and Wong, 2013). Concentrations of PCDD/Fs in air and soils near e-waste recycling operations were greater than those reported around municipal solid waste incinerators and chemical industries (Ma et al., 2008). The PCDD/F and DL-PCB concentrations in the blood and breast milk samples from EWRS were higher or comparable to the levels reported to be associated with observable adverse effects in epidemiological studies. It suggests that the health risk of DLC exposure on local workers and residents in EWRS should be assessed in a timely manner.

3.1. Atmosphere

Dioxin-like compounds can be generated when incineration temperatures are not high enough and will then be released into the atmosphere (Shibamoto et al., 2007; Zhang et al., 2017a; Zhang et al., 2016a). The atmospheric particulates act as an important vector for the transport of DLCs in the environment from the emission sources to other environmental matrices and may be the largest exposure route for e-

waste recycling workers (Ma et al., 2008; Qin et al., 2019). However, possibly due to the methodological complexity of air sampling and analysis, data on DLC concentrations in the air of EWRS is scarce, and virtually absent in developing countries except China (Table 2). Air samples taken near Guiyu, the "World Electronic Waste Terminal," in 2005 contained the highest DLC level, with PCDD/F concentrations of 64.9–2765.0 (mean 891.4) pg m^{-3} and 2,3,7,8-PBDD/F concentrations of 8.12–461.0 (mean 118.0) pg m^{-3} (Li et al., 2007). These are 12–18 times higher than in Chendian, a non-EWRS only 9 km away from Guiyu, and 37–133 times higher than in Guangzhou, the nearest major city. Since the atmospheric PCDD/F level in Chendian is still much higher than that in other urban areas, the data indicate that the severe dioxin pollution in Guiyu may affect the nearby Chendian. Fortunately, due to the enhanced law enforcement and environmental regulations on centralized e-waste dismantling with advanced technology by the authorities of Guangdong province and local governments in 2010, air quality in Guiyu has improved greatly. The mean atmospheric TEQ concentrations of PCDD/Fs in 2013 was seven times lower than that in 2005 (Xiao et al., 2012; Zhang et al., 2017b). Similarly, in 2013, atmospheric PCDD/F concentrations in Qingyuan (Guangdong, China), famous for its e-waste recycling industry, significantly decreased by 31 times compared with the values measured in 2010, and by 49 times than in 2006, possibly due to implementation in recent years of laws banning open burning of waste wires, acid washing, and other uncontrolled e-waste recycling activities (Ren et al., 2015; Xiao et al., 2014; Zhang et al., 2017b). Consistent results were also observed in Taizhou (Zhejiang, China), another large e-waste recycling region with a nearly 40-year history of informal e-waste disposal and recycling. The average atmospheric PCDD/F concentration (0.4 pg TEQ m^{-3}) in 2010 was 62% lower than that in 2005 (1.1 pg TEQ m^{-3}) (Zhang et al., 2012b). This may have benefited when the local government started to standardize the dismantling processes in 2005. Small-sized informal workshops were urged to close and replaced with formal e-waste dismantling centers. Sophisticated recycling technologies were encouraged to minimize open burning activities (Fu et al., 2012). These data indicate that the strengthened regulations and centralized dismantling measures in EWRS showed a significant reduction in the release of PCDD/Fs. However, the atmospheric PCDD/F concentrations are still much higher than reference areas and municipal solid waste incinerators and heavily industrialized areas.

3.2. Soil

Levels of DLCs in soils of EWRS and nearby agricultural lands have been examined in many studies (Table 3). As expected, relatively high PCDD/F levels were found in the soils from an open e-waste burning site [2.1 × 10^4 pg g^{-1} dry weight (dw)] and an acid leaching site (3.9 × 10^4 pg g^{-1} dw) in Guiyu (Leung et al., 2007), which were comparable to those reported for EWRS in Qingyuan (2.1 × 10^4 pg g^{-1} dw) (Hu et al., 2013). The soil TEQ levels of PCDD/Fs in Guiyu were comparable or even higher than that of the former storage of Agent Orange in A-So airbase collected in 1996 (nearly 26 years after last exposure), which is hotspot during the Vietnam War (112.6 pg TEQ g^{-1} dw) (Dwernychuk et al., 2002). Open burning and dismantling of e-waste and acid leaching activities are identified as the major sources of high PCDD/F concentrations (Leung et al., 2007; Tue et al., 2019). The mean soil PCDD/F concentration of household e-waste facilities in Fengjiang, Taizhou (4.3 × 10^3 pg g^{-1} dw) (Ma et al., 2008), was one order of magnitude greater than that of a nearby agricultural field (5.0 × 10^2 pg g^{-1} dw) (Shen et al., 2009), and a chemical industrial complex in Wujing, Shanghai (2.9 × 10^2 pg g^{-1} dw) (Ma et al., 2008). Soils from informal backyard EWRS in Bangalore (India) where crude processes, like heating, acid treatment, and open burning, were employed, also contained high levels of PCDD/Fs, DL-PCBs, and PBDD/Fs, with mean concentrations of 3.6 × 10^4, 1.3 × 10^4, and 1.1 × 10^5 pg g^{-1} dw, respectively (Karri et al., 2008). These concentrations were much higher than those in soils of an Indian e-waste facility where recycling of e-waste did not involve any thermal processes, with mean PCDD/F, DL-PCB, and PBDD/F concentrations of 6.4 × 10^2, 6.5 × 10^3, and 2.9 × 10^4 pg g^{-1} dw, respectively (Karri et al., 2008). However, in India, 95% of the e-waste is informally treated and crude processed (Raghupathy et al., 2010). With the awareness about e-waste among government and general public, in 2016, the Indian Government released a more stringent and powerful legislative management framework, where e-waste is collected by municipalities, authorized retailers or commercial pick-up services and then sent to different centers for further processing. The whole process is controlled by the Central Pollution Control Board to ensure the collection and disposal of e-waste in a sustainable manner according to the principle of Producer Responsibility. Such rules are expected to control the release of hazardous substances in the e-waste disposal stream (Government of India, 2016;

Table 2
Mean concentrations of atmospheric 2,3,7,8-substituted PCDD/Fs and PBDD/Fs at typical EWRS and some other locations.

City/Country	Site	PCDD/Fs (pg m^{-3})	PBDD/Fs (pg m^{-3})	Type	Time	Reference
Guiyu, China	E-waste open-burning sites	6.5 (0.7[a])		Gas + TSP	2004	(Wong et al., 2007)
Guiyu, China	EWRS, summer/winter	127.3/253.0 (8.8[b]/16.0[b])	21.9/118.0 (4.5[b]/26.9[b])	Gas + TSP	2005	(Li et al., 2007)
Guiyu, China	Circuit boards recycling sites	317 (14.5[a])	481 (91.3[a])	TSP	2007	(Ren et al., 2014)
Guiyu, China	Circuit board recycling sites	17.6 (0.8[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Guiyu, China	Plastic recycling workshops	31.1 (1.7[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Guiyu, China	Remote small villages	1.1 (0.02[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Chendian, China	Underwear industry	22.9 (1.2[a], 1.4[b])	3.6 (0.9[b])	Gas + TSP	2005	(Li et al., 2007)
Guangzhou, China	Urban	6.7 (0.3[a], 0.4[b])	1.0 (0.2[b])	Gas + TSP	2005	(Li et al., 2007)
Taizhou, China	EWRS	14.3 (1.1[b])		Gas + TSP	2005	(Li et al., 2008)
Taizhou, China	EWRS, summer/winter	84.5/212.2 (4.9[a]/12.7[a])	5.4/17.6 (0.8[a]/2.4[a])	Gas + TSP	2006–2007	(Zhou, 2011)
Taizhou, China	EWRS, summer/winter	32.8/32.9 (0.5[a]/0.4[a])	58.9/73.7 (0.2[a]/0.2[a])	Gas + TSP	2010	(Zhang et al., 2012b)
Hangzhou, China	Solid waste incinerator	31.9 (0.5[b])		Gas + TSP	2007–2008	(Xu et al., 2009)
Qingyuan, China	Courtyard open burning sites	237.0 (13.6[a])		Gas + TSP	2006	(Ren et al., 2015)
Qingyuan, China	Courtyard open burning sites	159.4 (8.0[a]/8.5[b])		Gas + TSP	2009–2010	(Xiao et al., 2014)
Qingyuan, China	A green recycling center	34 (0.6[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Qingyuan, China	Neighborhoods near EWRS	5.0 (0.3[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Qingyuan, China	Remote small villages	2.9 (0.1[b])		Gas + TSP	2013	(Zhang et al., 2017b)
Chennai, India	EWRS	(1.65[c])		Gas		(Chakraborty et al., 2016a)
Korea	Solid waste incinerators	(0.2[b])		Gas + TSP		(Kim et al., 2008)
Duisburg, Germany	Heavily industrialized areas	(0.3[b], 0.1[b])		Gas + TSP TSP	1987, 1993	(Hiester et al.,1997)

TEQs are given in parentheses.
[a] pg WHO-TEQ m^{-3}.
[b] pg I-TEQ m^{-3}.
[c] pg CALUX-TEQ m^{-3}; TSP, total suspended particulate.

Table 3
Concentrations of soil/dust/sediment DLCs at typical EWRS and some other locations.

Country	City	Site	Data type (sampling year)	PCDD/Fs	DL-PCBs	PBDD/Fs	Reference
Soil (pg g^{-1} dw)							
China	Guiyu	Open-burning sites	Range (2004)	3.1 × 10^4–9.7 × 10^5 (627.0[b]–13,900.0[b])	2.2 × 10^4–4.5 × 10^5 (7.0[a]–878.0[a])		(Wong et al., 2007; Yu et al., 2008)
China	Guiyu	Combusted residue	Mean (2004)	2.1 × 10^4 (129.0[a])			(Leung et al., 2007)
China	Guiyu	Acid leaching area	Mean (2004)	3.9 × 10^4 (506.0[a])			(Leung et al., 2007)
China	Guiyu	Open burning and acid leaching sites	Mean (2009)			9.7[b]	(Xu et al., 2017)
China	Guiyu	E-waste roasting sites	Mean (2009)			8.4[b]	(Xu et al., 2017)
China	Guiyu	Manual disassembly and shredding sites	Mean (2009)			5.4[b]	(Xu et al., 2017)
China	Taizhou	Large EWRS	Mean (2007)	1.0 × 10^3 (49.3[a])		1.1 × 10^5 (799.0)	(Ma et al., 2008, 2009)
China	Taizhou	Household EWRS	Mean (2007)	1.5 × 10^3 (92.0[a])			(Ma et al., 2008)
China	Wujing	Chemical industrial complex	Mean (2007)	1.6 × 10^2 (5.4[a])		57.8 (0.5)	(Ma et al., 2008, 2009)
China	Taizhou	Farmland near EWRS	Mean (2006)	5.0 × 10^2 (12.2[a])	2.1 × 10^4 (6.7[a])		(Shen et al., 2009)
China	Qingyuan	EWRS	Mean (2009)			2.9 × 10^2 (68.4[a])	(Xiao et al., 2016)
China	Qingyuan	EWRS	Mean (2009)	2.1 × 10^4 (43.0[a])			(Hu et al., 2013)
China	Qingyuan	Farmland near EWRS	Mean (2006)	(7.1[a])			(Ren et al., 2015)
China	East	Disassembly industrial park	Mean	6.9 × 10^2 (7.2[a])	6.0 × 10^3		(Liu and Liu, 2009)
China	Yangtze River Delta	Farmland in EWRS	Mean (2004)	2.6 × 10^3 (21.0[a])			(Luo et al., 2005)
India	Bangalore and Chennai	Backyard recycling site	Mean (2006)	3.6 × 10^4	1.3 × 10^4	1.1 × 10^5	(Karri et al., 2008)
India	Bangalore and Chennai	E-waste facility	Mean (2006)	6.4 × 10^2	6.5 × 10^3	2.9 × 10^4	(Karri et al., 2008)
India	New Delhi, Kolkata, Mumbai and Chennai	EWRS	Mean (2014)	5.0 × 10^3 (31.0[a])	4.6 × 10^4 (39.0[a])		(Chakraborty et al., 2018)
India	New Delhi, Kolkata, Mumbai and Chennai	Open dump	Mean (2014)	2.5 × 10^3 (16.0[a])	1.8 × 10^3 (11.5[a])		(Chakraborty et al., 2018)
Ghana	Agbogbloshie	Open burning areas	Median (2010)	2.8 × 10^5	4.2 × 10^4	9.3 × 10^5	(Tue et al., 2016)
Ghana	Agbogbloshie	Non-burning areas	Median (2010)	3.8 × 10^3	1.9 × 10^3	7.1 × 10^3	(Tue et al., 2016)
Ghana	Agbogbloshie	Open burning areas	Median (2013)	3.3 × 10^4 (360.0[a])		1.8 × 10^5 (870.0[a])	(Tue et al., 2019)
Ghana	Agbogbloshie	Dismantling area	Median (2013)	1.6 × 10^4 (270.0[a])		4.5 × 10^5 (2200.0[a])	(Tue et al., 2019)
Vietnam	Bui Dau	Open burning sites	Median (2012)	(77.0[a])	(4.8[a])	(14.0[a])	(Suzuki et al., 2016)
Vietnam	Bui Dau	E-waste-processing workshop	Median (2012)	(4.5[a])	(1.3[a])	(20.0[a])	(Suzuki et al., 2016)
Vietnam	Bui Dau	Farmland near EWRS	Median (2012)	(1.2[a])	(0.3[a])	(0.3[a])	(Suzuki et al., 2016)
Vietnam	A-So	Storage for herbicides during Vietnam War	(1996 ~ 26 y) Mean (2014 ~ 44 y)	(112.6[b]) 8.5 × 10^2 (91.1[a])			(Le et al., 2019; Dwernychuk et al., 2002)
Dust (pg g^{-1} dw)							
China	Guiyu	Workshop floor, EWRS	2004	1.3 × 10^3 (76.2[a])			(Leung et al., 2011)
China	Guiyu	Schoolyard near EWRS	2004	1.3 × 10^3 (103.0[a])			(Leung et al., 2011)
China	Guiyu	Street-lined with workshops	2004	6.5 × 10^2 (53.1[a])			(Leung et al., 2011)
China	Guiyu	Workshop, EWRS	Mean (2013)	(2.7 × 10^3)			(Zhang et al., 2017b)
China	Qingyuan	Workshop, EWRS	Range (2013)	(49.0–446.0)			(Zhang et al., 2017b)
China	Qingyuan	Workshop, EWRS	Mean (2009)	5.7 × 10^4 (380.0[a])		2.0 × 10^3 (400.0[a])	(Hu et al., 2013; Xiao et al., 2016)
China	Taizhou	Floor, EWRS	Mean (2007)	1.3 × 10^4 (1070.0[a])		1.2 × 10^5 (1480.0[a])	(Ma et al., 2008, 2009)
China	Taizhou	Floor, EWRS	Mean (2006)	2.6 × 10^4 (724.1[a])	26,200.0[a]		(Wen et al., 2008)
India	Chennai	Metal recovery workshop	Mean (2014)		5.8 × 10^4 (1000.0[a])		(Chakraborty et al., 2016b)
India	Chennai	Dismantling and shredding workshop	Mean (2014)		1.3 × 10^3 (20.0[a])		(Chakraborty et al., 2016b)
Vietnam	Bui Dau	Furniture and fan blades surface, EWRS	Median (2008)	1.4 × 10^3	1.0 × 10^3	4.9 × 10^4	(Tue et al., 2010)
Vietnam	Trang Minh	Furniture and fan blades surface, EWRS	Median (2008)	2.4 × 10^3	2.2 × 10^3	2.3 × 10^4	(Tue et al., 2010)
Sediment (pg g^{-1} dw)							

(*continued on next page*)

Table 3 (*continued*)

Country	City	Site	Data type (sampling year)	PCDD/Fs	DL-PCBs	PBDD/Fs	Reference
China	Guiyu	Ash-dumped riverbank		(3.5×10^4[a])			(Luksemburg et al., 2002)
China	Guiyu	Residential areas near the river		(2.7×10^3[a])			(Luksemburg et al., 2002)
China	Qingyuan	Pond in EWRS	Mean (2009)	3.4×10^4 (128.0[a])		5.3×10^2 (146.0[a])	(Hu et al., 2013; Xiao et al., 2016)
China	East	Disassembly industrial park	Mean	643.0 (8.9[a])	1.3×10^4		(Liu and Liu, 2009)
Vietnam	Bui Dau	E-waste-processing area	Median (2012)	1.2×10^3 (7.3[a])	(0.9[a])	1.7×10^3 (4.4[a])	(Suzuki et al., 2016)
Ghana	Agbogbloshie	Lagoon near EWRS		(988.0)			(Brigden et al., 2008)
Vietnam	A-So	Hotspots in Vietnam War	(1996 ~ 26 y) Mean (2014 ~ 44 y)	(7.8[b]) 2.8×10^3 (22.0^a – 385[a])			(Le et al., 2019; Dwernychuk et al., 2002)

TEQs are given in parentheses; [a]pg WHO-TEQ g^{-1} dw; [b]pg I-TEQ g^{-1} dw.

Chakraborty et al., 2018). In Agbogbloshie, Ghana, concentrations of PCDD/Fs and PBDD/Fs found in soils from open burning (3.3×10^4 and 1.8×10^5 pg g^{-1} dw, respectively) and dismantling areas (1.6×10^4 and 4.5×10^5 pg g^{-1} dw, respectively) in 2013 were lower than in soil samples collected in 2010 (2.8×10^5 and 9.3×10^5 pg g^{-1} dw, respectively) and were comparable to the highest reported for informal EWRS (Tue et al., 2019). These data suggest that low-tech e-waste recycling facilities have been an important emission source for DLCs, and have contaminated the nearby agricultural environment (Shen et al., 2008).

3.3. Dust and sediment

Dust is a complex mixture of particulate matter and acts as a repository of environmental pollutants which represents average levels of contamination over long periods of time (Butte et al., 2002). Dust ingestion is an important pathway for human DLC exposure in EWRS (Tue et al., 2014). However, investigations of DLC levels in dust and sediment of EWRS are so far scarce (Table 3). The PCDD/F concentrations in dust from an e-waste recycling workshop in Guiyu (1.3×10^3 pg g^{-1} dw) were approximately 13 times greater than the concentrations found in the dust from a reference site (96.1 pg g^{-1} dw) (Leung et al., 2011). Zhang et al., 2017b detected even higher TEQ concentrations of PCDD/Fs in indoor dust in Guiyu (1020.0–3637.0, mean 2662.0 pg TEQ g^{-1} dw). These were 59 times higher than the reference site (45.4 pg TEQ g^{-1} dw) and 10 times higher than that from Qingyuan (49.0–446.0 pg TEQ g^{-1} dw). The PCDD/F concentrations of dust samples collected from Taizhou e-waste workshop floor were 17–28 times higher than that of dust on the surface of furniture and fan blades from Vietnamese EWRS (Ma et al., 2008; Tue et al., 2010). The average TEQ concentrations of PCDD/Fs and PBDD/Fs in Taizhou (1070.0 and 1480.0 pg WHO-TEQ g^{-1} dw, respectively) were three times higher than that collected from large-scale e-waste facilities in Qingyuan (380.0 and 400.0 pg WHO-TEQ g^{-1} dw, respectively) (Ma et al., 2008, 2009; Hu et al., 2013; Xiao et al., 2016). Dust from informal e-waste recycling workshops engaged in metal recovery in Chennai, India, showed a mean DL-PCB concentration of 5.8×10^4 pg g^{-1} dw, much higher than that from shredding and dismantling sites (1.3×10^3 pg g^{-1} dw) (Chakraborty et al., 2016b). This might have resulted from recycling activities like burning electric wires to recover copper, heating printed circuit boards to recover lead-tin solder and integrated components, and using acid chemical strippers to recover gold and other metals (Chakraborty et al., 2016b). These data show that high PCDD/F values of dust samples derived from primitive crude e-waste recycling activities may ultimately transfer to the indoor environments in these EWRS.

Sediments have a large adsorption capacity which makes them major reservoirs and sinks for chemicals. DLCs prefer adsorption to sediments because of their hydrophobic properties (Evenset et al., 2007). The sediment PCDD/F concentrations in Lianjiang river of Guiyu ranged from 21.2 to 35,200.0 pg WHO-TEQ g^{-1} dw, which were noticeably higher than that in locations downstream from Guiyu (Luksemburg et al., 2002), and in Korle lagoon adjacent to Agbogbloshie e-waste disposal and burning areas (988.0 pg WHO-TEQ g^{-1} dw) (Brigden et al., 2008). For sediments collected from an EWRS of Qingyuan, the mean TEQ concentrations of PCDD/Fs and PBDD/Fs were 128.0 and 146.0 pg WHO-TEQ g^{-1} dw, respectively (Hu et al., 2013), higher than that in sediments of an EWRS in Bui Dau (7.3 and 4.4 pg WHO-TEQ g^{-1} dw, respectively) (Suzuki et al., 2016).

3.4. Human body burdens

In recent years, DLC concentrations in human matrices, such as human hair, breast milk and blood, have been extensively measured to assess individual exposure (Table 4) and the health effects (Table 1). Hair is one of the best mediums to reflect short-term contaminant

exposure derived from direct atmospheric deposition (Covaci et al., 2002; Nakao et al., 2005). Mean PCDD/F concentrations in the hair of residents from EWRS of China, such as Guiyu, Taizhou and Fengjiang, have been measured at 21.0, 36.1 and 33.8 pg WHO-TEQ g^{-1} dw, respectively (Chan et al., 2007; Luksemburg et al., 2002; Ma et al., 2011). These levels are markedly higher than hair samples of municipal solid waste incineration workers (Liu et al., 2019b) and the general population from Shanghai (2.2 pg WHO-TEQ g^{-1} dw) and Hangzhou (5.6 pg WHO-TEQ g^{-1} dw) (Li et al., 2007). The average PCDD/F concentration of maternal breast milk (21.0 pg WHO-TEQ g^{-1} lipid) in Taizhou is higher than that of Vietnam residents living near Da Nang Air Base (12.7 pg WHO-TEQ g^{-1} lipid) which has been proved to be adversely associated with the growth and neurodevelopment of children (Chan et al., 2007; Pham et al., 2015; Tai et al., 2016; Tran et al., 2016). Compared with maternal breast milk samples collected in 2005 (21.0 pg WHO-TEQ g^{-1} lipid), the PCDD/F concentrations in breast milk were notably lower in 2015 (12.9 pg WHO-TEQ g^{-1} lipid) (Wang et al., 2019), but were still much higher than the average level of the Chinese general population (4.9 pg WHO-TEQ g^{-1} lipid) (Zhang et al., 2016b). Breast milk PCDD/F levels were reported to be associated with physical growth of 3-year-old children (Wang et al., 2019). The placenta PCDD/F and DL-PCB concentrations in Taizhou (31.2 pg WHO-TEQ g^{-1} lipid) were much higher than that in Taiwan (14.8 pg WHO-TEQ g^{-1} lipid) which have been reported to be associated with growth, hormone levels and reproductive development (Su et al., 2012). The blood PCDD/F and DL-PCB levels of children in Taizhou (22.2 pg WHO-TEQ g^{-1} lipid) were comparable to that of Russian boys (21.1 pg WHO-TEQ g^{-1} lipid) which were reported to be associated with delayed pubertal onset and sexual maturity (Shen et al., 2010; Burns et al., 2016). Maternal blood PCDD/F and DL-PCB concentrations of primiparous Ghanaians living near EWRS (3.1 pg WHO-TEQ g^{-1} lipid) were lower than that of the Sapporo cohort of the Hokkaido Study on Environment and Children's Health in Japan (14.9 pg WHO-TEQ g^{-1} lipid) which were known to be related with lower birth weight, immune function and neurodevelopment of their infants (Bruce-Vanderpuije et al., 2019; Kishi et al., 2013). However, limited information was found on maternal blood DLC levels in other EWRS.

The blood PCDD/F and DL-PCB concentrations of these high (New

Table 4
Body burdens of PCDD/Fs and DL-PCBs at typical EWRS and some other locations.

Country	City	Study population	Data type	PCDD/Fs	DL-PCBs	Sampling year	Reference
Hair (pg WHO-TEQ g^{-1} dw)							
China	Guiyu	Residents living near EWRS	Mean	21.0			(Luksemburg et al., 2002)
China	Taizhou	Mothers living near EWRS	Mean (2005)	33.8		2005	(Chan et al., 2007)
China	Taizhou	E-waste workers	Mean (2006)	42.4	41.5	2006	(Wen et al., 2008)
China	Taizhou	E-waste workers	Mean (2007)	36.1		2007	(Ma et al., 2011)
China	South	Waste incineration workers	Median	1.7			(Liu et al., 2019b)
China	Hangzhou	General mothers	Mean	5.6		2005	(Chan et al., 2007)
China	Shanghai	General population	Mean	2.2		2007	(Ma et al., 2011)
Cord blood (pg WHO-TEQ g^{-1} lipid)							
China	Guiyu	Neonates born near EWRS	Median	3.9	16.0	2007	(Liu et al., 2019a)
China	Taizhou	Neonates born near EWRS	Median		18.0	2002	(Zhao et al., 2007)
China	Taiwan	General neonates	Mean	5.4	1.3	2000–2001	(Wang et al., 2004)
Vietnam	Bien Hoa	Neonates born near airbase	Mean	14.5		2012	(Boda et al., 2018)
Blood (pg WHO-TEQ g^{-1} lipid)							
Ghana	Agbogbloshie	E-waste workers	Median	6.2		2011	(Wittsiepe et al., 2015)
Ghana	Agbogbloshie	Mothers living near EWRS	Mean	3.8	1.5	2017	(Bruce-Vanderpuije et al., 2019)
China	Taizhou	Children living near EWRS	Mean	10.3	11.9	2008	(Shen et al., 2010)
China	Taizhou	Children living near EWRS	Mean	8.4			(Xu et al., 2014)
Japan	Sapporo	General mothers	Mean	10	4.9	2002–2005	(Konishi et al., 2009)
China	Taiwan	General mothers	Mean	9.1	4.5	2000–2001	(Wang et al., 2004)
Russia	Chapaevsk	Boys living near chemical industries	Median DLCs	21.1		2003–2005	(Burns et al., 2016)
America		Ranch Hand veterans	Mean	(40.8[a])		1982 ~ 15 y	(Michalek and Tripathi, 1999)
America		Ranch Hand veterans	Median PCDDs PCDFs	18.7 (5.0[a]) 3.4		2002 ~ 33 y	(Pavuk et al., 2014)
Vietnam	Bien Hoa	Men living near airbase	Mean	34.0 (7.3[a])	3.3	2014	(Van Luong et al., 2018)
Germany	Duisburg	Women living in industrialized area	Median	15.3	10.8	2000–2003	(Wittsiepe et al., 2007)
New Zealand		Herbicide production plant workers	Mean	(109.0[a])		1987 ~ 0 y	('t Mannetje et al., 2016)
New Zealand		Herbicide production plant workers	Mean	30.0 (19.1[a])	3.7	2007 ~ 20 y	('t Mannetje et al., 2016)
Italy	Seveso	Women experienced chemical explosion	Median	(105.0[a])		1976 ~ 0 y	(Warner et al., 2013a)
Italy	Seveso	Women experienced chemical explosion	Median DLCs	26.2 (7.3[a])		1996 ~ 20 y	(Warner et al., 2013a)
Breast milk (pg WHO-TEQ g^{-1} lipid)							
China	Guiyu	Mothers living near EWRS	Mean		0.9	2006	(Xing et al., 2009)
China	Taizhou	Mothers living near EWRS	Mean	21.0		2005	(Chan et al., 2007)
China	Taizhou	Mother living near EWRS	Mean	12.9		2015	(Wang et al., 2019)
China	Hangzhou	General mothers	Mean	9.4		2005	(Chan et al., 2007)
Vietnam	Bui Dau	Mothers living near EWRS	Range PCDFs	13.0[a]–15.0[a]	6600.0[a]–7600.0[a]	2008	(Tue et al., 2014)
China	Taiwan	General mothers	Mean	7.6	5.2	2000–2001	(Wang et al., 2004)
Vietnam	Bien Hoa	Mothers living near airbase	Mean	11.3		2012	(Boda et al., 2018)
Spain	Tarragon	Mothers living near incinerators		7.6		2007	(Schuhmacher et al., 2009)
Germany	Duisburg	Mothers living in industrialized area	Median	23.9	24.5	2000–2003	(Wittsiepe et al., 2007)
Placenta (pg WHO-TEQ g^{-1} lipid)							
China	Taizhou	Mothers living near EWRS	Mean	31.2		2005	(Chan et al., 2007)
China	Hangzhou	General mothers	Mean	11.9		2005	(Chan et al., 2007)
China	Taiwan	General mothers	Mean	10.3	2.9	2000–2001	(Wang et al., 2004)
Meconium (pg WHO-TEQ g^{-1} dw)							
China	Taizhou	Neonates born near EWRS	Median		0.8	2002	(Zhao et al., 2007)

[a] pg g^{-1} lipid; TCDD concentrations are given in parentheses.

Zealand, Seveso, Vietnam, Ranch Hand veterans) and background (Japan, Taiwan) exposed cohorts ranged from 13.6 to 37.8 pg WHO-TEQ g^{-1} lipid, which were reported to be associated with numerous observable adverse health effects. The average blood PCDD/F and DL-PCB levels of children in Taizhou were in the middle range. Although there is a lack of comprehensive data on the DLC body burden of people in EWRS, considering the high environmental levels in EWRS, we can infer that they are at high health risks, especially in the case of children and infants. Health effects related to DLC exposure of people in EWRS have to our knowledge been rarely studied. Meanwhile, information on human body burdens of PBDD/Fs and PXDD/Fs in EWRS is notably scarce, and is currently available only for small numbers of maternal serum samples of women living near Agbogbloshie EWRS (0.49 and 0.50 pg WHO-TEQ g^{-1} lipid, respectively) (Bruce-Vanderpuije et al., 2019) and breast milk samples of women living in Vietnamese EWRS (Tue et al., 2014). The data suggest that e-waste recycling activities contribute to high DLC body burdens of people in EWRS and may put them at high health risk.

3.5. Exposure and health risk assessment

Human exposures to PCDD/Fs and PBDD/Fs in EWRS through air inhalation, soil/dust ingestion, dermal absorption, and dietary intake are either adopted or derived from the published data (Table 5), which are estimated based on the models, originated from Nouwen et al. (2001) and simplified by Minh et al. (2003). Although direct summation and comparison of daily intakes from different exposure pathways can in some cases be confounding as the differences in sampling, analyzing, and treating data of the studies, it provides some generalizations on the total PCDD/Fs and PBDD/Fs exposures via different pathways in EWRS (Chan and Wong, 2013).

Total daily intakes of PCDD/Fs through four exposure ways in EWRS of China are much higher than that in waste incinerators of Wilrijk, Belgium (Chan and Wong, 2013; Nouwen et al., 2001). Soil ingestion and dermal absorption of PCDD/Fs and PBDD/Fs in EWRS of China are comparable to that of Ghana (Hu et al., 2013; Ma et al., 2008, 2009; Tue et al., 2019; Xiao et al., 2016). PCDD/F exposures through soil ingestion and dermal absorption in India and Vietnam are much lower than that in EWRS of China and Ghana, comparable to that in open dumping sites (Chakraborty et al., 2018; Suzuki et al., 2016; Minh et al., 2003). Although there is a lack of data on air and food DLC concentrations in EWRS in other countries, according to the data from EWRS in China, we can infer that the total daily intake of dioxins in EWRS are comparable or much higher than the contaminated areas of open dumping and waste incineration sites.

Food consumption is the main route for the general population, accounting for approximately 90% of the tolerable daily intake (WHO, 2016). However, this estimate is not appropriate for workers involved in e-waste recycling and residents living near EWRS (Zhang et al., 2017b). They are chronically highly-exposed via inhalation and dermal absorption of DLC-contaminated vapors, fumes, fly ashes and dust (Chakraborty et al., 2016b; Wu et al., 2016). Non-dietary exposure of DLCs may contribute more to the total body burdens than dietary exposure, and may cause more severe effects on human health (Ma et al., 2008; Qin et al., 2019; Tue et al., 2010, 2014; Xing et al., 2009; Leung, 2006). Dietary ingestion of food grown on DLC-contaminated cropland next to EWRS can further increase their DLC exposure. The estimated non-dietary daily intake doses of PCDD/Fs for children and adults in

Table 5
Comparision of estimated daily intakes of PCDD/Fs and PBDD/Fs from different exposure pathways at EWRS and some other polluted sites.

City	Site	Air inhalation		Soil/dust ingestion		Dermal exposure		Dietary intake			Total intake		
		Adults	Children	Adults	Children	Adults	Children	Adults	Children	Infants	Adults	Children	Infants
PCDD/Fs (pg TEQ kg^{-1} bw day^{-1})													
Guiyu, China	EWRS	2.54[a]	4.50[a]	0.15[b]	1.68[b]	0.35[b]	0.30[b]	4.55[d]	6.67[d,e]	102.98[f]	7.59	13.15	105.14
Taizhou, China	EWRS	0.68[c]	1.21[c]	0.22[b]	2.25[b]	0.14[b]	0.048[b]	4.55[d]	6.67[d,e]	102.98[f]	5.59	10.18	104.15
Qingyuan, China	EWRS	1.82[g]	3.22[g]	0.081[h]	0.84[h]	0.065[h]	0.032[h]	4.55[d]	6.67[d,e]	102.98[f]	6.52	10.76	104.34
New Delhi, Kolkata, Mumbai, Chennai, India	EWRS			0.0090[i]	0.10[i]	0.021[i]	0.018 [i]						
Agbogbloshie, Ghana	EWRS			0.11[j]	1.20[j]	0.25[j]	0.21[j]						
Bui Dau, Vietnam	EWRS			0.023[k]	0.26[k]	0.053[k]	0.046[k]						
Chennai, India	Open dumping sites			0.015[l]	0.17[l]	0.036[l]	0.031[l]						
Hanoi, Vietnam	Open dumping sites			0.030[l]	0.34[l]	0.071[l]	0.061[l]						
Wilrijk, Belgium	Waste incinerators	0.0065[m]	0.001[m]	0.008[m]	0.068[m]	0.0073[m]	0.015[m]	0.71[m]	2.63[m]		0.73	2.72	
PBDD/Fs (pg TEQ kg^{-1} bw day^{-1})													
Guiyu, China	EWRS	3.37[a]	5.98[a]										
Taizhou, China	EWRS	0.45[n]	0.79[n]	0.37[o]	4.06[o]	0.63[o]	0.11[o]	6.26[p]			7.71		
Qingyuan, China	EWRS	0.30[q]	0.71[q]	0.081[q]	0.94[q]	0.33[q]	0.28[q]	7.56[p]			8.27		
Agbogbloshie, Ghana	EWRS			0.25[j]	2.89[j]	0.60[j]	0.52[j]						
Bui Dau, Vietnam	EWRS			0.004[k]	0.047[k]	0.0097[k]	0.0084[k]						

[a] Li et al. (2007).
[b] Ma et al. (2008).
[c] Wen et al. (2011).
[d] Song et al. (2011).
[e] Liu et al. (2010).
[f] Chan et al. (2007).
[g] Xiao et al. (2014).
[h] Hu et al. (2013).
[i] Chakraborty et al. (2018).
[j] Tue et al. (2019).
[k] Suzuki et al. (2016).
[l] Minh et al. (2003).
[m] Nouwen et al. (2001).
[n] Zhou (2011).
[o] Ma et al. (2009).
[p] Miyake et al. (2008).
[q] Xiao et al. (2016).

three major EWRS of China account for 19% − 54% (mean 40%) of the total daily intake, which far exceeds the WHO recommended total daily intake limit [1–4 pg TEQ kg^{-1} body weight (bw) day^{-1}] (WHO, 1998b; van Leeuwen et al., 2000). High exposure quantity and absorption rate lead to higher intake of PCDD/Fs by infants (103.0 pg WHO-TEQ kg^{-1} bw day^{-1}) for their exclusive consumption of breast milk with relatively high PCDD/F concentration in Taizhou (Li et al., 2007; Gies et al., 2007). That is higher than the daily intake of Taiwan infants (38.4 pg WHO-TEQ kg^{-1} bw day^{-1}) (Wang et al., 2004) and comparable to that of Duisburg infants (131.0 pg WHO-TEQ kg^{-1} bw day^{-1}) (Wittsiepe et al., 2007), both of which have been reported to adversely affect their neurological and reproductive development (Su et al., 2012; Nowack et al., 2015). Infants and Children are more vulnerable to DLCs because they are at critical windows of growth and development with immature body defenses and faster absorption (Chen et al., 2011). Their lower body weight and larger ingestion of contaminated dust and soil than adults can further increase their toxicant body load. There is need for additional investigation and priority protection (Song and Li, 2014; Heacock et al., 2016; UN Human Rights, 2016; WHO, 2017).

4. Foresight from current knowledge

4.1. Data gaps

Since the Stockholm Convention came into force in 2004, many countries have carried out nationwide periodical monitoring of background concentrations of DLCs (UNEP, 2016). However, there are limited case studies on reducing environment levels and body burdens of DLCs after action was taken. Although there are many epidemiological studies on the health effects of PCDD/F and DL-PCB exposure in the world, weak associations, inconsistent findings across studies, complex contaminant mixture, and poor understanding of biological mechanisms make it hard to establish causal relationships. There are also few studies of the body burdens of DLCs and their related health outcomes among people in EWRS with such high DLC contamination. Possible reasons for the scarce data may be the complexity and high costs of sampling and analysis, and the difficulties in assessing compounded health risks posed by multi-contaminant exposure derived from informal e-waste recycling. The potential complex interactions for synergistic effects between the chemical components of e-waste have not been well explored or understood. We can only compare the body burdens of DLCs in EWRS with levels observed in epidemiological studies that are associated with various health outcomes to assess the health risk of people living in EWRS.

4.2. Future work

In the future, intervention and prevention approaches should be adopted to address the DLC problems in EWRS, including enhancing regulations, developing a new generation of electronics, assessing exposures and related health effects in informal e-recycling, improving formal recycling technologies, and developing effective remedial techniques to contain and eliminate legacy sources of exposure (Ceballos and Dong, 2016; Bakhiyi et al., 2018; Heacock et al., 2016; Asante et al., 2019). Stakeholders in the international health community, academia, industry, policy experts and governments should then cooperate to build a more recyclable electronics system, promote e-waste recovery, re-use, and prevention, to control the release of DLCs in the e-waste disposal stream (Heacock et al., 2018; WEF, 2019). Although the existing measures have led to progress in reduced releases of DLCs, the pollution status in EWRS is still considered severe (Fu et al., 2012; Zhang et al., 2017b). This will require further industrial reforms and scientific investigations.

For effective assessment of environmental and human exposure to DLCs in informal EWRS, comprehensive emission inventories of DLCs from e-waste processing and their environmental emission factors need to be investigated and linked with atmospheric deposition or ambient air monitoring data. Continuous monitoring in EWRS of DLC release, levels in different environmental media, food and the human body, potential trends over time, and related human health effects are urgently needed. PBDD/Fs and PXDD/Fs should be considered and included in future biomonitoring studies on DLCs because of their significant TEQ contribution. Further investigations on the potencies and toxicokinetics of PBDD/F and PXDD/Fs are necessary to develop a consensus for their TEF. E-waste groups worldwide should work together to develop unified environmental and biological monitoring indicators and harmonize survey instruments. Since expensive chemical DLC analytical techniques are out of reach for many resource-poor laboratories in developing countries, cheap and robust sensitive bioanalytical techniques that are easy to set up should be developed and validated. Moreover, large and high-quality epidemiological studies on human health effects of DLCs and their potential pathogenic mechanism should be conducted. Future research should pay more attention to the unity of survey methods and the standardization of the exposure reference category to control heterogeneity.

5. Conclusion

This review presents the health effects of DLCs and the severe contamination in EWRS. High DLC-contaminant concentrations derived from informal e-waste recycling put the DLC body burden of workers and residents in EWRS at a high level. Comparison with the levels reported to be associated with observable adverse effects indicate that people in EWRS may suffer higher health risks, especially for infants and children. Given the current paucity of information on the human body burdens and health effects of DLCs in EWRS, these data and findings can serve as reference values for the population in EWRS who have had long-term exposure to high DLC contamination. More importantly, intervention and prevention approaches, as well as continuous monitoring of DLCs, should be taken in EWRS to promote the reuse of e-waste and minimize the adverse impacts on people.

Funding

This work was supported by research grant of the National Natural Science Foundation of China, China (21876065).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to express our deepest appreciation to Dr. Stanley Lin and Dr. Nick Webber who devoted their time and efforts giving constructive comments and editing the English language.

References

Ahmed, O.M., El-Gareib, A.W., El-Bakry, A.M., Abd El-Tawab, S.M., Ahmed, R.G., 2008. Thyroid hormones states and brain development interactions. Int. J. Dev. Neurosci. 26, 147–209.

Alonso-Magdalena, P., Quesada, I., Awasthi, A., 2011. Endocrine disruptors in the etiology of type 2 diabetes mellitus. Nat. Rev. Endocrinol. 7, 346.

Ames, J., Warner, M., Brambilla, P., Mocarelli, P., Satariano, W.A., Eskenazi, B., 2018a. Neurocognitive and physical functioning in the Seveso Women's Health Study. Environ. Res. 162, 55–62.

Ames, J., Warner, M., Mocarelli, P., Brambilla, P., Signorini, S., Siracusa, C., Huen, K., Holland, N., Eskenazi, B., 2018b. AHR gene-dioxin interactions and birthweight in the Seveso Second Generation Health Study. Int. J. Epidemiol. 47, 1992–2004.

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, 425–433.
Asante, K.A., Amoyaw-Osei, Y., Agusa, T., 2019. E-waste recycling in Africa: risks and opportunities. Curr. Opin. Green Sustain. Chem. 18, 109–117.
Awasthi, A.K., Cucchiella, F., D'Adamo, I., Li, J., Rosa, P., Terzi, S., Wei, G., Zeng, X., 2018. Modelling the correlations of e-waste quantity with economic increase. Sci. Total Environ. 613–614, 46–53.
Baccarelli, A., Giacomini, S.M., Corbetta, C., Landi, M.T., Bonzini, M., Consonni, D., Grillo, P., Patterson Jr., D.G., Pesatori, A.C., Bertazzi, P.A., 2008. Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. PLoS Med. 5, e161.
Baccarelli, A., Hirt, C., Pesatori, A.C., Consonni, D., Patterson Jr., D.G., Bertazzi, P.A., Dölken, G., Landi, M.T., 2006. t(14;18) translocations in lymphocytes of healthy dioxin-exposed individuals from Seveso, Italy. Carcinogenesis 27, 2001–2007.
Baccarelli, A., Mocarelli, P., Patterson Jr., D.G., Bonzini, M., Pesatori, A.C., Caporaso, N., Landi, M.T., 2002. Immunologic effects of dioxin: new results from Seveso and comparison with other studies. Environ. Health Perspect. 110, 1169–1173.
Baccarelli, A., Pesatori, A.C., Masten, S.A., Patterson, D.G., Needham, L.L., Mocarelli, P., Caporaso, N.E., Consonni, D., Grassman, J.A., Bertazzi, P.A., Landi, M.T., 2004. Aryl-hydrocarbon receptor-dependent pathway and toxic effects of TCDD in humans: a population-based study in Seveso, Italy. Toxicol. Lett. 149, 287–293.
Bakhiyi, B., Gravel, S., Ceballos, D., Flynn, M.A., Zayed, J., 2018. Has the question of e-waste opened a Pandora's box? An overview of unpredictable issues and challenges. Environ. Int. 110, 173–192.
Balde, C.P., Forti, V., Gray, V., Kuehr, R., Stegmann, P., 2017. The global e-waste monitor 2017: quantities, flows and resources. United Nations University, International Telecommunication Union, and International Solid Waste Association, Bonn, Geneva, and Vienna.
Bergman, Å., Heindel, J.J., Jobling, S., Kidd, K., Zoeller, T.R., 2013. State of the science of endocrine disrupting chemicals – 2012. United Nations Environment Programme/World Health Organization. http://apps.who.int/iris/bitstream/10665/78102/1/WHO_HSE_PHE_IHE_2013.1_eng.pdf/ (accessed 1 October 2019).
Berry, R.M., Luthe, C.E., Voss, R.H., 1993. Ubiquitous nature of dioxins: a comparison of the dioxins content of common everyday materials with that of pulps and papers. Environ. Sci. Technol. 27, 1164–1168.
Bertazzi, P.A., Bernucci, I., Brambilla, G., Consonni, D., Pesatori, A.C., 1998. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ. Health Perspect. 106, 625–633.
Bertazzi, P.A., Consonni, D., Bachetti, S., Rubagotti, M., Baccarelli, A., Zocchetti, C., Pesatori, A.C., 2001. Health effects of dioxin exposure: a 20-year mortality study. Am. J. Epidemiol. 153, 1031–1044.
Beszterda, M., Franski, R., 2018. Endocrine disruptor compounds in environment: as a danger for children health. Pediatr. Endocrinol. Diabetes Metab. 24, 88–95.
Birnbaum, L.S., Staskal, D.F., Diliberto, J.J., 2003. Health effects of polybrominated dibenzo-p-dioxins (PBDDs) and dibenzofurans (PBDFs). Environ. Int. 29, 855–860.
Boda, H., Nghi, T.N., Nishijo, M., Thao, P.N., Tai, P.T., Van Luong, H., Anh, T.H., 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.
Breivik, K., Armitage, J.M., Wania, F., Jones, K.C., 2014. Tracking the global generation and exports of e-waste. Do existing estimates add up? Environ. Sci. Technol. 48, 8735–8743.
Brigden, K., Labunska, I., Santillo, D., Johnston, P., 2008. Chemical contamination at e-waste recycling and disposal sites in Accra and Korforidua, Ghana. Greenpeace Research Laboratories Technical Note. http://www.greenpeace.to/greenpeace/wp-content/uploads/2011/05/chemical-contamination-at-e-wa.pdf/ (accessed 16 July 2019).
Bruce-Vanderpuije, P., Megson, D., Jobst, K., Jones, G.R., Reiner, E., Sandau, C.D., Clarke, E., Adu-Kumi, S., Gardella, J.A., 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.
Buffler, P.A., Ginevan, M.E., Mandel, J.S., Watkins, D.K., 2011. The Air Force health study: an epidemiologic retrospective. Ann. Epidemiol. 21, 673–687.
Burns, J.S., Lee, M.M., Williams, P.L., Korrick, S.A., Sergeyev, O., Lam, T., Revich, B., Hauser, R., 2016. Associations of peripubertal serum dioxin and polychlorinated biphenyl concentrations with pubertal timing among Russian boys. Environ. Health Perspect. 124, 1801–1807.
Butte, W., Heinzow, B., 2002. Pollutants in house dust as indicators of indoor contamination. In: Ware, G.W. (Ed.), Reviews of Environmental Contamination and Toxicology. Springer-Verlag, New York, pp. 1–46.
Calvert, G.M., Sweeney, M.H., Deddens, J., Wall, D.K., 1999. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Occup. Environ. Med. 56, 270–276.
Camacho, I.A., Nagarkatti, M., Nagarkatti, P.S., 2004. Evidence for induction of apoptosis in T cells from murine fetal thymus following perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol. Sci. 78, 96–106.
Cano-Sancho, G., Ploteau, S., Matta, K., Adoamnei, E., Louis, G.B., Mendiola, J., Darai, E., Squifflet, J., Le Bizec, B., Antignac, J.P., 2019. Human epidemiological evidence about the associations between exposure to organochlorine chemicals and endometriosis: systematic review and meta-analysis. Environ. Int. 123, 209–223.
Caspersen, I.H., Aase, H., Biele, G., Brantsæter, A.L., Haugen, M., Kvalem, H.E., Skogan, A.H., Zeiner, P., Alexander, J., Meltzer, H.M., Knutsen, H.K., 2016a. The influence of maternal dietary exposure to dioxins and PCBs during pregnancy on ADHD symptoms and cognitive functions in Norwegian preschool children. Environ. Int. 94, 649–660.
Caspersen, I.H., Haugen, M., Schjølberg, S., Vejrup, K., Knutsen, H.K., Brantsæter, A.L., Meltzer, H.M., Alexander, J., Magnus, P., Kvalem, H.E., 2016b. Maternal dietary exposure to dioxins and polychlorinated biphenyls (PCBs) is associated with language delay in 3 year old Norwegian children. Environ. Int. 91, 180–187.
Ceballos, D.M., Dong, Z., 2016. The formal electronic recycling industry: challenges and opportunities in occupational and environmental health research. Environ. Int. 95, 157–166.
Chakraborty, P., Prithiviraj, B., Selvaraj, S., Kumar, B., 2016b. Polychlorinated biphenyls in settled dust from informal electronic waste recycling workshops and nearby highways in urban centers and suburban industrial roadsides of Chennai city, India: levels, congener profiles and exposure assessment. Sci. Total Environ. 573, 1413–1421.
Chakraborty, P., Selvaraj, S., Nakamura, M., Prithiviraj, B., Cincinelli, A., Bang, J.J., 2018. PCBs and PCDD/Fs in soil from informal e-waste recycling sites and open dumpsites in India: levels, congener profiles and health risk assessment. Sci. Total Environ. 621, 930–938.
Chakraborty, P., Selvaraj, S., Nakamura, M., Prithiviraj, B., Ko, S., Loganathan, B., 2016a. E-waste and associated environmental contamination in the Asia/Pacific region (Part2): A case study of dioxins and furansin e-waste recycling/dump sites in India, in Loganathan, B.G., Khim, J.S., Kodavanti, P.R.S., Masunaga, S., (Eds.), Persistent organic chemicals in the environment: Status and trends in the Pacific asin countries I contamination status. ACS Publications, pp. 139–154.
Chan, J.K.Y., Wong, M.H., 2013. A review of environmental fate, body burdens, and human health risk assessment of PCDD/Fs at two typical electronic waste recycling sites in China. Sci. Total Environ. 463–464, 1111–1123.
Chan, J.K.Y., Xing, G.H., Xu, Y., Liang, Y., Chen, L.X., Wu, S.C., Wong, C.K.M., Leung, C.K.M., Wong, M.H., 2007. Body loadings and health risk assessment of polychlorinated dibenzo-p-dioxins and dibenzofurans at an intensive electronic waste recycling site in China. Environ. Sci. Technol. 41, 7668–7674.
Chang, J.W., Chen, H.L., Su, H.J., Liao, P.C., Guo, H.R., Lee, C.C., 2011. Simultaneous exposure of non-diabetics to high levels of dioxins and mercury increases their risk of insulin resistance. J. Hazard. Mater. 185, 749–755.
Chang, J.W., Chen, H.L., Su, H.J., Liao, P.C., Guo, H.R., Lee, C.C., 2010. Dioxin exposure and insulin resistance in Taiwanese living near a highly contaminated area. Epidemiology. 21, 56–61.
Chen, A., Dietrich, K.N., Huo, X., Ho, S.M., 2011. Developmental neurotoxicants in e-waste: an emerging health concern. Environ. Health Perspect. 119, 431–438.
Chen, H.L., Su, H.J., Guo, Y.L., Liao, P.C., Hung, C.F., Lee, C.C., 2006. Biochemistry examinations and health disorder evaluation of Taiwanese living near incinerators and with low serum PCDD/Fs levels. Sci. Total Environ. 366, 538–548.
Chevrier, J., Warner, M., Gunier, R.B., Brambilla, P., Eskenazi, B., Mocarelli, P., 2014. Serum dioxin concentrations and thyroid hormone levels in the Seveso Women's Health Study. Am. J. Epidemiol. 180, 490–498.
Colborn, T., vom Saal, F.S., Soto, A.M., 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ. Health Perspect. 101, 378–384.
Consonni, D., Pesatori, A.C., Zocchetti, C., Sindaco, R., D'Oro, L.C., Rubagotti, M., Bertazzi, P.A., 2008. Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. Am. J. Epidemiol. 167, 847–858.
Covaci, A., Tutudaki, M., Tsatsakis, A.M., Schepens, P., 2002. Hair analysis: Another approach for the assessment of human exposure to selected persistent organochlorine pollutants. Chemosphere 46, 413–418.
Cranmer, M., Louie, S., Kennedy, R.H., Kern, P.A., Fonseca, V.A., 2000. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is associated with hyperinsulinemia and insulin resistance. Toxicol. Sci. 56, 431–436.
Damstra, T., Barlow, S., Bergman, A., Kavlock, R., Van Der Kraak, G., 2002. Global assessment of the state of the science of endocrine disruptors. World Health Organization/International Programme on Chemical Safety. Geneva, Switzerland.
Danjou, A.M.N., Coudon, T., Praud, D., Lévêque, E., Faure, E., Salizzoni, P., Le Romancer, M., Severi, G., Mancini, F.R., Leffondré, K., Dossus, L., Fervers, B., 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.
Den Hond, E., Roels, H.A., Hoppenbrouwers, K., Nawrot, T., Thijs, L., Vandermeulen, C., Winneke, G., Vanderschueren, D., Staessen, J.A., 2002. Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. Environ. Health Perspect. 110, 771–776.
Department of Veterans Affairs, 2001. Disease associated with exposure to certain herbicide agents: type 2 diabetes. https://www.federalregister.gov/d/01-11569/ (accessed 16 July 2019). Final rule. Fed. Regist. 23, 166-169.
Dietert, R.R., 2009. Developmental immunotoxicology: focus on health risks. Chem. Res. Toxicol. 22, 17–23.
Duan, H., Li, J., Liu, Y., Yamazaki, N., Jiang, W., 2011. Characterization and inventory of PCDD/Fs and PBDD/Fs emissions from the incineration of waste printed circuit board. Environ. Sci. Technol. 45, 6322–6328.
Dzierlenga, M.W., Yoon, M., Wania, F., Ward, P.L., Armitage, J.M., Wood, S.A., Clewell, H.J., Longnecker, M.P., 2019. Quantitative bias analysis of the association of type 2 diabetes mellitus with 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153). Environ. Int. 125, 291–299.
Dwernychuk, L.W., Cau, H.D., Hatfield, C.T., Boivin, T.G., Hung, T.M., Dung, P.T., Thai, N.D., 2002. Dioxin reservoirs in southern Viet Nam—a legacy of Agent Orange. Chemosphere 47, 117–137.
Ebert, E., Bahadir, M., 2003. Formation of PBDD/F from flame-retarded plastic materials under thermal stress. Environ. Int. 29, 711–716.
Egeland, G.M., Sweeney, M.H., Fingerhut, M.A., Wille, K.K., Schnorr, T.M., Halperin, W.E., 1994. Total serum testosterone and gonadotropins in workers exposed to dioxin. Am. J. Epidemiol. 139, 272–281.
Eurostat Statistics Explained, 2019. Waste statistics - electrical and electronic equipment. https://ec.europa.eu/eurostat/statistics-explained/index.php/Waste_statistics_-_electrical_and_electronic_equipment/ (accessed 8 August 2019).
Eskenazi, B., Mocarelli, P., Warner, M., Chee, W.Y., Gerthoux, P.M., Samuels, S.,

Needham, L.L., Patterson Jr., D.G., 2003. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. Environ. Health Perspect. 111, 947–953.
Eskenazi, B., Mocarelli, P., Warner, M., Samuels, S., Vercellini, P., Olive, D., Needham, L.L., Patterson Jr., D.G., Brambilla, P., Gavoni, N., Casalini, S., Panazza, S., Turner, W., Gerthoux, P.M., 2002a. Serum dioxin concentrations and endometriosis: a cohort study in Seveso. Italy. Environ. Health Perspect. 110, 629–634.
Eskenazi, B., Warner, M., Brambilla, P., Signorini, S., Ames, J., Mocarelli, P., 2018. The Seveso accident: a look at 40 years of health research and beyond. Environ. Int. 121, 71–84.
Eskenazi, B., Warner, M., Marks, A.R., Samuels, S., Gerthoux, P.M., Vercellini, P., Olive, D.L., Needham, L., Patterson Jr., D.G., Mocarelli, P., 2005. Serum dioxin concentrations and age at menopause. Environ. Health Perspect. 113, 858–862.
Eskenazi, B., Warner, M., Marks, A.R., Samuels, S., Needham, L., Brambilla, P., Mocarelli, P., 2010. Serum dioxin concentrations and time to pregnancy. Epidemiology 21, 224–231.
Eskenazi, B., Warner, M., Mocarelli, P., Samuels, S., Needham, L.L., Patterson Jr., D.G., Lippman, S., Vercellini, P., Gerthoux, P.M., Brambilla, P., Olive, D., 2002b. Serum dioxin concentrations and menstrual cycle characteristics. Am. J. Epidemiol. 156, 383–392.
Evenset, A., Christensen, G.N., Carroll, J., Zaborska, A., Berger, U., Herzke, D., Gregor, D., 2007. Historical trends in persistent organic pollutants and metals recorded in sediment from Lake Ellasjøen, Bjørnøya, Norwegian Arctic. Environ. Pollut. 146, 196–205.
Everett, C.J., Frithsen, I.L., Diaz, V.A., Koopman, R.J., Simpson, W.M., Mainous, A.G., 2007. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999–2002 National Health and Nutrition Examination Survey. Environ. Res. 103, 413–418.
Fierens, S., Mairesse, H., ois Heilier, J.F., De Burbure, C., ois Focant, J.F., Eppe, G., De Pauw, E., Bernard, A., 2003. Dioxin/polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. Biomark. 8, 529–534.
Fine, J.S., Gasiewicz, T.A., Silverstone, A.E., 1989. Lymphocyte stem cell alterations following perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Mol. Pharmacol. 35, 18–25.
Fu, J., Wang, T., Wang, P., Qu, G., Wang, Y., Zhang, Q., Zhang, A., Jiang, G., 2012. Temporal trends (2005–2009) of PCDD/Fs, PCBs, PBDEs in rice hulls from an e-waste dismantling area after stricter environmental regulations. Chemosphere 88, 330–335.
Fu, J., Zhang, H., Zhang, A., Jiang, G., 2018. E-waste recycling in China: a challenging field. Environ. Sci. Technol. 52, 6727–6728.
Garg, N., Adhana, D., 2019. E-waste management in India: a study of current scenario. Int. J. Manag. Technol. Eng. 9, 2249–7455.
Gehrs, B.C., Riddle, M.M., Williams, W.C., Smialowicz, R.J., 1997. Alterations in the developing immune system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin II. Effects on the fetus and the neonate. Toxicology 122, 219–228.
Giacomini, S.M., Hou, L., Bertazzi, P.A., Baccarelli, A., 2006. Dioxin effects on neonatal and infant thyroid function: routes of perinatal exposure, mechanisms of action and evidence from epidemiology studies. Int. Arch. Occup. Environ. Health 79, 396–404.
Gies, A., Neumeier, G., Rappolder, M., Konietzka, R., 2007. Risk assessment of dioxins and dioxin-like PCBs in food—comments by the German Federal Environmental Agency. Chemosphere 67, S344–S349.
Government of India (GOI), 2016. Hazardous and Other Wastes (Management and Transboundary Movement) Rules, Ministry of Environment, Forest and Climate Change (MoEFCC), New Delhi.
Goodman, M., Narayan, K.M.V., Flanders, D., Chang, E.T., Adami, H.O., Boffetta, P., Mandel, J.S., 2015. Dose-response relationship between serum 2,3,7,8-tetrachlorodibenzo-p-dioxin and diabetes mellitus: a meta-analysis. Am. J. Epidemiol. 181, 374–384.
Grant, K., Goldizen, F.C., Sly, P.D., Brune, M.N., Neira, M., van den Berg, M., Norman, R.E., 2013. Health consequences of exposure to e-waste: a systematic review. Lancet Glob. Health 1, e350–e361.
Guo, Y.L., Lambert, G.H., Hsu, C.C., Hsu, M.M.L., 2004. Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. Int. Arch. Occup. Environ. Health 77, 153–158.
Guo, Z., Xie, H.Q., Zhang, P., Luo, Y., Xu, T., Liu, Y., Fu, H., Xu, L., Valsami-Jones, E., Boksa, P., Zhao, B., 2018. Dioxins as potential risk factors for autism spectrum disorder. Environ. Int. 121, 906–915.
Gupta, A., Ketchum, N., Roehrborn, C.G., Schecter, A., Aragaki, C.C., Michalek, J.E., 2006. Serum dioxin, testosterone, and subsequent risk of benign prostatic hyperplasia: a prospective cohort study of Air Force veterans. Environ. Health Perspect. 114, 1649–1654.
Guyton, K.Z., Kyle, A.D., Aubrecht, J., Cogliano, V.J., Eastmond, D.A., Jackson, M., Keshava, N., Sandy, M.S., Sonawane, B., Zhang, L., Waters, M.D., Smith, M.T., 2009. Improving prediction of chemical carcinogenicity by considering multiple mechanisms and applying toxicogenomic approaches. Mutat. Res. 681, 230–240.
Haijima, A., Endo, T., Zhang, Y., Miyazaki, W., Kakeyama, M., Tohyama, C., 2010. In utero and lactational exposure to low doses of chlorinated and brominated dioxins induces deficits in the fear memory of male mice. Neurotoxicology 31, 385–390.
He, X., Jing, Y., Wang, J., Li, K., Yang, Q., Zhao, Y., Li, R., Ge, J., Qiu, X., Li, G., 2015. Significant accumulation of persistent organic pollutants and dysregulation in multiple DNA damage repair pathways in the electronic-waste-exposed populations. Environ. Res. 137, 458–466.
Heacock, M., Kelly, C.B., Asante, K.A., Birnbaum, L.S., Bergman, Å.L., Bruné, M.-N., Buka, I., Carpenter, D.O., Chen, A., Huo, X., Kamel, M., Landrigan, P.J., Magalini, F., Diaz-Barriga, F., Neira, M., Omar, M., Pascale, A., Ruchirawat, M., Sly, L., Sly, P.D., Van den Berg, M., Suk, W.A., 2016. E-waste and harm to vulnerable populations: a growing global problem. Environ. Health Perspect. 124, 550–555.
Heacock, M., Trottier, B., Adhikary, S., Asante, K.A., Basu, N., Brune, M.N., Caravanos, J., Carpenter, D., Cazabon, D., Chakraborty, P., Chen, A., Barriga, F.D., Ericson, B., Fobil, J., Haryanto, B., Huo, X., Joshi, T.K., Landrigan, P., Lopez, A., Magalini, F., Navasumrit, P., Pascale, A., Sambandam, S., Aslia Kamil, U.S., Sly, L., Sly, P., Suk, A., Suraweera, I., Tamin, R., Vicario, E., Suk, W., 2018. Prevention-intervention strategies to reduce exposure to e-waste. Rev. Environ. Health 33, 219–228.
Henriksen, G.L., Ketchum, N.S., Michalek, J.E., Swaby, J.A., 1997. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8, 252–258.
Hens, B., Dyke, P.H., Hens, L., 2016. What can we learn from 'dioxin incidents'? Int. J. Environ. Pollut. 60, 34–62.
Hiester, E., Bruckmann, P., Böhm, R., Eynck, P., Gerlach, A., Mülder, W., Ristow, H., 1997. Pronounced decrease of PCDD/PCDF burden in ambient air. Chemosphere 34, 1231–1243.
Hill, A., Howard, C.V., Strahle, U., Cossins, A., 2003. Neurodevelopmental defects in zebrafish (Danio rerio) at environmentally relevant dioxin (TCDD) concentrations. Toxicol. Sci. 76, 392–399.
Hsu, P., Huang, W., Yao, W., Wu, M., Guo, Y., Lambert, G.H., 2003. Sperm changes in men exposed to polychlorinated biphenyls and dibenzofurans. JAMA 289, 2943–2944.
Hu, J., Xiao, X., Peng, P., Huang, W., Cqweraeeyttehen, D., Cai, Y., 2013. Spatial distribution of polychlorinated dibenzo-p-dioxins and dibenzo-furans (PCDDs/Fs) in dust, soil, sediment and health risk assessment from an intensive electronic waste recycling site in Southern China. Environ. Sci. Process. Impacts 15, 1889–1896.
Huang, C.Y., Wu, C.L., Yang, Y.C., Chang, J.W., Kuo, Y.C., Cheng, Y.Y., Wu, J.S., Lee, C.C., Guo, H.R., 2015. Association between dioxin and diabetes mellitus in an endemic area of exposure in Taiwan: a population-based study. Medicine 94, e1730.
International Agency for Research on Cancer (IARC), 1997. Monographs on the evaluation of carcinogenic risk to humans. Vol. 69. Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. World Health Organization, International Agency for Research on Cancer, Lyon, France.
International Agency for Research on Cancer (IARC), 2012. Monographs on the evaluation of carcinogenic risk to humans. Vol. 100 F. Chemical agents and related occupations. World Health Organization, International Agency for Research on Cancer, Lyon, France.
International Agency for Research on Cancer (IARC), 2016. Monographs on the evaluation of carcinogenic risks to humans. Vol. 107. Polychlorinated biphenyls and polybrominated biphenyls. World Health Organization, International Agency for Research on Cancer, Lyon, France.
Ip, S., Chung, M., Raman, G., Chew, P., Magula, N., DeVine, D., Trikalinos, T., Lau, J., 2007. Breastfeeding and maternal and infant health outcomes in developed countries. Evid. Rep. Technol. Assess. 153, 1–186.
Ishihara, A., Sawatsubashi, S., Yamauchi, K., 2003. Endocrine disrupting chemicals: interference of thyroid hormone binding to transthyretins and to thyroid hormone receptors. Mol. Cell. Endocrinol. 199, 105–117.
Iszatt, N., Stigum, H., Govarts, E., Murinova, L.P., Schoeters, G., Trnovec, T., Legler, J., Thomsen, C., Koppen, G., Eggesbø, M., 2016. Perinatal exposure to dioxins and dioxin-like compounds and infant growth and body mass index at seven years: a pooled analysis of three European birth cohorts. Environ. Int. 94, 399–407.
Iwegbue, C.M.A., Eyengho, S.B., Egobueze, F.E., Odali, E.W., Tesi, G.O., Nwajei, G.E., Martincigh, B.S., 2019. Polybrominated diphenyl ethers and polychlorinated biphenyls in indoor dust from electronic repair workshops in southern Nigeria: implications for onsite human exposure. Sci. Total Environ. 671, 914–927.
Jaacks, L.M., Staimez, L.R., 2015. Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: a systematic review. Environ. Int. 76, 57–70.
Kajiwara, N., Yukio, N., Takigami, H., 2008. Photolysis studies of technical decabromodiphenyl ether (DecaBDE) and ethane (DeBDethane) in plastics under natural sunlight. Environ. Sci. Technol. 42, 4404–4409.
Kang, H.K., Dalager, N.A., Needham, L.L., Patterson Jr., D.G., Lees, P.S.J., Yates, K., Matanoski, G.M., 2006. Health status of Army Chemical Corps Vietnam veterans who sprayed defoliant in Vietnam. Am. J. Ind. Med. 49, 875–884.
Kang, H.K., Mahan, C.M., Lee, K.Y., Magee, C.A., Mather, S.H., Matanoski, G., 2000. Pregnancy outcomes among U.S. women Vietnam veterans. Am. J. Ind. Med. 38, 447–454.
Kannan, K., Liao, C.Y., Moon, H.B., 2012. Polybrominated dibenzo-p-dioxins and dibenzofurans, in: Schecter, A. (Eds.), Dioxins and Health. Springer Science & Business Media, New York, pp. 255–302.
Karri, R., Tomohiko, I., Shin, T., Annamalai, S., Peethambaram, P., Shinsuke, T., 2008. Brominated flame retardants and dioxins in soils from electronic waste recycling sites in India. Organohalogen Compd. 70, 2058–2061.
Kerkvliet, N.I., 2002. Recent advances in understanding the mechanisms of TCDD immunotoxicity. Int. Immunopharmacol. 2, 277–291.
Kern, P.A., Said, S., Jackson Jr., W.G., Michalek, J.E., 2004. Insulin sensitivity following Agent Orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Clin. Endocrinol. Metab. 89, 4665–4672.
Khoa, T.V., Truong, D.T., Bac, N.D., Tai, P.T., Quang, L.B., Luong, H.V., 2015. Effects of dioxin exposure on thyroid hormones of populations living in hotspots of dioxin contamination in Vietnam. Aging Sci. 3, 1000141.
Kim, J.S., Lim, H.S., Cho, S.I., Cheong, H.K., Lim, M.K., 2003. Impact of Agent Orange exposure among Korean Vietnam veterans. Ind. Health 41, 149–157.
Kim, K.S., Shin, S.K., Kim, K.S., Song, B.J., Kim, J.G., 2008. National monitoring of PCDD/DFs in environmental media around incinerators in Korea. Environ. Int. 34, 202–209.
Kim, K.W., Won, Y.L., Ogawa, Y., 2018. Associations between blood levels of polychlorinated dibenzo-p-dioxins/furans and polychlorinated biphenyls with immune systems. Toxicol. Environ. Health Sci. 10, 17–25.
Kim, Y.A., Park, J.B., Woo, M.S., Lee, S.Y., Kim, H.Y., Yoo, Y.H., 2019. Persistent organic

pollutant-mediated insulin resistance. Int. J. Environ. Res. Public Health 16, 448.
Kincaid, J., 2019. Organohalogen contamination in Vietnamese women electronic waste recyclers living and working in rural northern Vietnam. Prehosp. Disaster Med. 34, s155.
Kishi, R., Kobayashi, S., Ikeno, T., Araki, A., Miyashita, C., Itoh, S., Sasaki, S., Okada, E., Kobayashi, S., Kashino, I., Itoh, K., Nakajima, S., 2013. Ten years of progress in the Hokkaido birth cohort study on environment and children's health: cohort profile—updated 2013. Environ. Health Prev. Med. 18, 429–450.
Kishi, R., Sasaki, S., Yoshioka, E., Yuasa, M., Sata, F., Saijo, Y., Kurahashi, N., Tamaki, J., Endo, T., Sengoku, K., Nonomura, K., Minakami, H., 2010. Cohort profile: the Hokkaido Study on Environment and Children's Health in Japan. Int. J. Epidemiol. 40, 611–618.
Klein, J., Dahlgren, J., Peckham, T., Pierce, C.H., 2011. Diabetes among residents exposed to higher chlorinated dioxins from a facility with a history of emitting pentachlorophenol. Toxicol. Lett. 205, S129.
Knafl, G.J., 2018. A reassessment of birth defects for children of participants of the Air Force Health Study. Open J. Epidemiol. 8, 187–200.
Knerr, S., Schrenk, D., 2006. Carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in experimental models. Mol. Nutr. Food Res. 50, 897–907.
Koenigsknecht, R.A., Friedman, P., 1976. Syntax development in boys and girls. Child Dev. 47, 1109–1115.
Kogevinas, M., 2001. Human health effects of dioxins: cancer, reproductive and endocrine system effects. Hum. Reprod. Update. 7, 331–339.
Kogevinas, M., Becher, H., Benn, T., Bertazzi, P.A., Boffetta, P., Bueno-de-Mesqurta, H.B., Coggon, D., Colin, D., Flesch-Janys, D., Fingerhut, M., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J.D., Neuberger, M., Pearce, N., Saracci, R., 1997. Cancer mortality in workers exposed to phenoxy herbicides, chloroophenols, and dioxin. An expanded and updated international cohort study. Am. J. Epidemiol. 145, 1061–1075.
Kokichi, A., 2018. Recent decreasing trends of exposure to PCDDs/PCDFs/dioxin like PCBs in general populations, and associations with diabetes, metabolic syndrome, and gout/hyperuricemia. J. Med. Invest. 65, 151–161.
Kondo, H., Tanio, K., Nagaura, Y., Nagayoshi, M., Mitoma, C., Furue, M., Maeda, T., 2018. Sleep disorders among Yusho patients highly intoxicated with dioxin-related compounds: a 140-case series. Environ. Res. 166, 261–268.
Koninckx, P.R., Braet, P., Kennedy, S.H., Barlow, D.H., 1994. Dioxin pollution and endometriosis in Belgium. Hum. Reprod. 9, 1001–1002.
Konishi, K., Sasaki, S., Kato, S., Ban, S., Washino, N., Kajiwara, J., Todaka, T., Hirakawa, H., Hori, T., Yasutake, D., Kishi, R., 2009. Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight. Environ. Res. 109, 906–913.
Koopman-Esseboom, C., Morse, D.C., Weisglas-Kuperus, N., Lutkeschipholt, I.J., Van Der Paauw, C.G., Tuinstra, L.G., Brouwer, A., Sauer, P.J., 1994. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr. Res. 36, 468–473.
Kulkarni, P.S., Crespo, J.G., Afonso, C.A.M., 2008. Dioxins sources and current remediation technologies — a review. Environ. Int. 34, 139–153.
Kumar, A., Holuszko, M., Espinosa, D.C.R., 2017. E-waste: An overview on generation, collection, legislation and recycling practices. Resour. Conserv. Recycl. 122, 32–42.
Le, L.T.H., Dat, N.D., Minh, N.H., Nguyen, K.A., 2019. Characteristics of PCDD/Fs in soil and sediment samples collected from A-So former airbase in Central Vietnam. Sci. Total Environ. 661, 27–34.
Le, T.N., Johansson, A., 2001. Impact of chemical warfare with agent orange on women's reproductive lives in Vietnam: a pilot study. Reprod. Health Matters. 9, 156–164.
Lee, D.H., Jacobs Jr., D.R., Porta, M., 2006a. Could low-level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes? J. Epidemiol. Community Health 60, 1006–1008.
Lee, D.H., Lee, I.K., Song, K., Steffes, M., Toscano, W., Baker, B.A., Jacobs Jr., D.R., 2006b. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. Diabetes Care 29, 1638–1644.
Lee, D.H., Porta, M., Jacobs Jr., D.R., Vandenberg, L.N., 2014. Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. Endocr. Rev. 35, 557–601.
Lee, Y.M., Ha, C.M., Kim, S.A., Thoudam, T., Yoon, Y.R., Kim, D.J., Kim, H.C., Moon, H.B., Park, S., Lee, I.K., Lee, D.H., 2017. Low-dose persistent organic pollutants impair insulin secretory function of pancreatic β-cells: human and in vitro evidence. Diabetes 66, 2669–2680.
Lei, R., Liu, W., Wu, X., Ni, T., Jia, T., 2020. A review of levels and profiles of polychlorinated dibenzo-p-dioxins and dibenzofurans in different environmental media from China. Chemosphere 239, 124685.
Leijs, M.M., Koppe, J.G., Olie, K., van Aalderen, W.M., de Voogt, P., Vulsma, T., Westra, M., ten Tusscher, G.W., 2008. Delayed initiation of breast development in girls with higher prenatal dioxin exposure; a longitudinal cohort study. Chemosphere 73, 999–1004.
Leijs, M.M., ten Tusscher, G.W., Olie, K., van Teunenbroek, T., van Aalderen, W.M., de Voogt, P., Vulsma, T., Bartonova, A., Krauss von Krauss, M., Mosoiu, C., Riojas-Rodriguez, H., Calamandrei, G., Koppe, J.G., 2012. Thyroid hormone metabolism and environmental chemical exposure. Environ. Health. 11, S10.
Leung, A.O.W., 2006. Assessment of persistent toxic substances in China and Hong Kong with emphasis on uncontrolled recycling of e-waste. Restricted Access Theses and Dissertations. https://repository.hkbu.edu.hk/etd_ra/715/ (accessed 16 July 2019).
Leung, A.O.W., 2019. Chapter 15 - Environmental contamination and health effects due to e-waste recycling. In: Prasad, M.N.V., Vithanage, M. (Eds.), Electronic Waste Management and Treatment Technology. Butterworth-Heinemann, pp. 335–362.
Leung, A.O.W., Cai, Z.W., Wong, M.H., 2006. Environmental contamination from electronic waste recycling at Guiyu, southeast China. J. Mater. Cycles Waste Manag. 8, 21–33.
Leung, A.O.W., Luksemburg, W.J., Wong, A.S., Wong, M.H., 2007. Spatial distribution of polybrominated diphenyl ethers and polychlorinated dibenzo-p-dioxins and dibenzofurans in soil and combusted residue at Guiyu, an electronic waste recycling site in southeast China. Environ. Sci. Technol. 41, 2730–2737.
Leung, A.O.W., Zheng, J., Yu, C.K., Liu, W.K., Wong, C.K.C., Cai, Z., Wong, M.H., 2011. Polybrominated diphenyl ethers and polychlorinated dibenzo-p-dioxins and dibenzofurans in surface dust at an E-waste processing site in Southeast China. Environ. Sci. Technol. 45, 5775–5782.
Li, H., Yu, L., Sheng, G., Fu, J., Peng, P., 2007. Severe PCDD/F and PBDD/F pollution in air around an electronic waste dismantling area in China. Environ. Sci. Technol. 41, 5641–5646.
Li, Y., Jiang, G., Wang, Y., Wang, P., Zhang, Q., 2008. Concentrations, profiles and gas-particle partitioning of PCDD/Fs, PCBs and PBDEs in the ambient air of an E-waste dismantling area, southeast China. Chin. Sci. Bull. 53, 521–528.
Lim, S., Cho, Y.M., Park, K.S., Lee, H.K., 2010. Persistent organic pollutants, mitochondrial dysfunction, and metabolic syndrome. Ann. N. Y. Acad. Sci. 1201, 166–176.
Lindén, J., Lensu, S., Tuomisto, J., Pohjanvirta, R., 2010. Dioxins, the aryl hydrocarbon receptor and the central regulation of energy balance. Front. Neuroendocrinol. 31, 452–478.
Liu, P., Wang, C., Song, X., Wu, Y., 2010. Dietary intake of lead and cadmium by children and adults – Result calculated from dietary recall and available lead/cadmium level in food in comparison to result from food duplicate diet method. Int. J. Hyg. Environ. Health 213, 450–457.
Liu, D.C., Xu, X.J., Zheng, X.B., Jiang, Y.S., Zhang, J.Q., Huo, X., 2019a. The study of exposure levels of dioxin-like compounds in cord blood of newborns in an e-waste dismantling area in Guangdong Province. Zhonghua yu fang yi xue za zhi (China) 53, 365–370.
Liu, H., Zhou, Q., Wang, Y., Zhang, Q., Cai, Z., Jiang, G., 2008. E-waste recycling induced polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins and dibenzo-furans pollution in the ambient environment. Environ. Int. 34, 67–72.
Liu, L.J., Chen, X.C., Fu, J.P., Qing, X., Huang, J.Q., Han, J.L., 2019b. Male workers' exposure characteristics of ΣPCDD/F from a municipal solid waste incinerator in south China through hair analysis. Ecotoxicol. Environ. Saf. 178, 105–112.
Liu, J., Liu, W., 2009. Distribution of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDDs/Fs) and dioxin-like polychlorinated biphenyls (dioxin-like PCBs) in the soil in a typical area of eastern China. J. Hazard. Mater. 163, 959–966.
Luksemburg, W.J., Mitzel, R., Peterson, R., Maier, M., Schuld, M., Hedin, J., Zhou, H., Wong, A., 2002. Polychlorinated dibenzodioxins and dibenzofurans (PCDD/PCDF) and polybrominated diphenylether (PBDE) levels in environmental and human hair samples around an electronic waste processing site in Guiyu, Guangdong province. China. Organohal. Compd. 55, 347–349.
Lundqvist, C., Zuurbier, M., Leijs, M., Johansson, C., Ceccatelli, S., Saunders, M., Schoeters, G., Tusscher, G.T., Koppe, J.G., 2008. The effects of PCBs and dioxins on child health. Acta Pædiatr. Suppl. 95, 55–64.
Luo, Y., Teng, Y., Li, Q., Wu, L., Li, Z., Zhang, Q., 2005. Soil environmental quality and remediation in Yangtze River Delta region 1. Composition and pollution of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDD/Fs) in a typical farmland. Acta Pedol. Sinic. (China) 42, 570–576.
Ma, J., Addink, R., Yun, S., Cheng, J., Wang, W., Kannan, K., 2009. Polybrominated dibenzo-p-dioxins/dibenzofurans and polybrominated diphenyl ethers in soil, vegetation, workshop-floor dust, and electronic shredder residue from an electronic waste recycling facility and in soils from a chemical industrial complex in Eastern China. Environ. Sci. Technol. 43, 7350–7356.
Ma, J., Cheng, J., Wang, W., Kunisue, T., Wu, M., Kannan, K., 2011. Elevated concentrations of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans and polybrominated diphenyl ethers in hair from workers at an electronic waste recycling facility in Eastern China. J. Hazard. Mater. 186, 1966–1971.
Ma, J., Kannan, K., Cheng, J., Horii, Y., Wu, Q., Wang, W., 2008. Concentrations, profiles, and estimated human exposures for polychlorinated dibenzo-p-dioxins and dibenzofurans from electronic waste recycling facilities and a chemical industrial complex in Eastern China. Environ. Sci. Technol. 42, 8252–8259.
Mandal, P.K., 2005. Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology. J. Comp. Physiol. B 175, 221–230.
't Mannetje, A., Eng, A., Walls, C., Dryson, E., Douwes, J., Bertazzi, P., Ryder-Lewis, S., Scott, D., Brooks, C., McLean, D., Cheng, S., Pearce, N., 2018. Morbidity in New Zealand pesticide producers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Environ. Int. 110, 22–31.
't Mannetje, A., McLean, D., Cheng, S., Boffetta, P., Colin, D., Pearce, N., 2005. Mortality in New Zealand workers exposed to phenoxy herbicides and dioxins. Occup. Environ. Med. 62, 34–40.
't Mannetje, A., Eng, A., Walls, C., Dryson, E., McLean, D., Kogevinas, M., Fowles, J., Borman, B., O'Connor, P., Cheng, S., Brooks, C., Smith, A.H., Pearce, N., 2016. Serum concentrations of chlorinated dibenzo-p-dioxins, furans and PCBs, among former phenoxy herbicide production workers and firefighters in New Zealand. Int. Arch. Occup. Environ. Health. 89, 307–318.
Manuwald, U., Velasco Garrido, M., Berger, J., Berger, J., Manz, A., Baur, X., 2012. Mortality study of chemical workers exposed to dioxins: follow-up 23 years after chemical plant closure. Occup. Environ. Med. 69, 636–642.
Marinkovic, N., Pasalic, D., Ferencak, G., Grskovic, B., Rukavina, A.S., 2010. Dioxins and human toxicity. Arh. Hig. Rada. Toksikol. 61, 445–453.
Martínez-Zamora, M.A., Mattioli, L., Parera, J., Abad, E., Coloma, J.L., van Babel, B., Galceran, M.T., Balasch, J., Carmona, F., 2015. Increased levels of dioxin-like substances in adipose tissue in patients with deep infiltrating endometriosis. Hum. Reprod. 30, 1059–1068.
Mayani, A., Barel, S., Soback, S., Almagor, M., 1997. Dioxin concentrations in women

with endometriosis. Hum. Reprod. 12, 373–375.
McBride, D.I., Collins, J.J., Bender, T.J., Bodner, K.M., Aylward, L.L., 2018. Cohort study of workers at a New Zealand agrochemical plant to assess the effect of dioxin exposure on mortality. BMJ Open. 8, e019243.
McBride, D.I., Collins, J.J., Humphry, N.F., Herbison, P., Bodner, K.M., Aylward, L.L., Burns, C.J., Wilken, M., 2009. Mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin at a trichlorophenol plant in New Zealand. J. Occup. Environ. Med. 51, 1049–1056.
McKinney, J.D., Chae, K., Oatley, S.J., Blake, C.C., 1985. Molecular interactions of toxic chlorinated dibenzo-p-dioxins and dibenzofurans with thyroxine binding prealbumin. J. Med. Chem. 28, 375–381.
Mennear, J.H., Lee, C.C., 1994. Polybrominated dibenzo-p-dioxins and dibenzofurans: literature review and health assessment. Environ. Health Perspect. 102 (Suppl. 1), 265–274.
Michalek, J.E., Pavuk, M., 2008. Diabetes and cancer in veterans of Operation Ranch Hand after adjustment for calendar period, days of spraying, and time spent in Southeast Asia. J. Occup. Environ. Med. 50, 330–340.
Michalek, J.E., Tripathi, R.C., 1999. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. J. Toxicol. Environ. Health 57, 369–378.
Minh, N.H., Minh, T.B., Watanabe, M., Kunisue, T., Monirith, I., Tanabe, S., Sakai, S., Subramanian, A., Sasikumar, K., Viet, P.H., Tuyen, B.C., Tana, T., Prudente, S.M.S., 2003. Open dumping site in Asian developing countries: a potential source of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans. Environ. Sci. Technol. 37, 1493–1502.
Miyake, Y., Jiang, Q., Yuan, W., Hanari, N., Okazawa, T., Wyrzykowska, B., So, M.K., Lam, P.K., Yamashita, N., 2008. Preliminary health risk assessment for polybrominated diphenyl ethers and polybrominated dibenzo-p-dioxins/furans in seafood from Guangzhou and Zhoushan, China. Mar. Pollut. Bull. 57, 357–364.
Miyashita, C., Araki, A., Mitsui, T., Itoh, S., Goudarzi, H., Sasaki, S., Kajiwara, J., Hori, T., Cho, K., Moriya, K., Shinohara, N., Nonomura, K., Kishi, R., 2018a. Sex-related differences in the associations between maternal dioxin-like compounds and reproductive and steroid hormones in cord blood: the Hokkaido study. Environ. Int. 117, 175–185.
Miyashita, C., Bamai, Y.A., Araki, A., Itoh, S., Minatoya, M., Kobayashi, S., Kajiwara, J., Hori, T., Kishi, R., 2018b. Prenatal exposure to dioxin-like compounds is associated with decreased cord blood IgE and increased risk of wheezing in children aged up to 7 years: the Hokkaido study. Sci. Total Environ. 610–611, 191–199.
Miyashita, C., Sasaki, S., Saijo, Y., Washino, N., Okada, E., Kobayashi, S., Konishi, K., Kajiwara, J., Todaka, T., Kishi, R., 2011. Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. Environ. Res. 111, 551–558.
Mocarelli, P., Brambilla, P., Gerthoux, P.M., Patterson Jr., D.G., Needham, L.L., 1996. Change in sex ratio with exposure to dioxin. Lancet 348, 409.
Mocarelli, P., Gerthoux, P.M., Needham, L.L., Patterson Jr., D.G., Limonta, G., Falbo, R., Signorini, S., Bertona, M., Crespi, C., Sarto, C., Scott, P.K., Turner, W.E., Brambilla, P., 2011. Perinatal exposure to low doses of dioxin can permanently impair human semen quality. Environ. Health Perspect. 119, 713–718.
Mocarelli, P., Gerthoux, P.M., Patterson Jr., D.G., Milani, S., Limonta, G., Bertona, M., Signorini, S., Tramacere, P., Colombo, L., Crespi, C., Brambilla, P., Sarto, C., Carreri, V., Sampson, E.J., Turner, W.E., Needham, L.L., 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ. Health Perspect. 116, 70–77.
Mocarelli, P., Gerthoux, P.M., Ferrari, E., Patterson Jr., D.G., Kieszak, S.M., Brambilla, P., Vincoli, N., Signorini, S., Tramacere, P., Carreri, V., Sampson, E.J., Turner, W.E., Needham, L.L., 2000. Paternal concentrations of dioxin and sex ratio of offspring. Lancet 355, 1858–1863.
Nagayama, J., Tsuji, H., Iida, T., Hirakawa, H., Matsueda, T., Ohki, M., 2001. Effects of contamination level of dioxins and related chemicals on thyroid hormone and immune response systems in patients with “Yusho”. Chemosphere 43, 1005–1010.
Nakajima, S., Saijo, Y., Kato, S., Sasaki, S., Uno, A., Kanagami, N., Hirakawa, H., Hori, T., Tobiishi, K., Todaka, T., 2006. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. Environ. Health Perspect. 114, 773–778.
Nakajima, S., Saijo, Y., Miyashita, C., Ikeno, T., Sasaki, S., Kajiwara, J., Kishi, R., 2017. Sex-specific differences in effect of prenatal exposure to dioxin-like compounds on neurodevelopment in Japanese children: Sapporo cohort study. Environ. Res. 159, 222–231.
Nakamoto, M., Arisawa, K., Uemura, H., Katsuura, S., Takami, H., Sawachika, F., Yamaguchi, M., Juta, T., Sakai, T., Toda, E., Mori, K., Hasegawa, M., Tanto, M., Shima, M., Sumiyoshi, Y., Morinaga, K., Kodama, K., Suzuki, T., Nagai, M., Satoh, H., 2013. Association between blood levels of PCDDs/PCDFs/dioxin-like PCBs and history of allergic and other diseases in the Japanese population. Int. Arch. Occup. Environ. Health 86, 849–859.
Nakao, T., Aozasa, O., Ohta, S., Miyata, H., 2005. Survey of human exposure to PCDDs, PCDFs, and coplanar PCBs using hair as an indicator. Arch. Environ. Contam. Toxicol. 49, 124–130.
Neugebauer, J., Wittsiepe, J., Kasper-Sonnenberg, M., Schöneck, N., Schölmerich, A., Wilhelm, M., 2015. The influence of low level pre- and perinatal exposure to PCDD/Fs, PCBs, and lead on attention performance and attention-related behavior among German school-aged children: results from the Duisburg Birth Cohort Study. Int. J. Hyg. Environ. Health 218, 153–162.
National Research Council, 2006. Health risks from dioxin and related compounds. Evaluation of the EPA Reassessment. The National Academies Press, Washington DC.
Ngo, A.D., Taylor, R., Roberts, C.L., Nguyen, T.V., 2006. Association between Agent Orange and birth defects: systematic review and meta-analysis. Int. J. Epidemiol. 35, 1220–1230.
Ngoc, V.T.N., Huong, L.T., Van Nhon, B., Tan, N.T.M., Van Thuc, P., Hien, V.T.T., Dung, T.M., Van Toan, N., Anh, L.Q., Son, L.H., Chu-Dinh, T., Chu, D.T., 2019. The higher prevalence of developmental defects of enamel in the dioxin-affected region than non-dioxin-affected region: result from a cross-sectional study in Vietnam. Odontology 107, 17–22.
Ni, H.G., Zeng, H., Tao, S., Zeng, E.Y., 2010. Environmental and human exposure to persistent halogenated compounds derived from e-waste in China. Environ. Toxicol. Chem. 29, 1237–1247.
Nishijo, M., Kuriwaki, J., Hori, E., Tawara, K., Nakagawa, H., Nishijo, H., 2007a. Effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin on fetal brain growth and motor and behavioral development in offspring rats. Toxicol. Lett. 173, 41–47.
Nishijo, M., Pham, T.T., Nguyen, A.T.N., Tran, N.N., Nakagawa, H., Hoang, L.V., Tran, A.H., Morikawa, Y., Ho, M.D., Kido, T., Nguyen, M.N., Nguyen, H.M., Nishijo, H., 2014. 2,3,7,8-tetrachlorodibenzo-p-dioxin in breast milk increases autistic traits of 3-year-old children in Vietnam. Mol. Psychiatry 19, 1220–1226.
Nishijo, M., Tawara, K., Nakagawa, H., Honda, R., Kido, T., Nishijo, H., Saito, S., 2007b. 2,3,7,8-tetrachlorodibenzo-p-dioxin in maternal breast milk and newborn head circumference. J. Expo. Sci. Environ. Epidemiol. 18, 246–251.
Nouwen, J., Cornelis, C., De Fre, R., Wevers, M., Viaene, P., Mensink, C., Patyn, J., Verschaeve, L., Hooghe, R., Maes, A., Collier, M., Schoeters, G., Van Cleuvenbergen, R., Geuzens, P., 2001. Health risk assessment of dioxin emissions from municipal waste incinerators: the Neerlandquarter (Wilrijk, Belgium). Chemosphere 43, 909–923.
Nowack, N., Wittsiepe, J., Kasper-Sonnenberg, M., Wilhelm, M., Scholmerich, A., 2015. Influence of low-level prenatal exposure to PCDD/Fs and PCBs on empathizing, systemizing and autistic traits: results from the Duisburg Birth Cohort Study. PLoS One 10, e0129906.
Nowak, K., Jabłońska, E., Ratajczak-Wrona, W., 2019. Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells. Environ. Int. 125, 350–364.
O'Driscoll, C.A., Owens, L.A., Hoffmann, E.J., Gallo, M.E., Afrazi, A., Han, M., Fechner, J.H., Schauer, J.J., Bradfield, C.A., Mezrich, J.D., 2019. Ambient urban dust particulate matter reduces pathologic T cells in the CNS and severity of EAE. Environ. Res. 168, 178–192.
Office of the High Commissioner for Human Rights (UN Human Rights), 2016. Report of the Special Rapporteur on the implications for human rights of the environmentally sound management and disposal of hazardous substances and wastes. https://www.ohchr.org/EN/Issues/Environment/ToxicWastes/Pages/TheRightsoftheChildandHazardousSubstancesandWastes.aspx/ (accessed 1 August 2019).
Ott, M.G., Messerer, P., Zober, A., 1993. Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin using blood lipid analyses. Int. Arch. Occup. Environ. Health 65, 1–8.
Ott, M.G., Zober, A., Germann, C., 1994. Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD. Chemosphere 29, 2423–2437.
Papadopoulou, E., Caspersen, I.H., Kvalem, H.E., Knutsen, H.K., Duarte-Salles, T., Alexander, J., Meltzer, H.M., Kogevinas, M., Brantsæter, A.L., Haugen, M., 2013. Maternal dietary intake of dioxins and polychlorinated biphenyls and birth size in the Norwegian Mother and Child Cohort Study (MoBa). Environ. Int. 60, 209–216.
Parajuly, K., Kuehr, R., Awasthi, A.K., Fitzpatrick, C., Lepawsky, J., Smith, E., Widmer, R., Zeng, X., 2019. Future E-waste Scenarios. StEP Initiative, UNU ViE-SCYCLE, UNEP IETC. https://collections.unu.edu/eserv/UNU:7440/FUTURE_E-WASTE_SCENARIOS_UNU_190829_low_screen.pdf/ (accessed 7 November 2019).
Parng, C., Roy, N.M., Ton, C., Lin, Y., McGrath, P., 2007. Neurotoxicity assessment using zebrafish. J. Pharmacol. Toxicol. Methods 55, 103–112.
Pascale, A., Bares, C., Laborde, A., 2018. E-waste: environmental and health challenges. In: Dellasala, D.A., Goldstein, M.I. (Eds.), Encyclopedia of the Anthropocene. Elsevier, Oxford, pp. 269–275.
Patandin, S., Lanting, C.I., Mulder, P.G., Boersma, E.R., Sauer, P.J., Weisglas-Kuperus, N., 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J. Pediatr. 134, 33–41.
Pavuk, M., Patterson Jr., D.G., Turner, W.E., 2014. Serum concentrations of TCDD and other dioxin-like compounds in US Air Force veterans of Operation Ranch Hand. Chemosphere 102, 18–23.
Pavuk, M., Schecter, A.J., Akhtar, F.Z., Michalek, J.E., 2003. Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels and thyroid function in Air Force veterans of the Vietnam War. Ann. Epidemiol. 13, 335–343.
Pelcl, T., Skrha Jr, J., Prazny, M., Vlckova, S., Fenclova, Z., Navratil, T., Malik, J., Diblik, P., Zikan, V., Pelclova, D., 2018. Diabetes, cardiovascular disorders and 2,3,7,8-tetrachlorodibenzo-p-dioxin body burden in Czech patients 50 years after the intoxication. Basic Clin. Pharmacol. Toxicol. 123, 356–359.
Pelclova, D., Fenclova, Z., Urban, P., Ridzon, P., Preiss, J., Kupka, K., Malik, J., Dubska, Z., Navratil, T., 2009. Chronic health impairment due to 2,3,7,8-tetrachloro-dibenzo-p-dioxin exposure. Neuro. Endocrinol. Lett. 30 (Suppl 1), 219–224.
Pelclova, D., Urban, P., Fenclova, Z., Vlckova, S., Ridzon, P., Kupka, K., Meckova, Z., Bezdicek, O., Navratil, T., Rosmus, J., Zakharov, S., 2018. Neurological and neurophysiological findings in workers with chronic 2,3,7,8-tetrachlorodibenzo-p-dioxin intoxication 50 years after exposure. Basic Clin. Pharmacol. Toxicol. 122, 271–277.
Pesatori, A.C., Consonni, D., Bachetti, S., Zocchetti, C., Bonzini, M., Baccarelli, A., Bertazzi, P.A., 2003. Short- and long-term morbidity and mortality in the population exposed to dioxin after the “Seveso accident”. Ind. Health 41, 127–138.
Pham, T.T., Nishijo, M., Nguyen, A.T.N., Tran, N.N., Hoang, L.V., Tran, A.H., Nguyen, T.V., Nishijo, H., 2015. Perinatal dioxin exposure and the neurodevelopment of Vietnamese toddlers at 1 year of age. Sci. Total Environ. 536, 575–581.
Pilsner, J.R., Parker, M., Sergeyev, O., Suvorov, A., 2017. Spermatogenesis disruption by dioxins: epigenetic reprograming and windows of susceptibility. Reprod. Toxicol. 69, 221–229.

Piskorska-Pliszczynska, J., Maszewski, S., 2014. Brominated dioxins: little-known new health hazards - a review. Bull. Vet. Inst. Pulawy. 58, 327–335.
Pluim, H.J., de Vijlder, J.J., Olie, K., Kok, J.H., Vulsma, T., van Tijn, D.A., van der Slikke, J.W., Koppe, J.G., 1993. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. Environ. Health Perspect. 101, 504–508.
Pluim, H.J., Koppe, J.G., Olie, K., van der Slikke, J.W., Slot, P.C., van Boxtel, C.J., 1994. Clinical laboratory manifestations of exposure to background levels of dioxins in the perinatal period. Acta Paediatr. 83, 583–587.
Qin, Q., Xu, X., Dai, Q., Ye, K., Wang, C., Huo, X., 2019. Air pollution and body burden of persistent organic pollutants at an electronic waste recycling area of China. Environ. Geochem. Health 41, 93–123.
Raghupathy, L., Krüger, C., Chaturvedi, A., Arora, R., Henzler, M., 2010. E-Waste Recycling In India—Bridging The Gap Between The Informal And Formal Sector. http://www.iswa.org/fileadmin/galleries/General%20Assembly%20and%20WC%202010%2011%20Hamburg/Presentations/Krueger.pdf (accessed 12 October 2019).
Remillard, R.B.J., Bunce, N.J., 2002. Linking dioxins to diabetes: epidemiology and biologic plausibility. Environ. Health Perspect. 110, 853–858.
Ren, M., Tang, Y.H., Peng, P.A., Cai, Y., 2015. PCDD/Fs in air and soil around an e-waste dismantling area with open burning of insulated wires in South China. Bull. Environ. Contam. Toxicol. 94, 647–652.
Ren, Z., Xiao, X., Chen, D., Bi, X., Huang, B., Liu, M., Hu, J., Peng, P., Sheng, G., Fu, J., 2014. Halogenated organic pollutants in particulate matters emitted during recycling of waste printed circuit boards in a typical e-waste workshop of Southern China. Chemosphere 94, 143–150.
Revich, B., Aksel, E., Ushakova, T., Ivanova, I., Zhuchenko, N., Klyuev, N., Brodsky, B., Sotskov, Y., 2001. Dioxin exposure and public health in Chapaevsk. Russia. Chemosphere. 43, 951–966.
Rice, D., Barone Jr., S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108, 511–533.
Rice, M.L., Taylor, C.L., Zubrick, S.R., 2008. Language outcomes of 7-year-old children with or without a history of late language emergence at 24 months. J. Speech Lang. Hear. Res. 51, 394–407.
Rodgers, K.M., Udesky, J.O., Rudel, R.A., Brody, J.G., 2018. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ. Res. 160, 152–182.
Rogan, W.J., Gladen, B.C., Hung, K.L., Koong, S.L., Shih, L.Y., Taylor, J.S., Wu, Y.C., Yang, D., Ragan, N.B., Hsu, C.C., 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 241, 334–336.
Prithiviraj, B., Chakraborty, P., 2019. Is informal electronic waste recycling a newer source for atmospheric industrial persistent organic pollutants in Indian metropolitan cities? Curr. Opin. Environ. Sci. Health. 8, 29–35.
Ruder, A.M., Yiin, J.H., 2011. Mortality of US pentachlorophenol production workers through 2005. Chemosphere 83, 851–861.
Sadler, R., Connell, D., 2012. Global distillation in an era of climate change. In: Puzyn, T., Mostrag-Szlichtyng, A. (Eds.), Organic Pollutants Ten Years after the Stockholm Convention—Environmental and Analytical Update. InTech, Croatia, pp. 191–216.
Schecter, A., 2013. Dioxins and Health. Springer Science & Business Media, New York.
Schmidt, C.W., 2017. Age at menopause: Do chemical exposures play a role? Environ. Health Perspect. 125, 062001.
Schuhmacher, M., Kiviranta, H., Ruokojärvi, P., Nadal, M., Domingo, J.L., 2009. Concentrations of PCDD/Fs, PCBs and PBDEs in breast milk of women from Catalonia, Spain: a follow-up study. Environ. Int. 35, 607–613.
Schwarz, M., Appel, K.E., 2005. Carcinogenic risks of dioxin: mechanistic considerations. Regul. Toxicol. Pharm. 43, 19–34.
Seo, B.W., Sparks, A.J., Medora, K., Amin, S., Schantz, S.L., 1999. Learning and memory in rats gestationally and lactationally exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Neurotoxicol. Teratol. 21, 231–239.
Sexton, K., Hattis, D., 2007. Assessing cumulative health risks from exposure to environmental mixtures—three fundamental questions. Environ. Health Perspect. 115, 825–832.
Shen, C., Chen, Y., Huang, S., Wang, Z., Yu, C., Qiao, M., Xu, Y., Setty, K., Zhang, J., Zhu, Y., Lin, Q., 2009. Dioxin-like compounds in agricultural soils near e-waste recycling sites from Taizhou area, China: chemical and bioanalytical characterization. Environ. Int. 35, 50–55.
Shen, C., Huang, S., Wang, Z., Qiao, M., Tang, X., Yu, C., Shi, D., Zhu, Y., Shi, J., Chen, X., Setty, K., Chen, Y., 2008. Identification of Ah receptor agonists in soil of e-waste recycling sites from Taizhou area in China. Environ. Sci. Technol. 42, 49–55.
Shen, H., Ding, G., Han, G., Wang, X., Xu, X., Han, J., Lou, X., Xu, C., Cai, D., Song, Y., Lu, W., 2010. Distribution of PCDD/Fs, PCBs, PBDEs and organochlorine residues in children's blood from Zhejiang, China. Chemosphere 80, 170–175.
Shibamoto, T., Yasuhara, A., Katami, T., 2007. Dioxin formation from waste incineration. Rev. Environ. Contam. Toxicol. 190, 1–41.
Slama, N., Warner, M., Mocarelli, P., Brambilla, P., Eskenazi, B., 2019. The 2nd to 4th digit length ratio (2D:4D) among children of Seveso women exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Early Hum. Dev. 131, 45–50.
Song, Q., Li, J., 2014. A systematic review of the human body burden of e-waste exposure in China. Environ. Int. 68, 82–93.
Song, Y., Chou, E.L., Baecker, A., You, N.C.Y., Song, Y., Sun, Q., Liu, S., 2016. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis. J. Diabetes 8, 516–532.
Song, Y., Wu, N., Han, J., Shen, H., Tan, Y., Ding, G., Xiang, J., Tao, H., Jin, S., 2011. Levels of PCDD/Fs and DL-PCBs in selected foods and estimated dietary intake for the local residents of Luqiao and Yuhang in Zhejiang, China. Chemosphere 85, 329–334.
Ssebugere, P., Sillanpää, M., Matovu, H., Mubiru, E., 2019. Human and environmental exposure to PCDD/Fs and dioxin-like PCBs in Africa: a review. Chemosphere 223, 483–493.
Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M., Chang, L.I., 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Natl Cancer Inst. 91, 779–786.
Stølevik, S.B., Nygaard, U.C., Namork, E., Haugen, M., Meltzer, H.M., Alexander, J., Knutsen, H.K., Aaberge, I., Vainio, K., van Loveren, H., Løvik, M., Granum, B., 2013. Prenatal exposure to polychlorinated biphenyls and dioxins from the maternal diet may be associated with immunosuppressive effects that persist into early childhood. Food Chem. Toxicol. 51, 165–172.
Su, P.H., Chen, J.Y., Chen, J.W., Wang, S.L., 2010. Growth and thyroid function in children with in utero exposure to dioxin: a 5-year follow-up study. Pediatr. Res. 67, 205–210.
Su, P.H., Huang, P.C., Lin, C.Y., Ying, T.H., Chen, J.Y., Wang, S.L., 2012. The effect of in utero exposure to dioxins and polychlorinated biphenyls on reproductive development in eight year-old children. Environ. Int. 39, 181–187.
Sun, X.L., Okamoto, R., Kido, T., Honma, S., Manh, H.D., Nguyen, H.V., Anh, L.T., Phuc, H.D., Oanh, N.T., Maruzeni, S., Nakagawa, H., Nakayama, S.F., Nhu, D.D., Tung, D.V., Tan, N.T., Giang, L.M., 2020. Association of dioxin in maternal breast milk and salivary steroid hormone levels in preschool children: A five-year follow-up study of a Vietnam cohort. Chemosphere 241, 124899.
Suzuki, G., Someya, M., Matsukami, H., Tue, N.M., Uchida, N., Tuyen, L.H., Viet, P.H., Takahashi, S., Tanabe, S., Brouwer, A., Takigami, H., 2016. Comprehensive evaluation of dioxins and dioxin-like compounds in surface soils and river sediments from e-waste-processing sites in a village in northern Vietnam: heading towards the environmentally sound management of e-waste. Emerg. Contam. 2, 98–108.
Sweeney, M.H., Calvert, G.M., Egeland, G.A., Fingerhut, M.A., Halperin, W.E., Piacitelli, L.A., 1997. Review and update of the results of the NIOSH medical study of workers exposed to chemicals contaminated with 2,3,7,8-tetrachlorodibenzodioxin. Teratog. Carcinog. Mutagen. 17, 241–247.
Tai, P.T., Nishijo, M., Anh, N.T.N., Maruzeni, S., Nakagawa, H., Van Luong, H., Anh, T.H., Honda, R., Kido, T., Nishijo, H., 2013. Dioxin exposure in breast milk and infant neurodevelopment in Vietnam. Occup. Environ. Med. 70, 656–662.
Tai, P.T., Nishijo, M., Nghi, T.N., Nakagawa, H., Van Luong, H., Anh, T.H., Nishijo, H., 2016. Effects of perinatal dioxin exposure on development of children during the first 3 years of life. J. Pediatr. 175, 159–166.
ten Tusscher, G.W., Steerenberg, P.A., van Loveren, H., Vos, J.G., von dem Borne, A.E., Westra, M., van der Slikke, J.W., Olie, K., Pluim, H.J., Koppe, J.G., 2003. Persistent hematologic and immunologic disturbances in 8-year-old Dutch children associated with perinatal dioxin exposure. Environ. Health Perspect. 111, 1519–1523.
Tran, N.N., Pham, T.T., Ozawa, K., Nishijo, M., Nguyen, A.T.N., Tran, T.Q., Hoang, L.V., Tran, A.H., Phan, V.H.A., Nakai, A., Nishino, Y., Nishijo, H., 2016. Impacts of perinatal dioxin exposure on motor coordination and higher cognitive development in Vietnamese preschool children: a five-year follow-up. PLoS One 11, e0147655.
Trinh, M.M., Chang, M.B., Asia, E., 2018. Review on occurrence and behavior of PCDD/Fs and dl-PCBs in atmosphere of East Asia. Atmos. Environ. 180, 23–36.
Tsukimori, K., Tokunaga, S., Shibata, S., Uchi, H., Nakayama, D., Ishimaru, T., Nakano, H., Wake, N., Yoshimura, T., Furue, M., 2008. Long-term effects of polychlorinated biphenyls and dioxins on pregnancy outcomes in women affected by the Yusho incident. Environ. Health Perspect. 116, 626–630.
Tsukimori, K., Uchi, H., Mitoma, C., Yasukawa, F., Chiba, T., Todaka, T., Kajiwara, J., Yoshimura, T., Hirata, T., Fukushima, K., Wake, N., Furue, M., 2012. Maternal exposure to high levels of dioxins in relation to birth weight in women affected by Yusho disease. Environ. Int. 38, 79–86.
Tue, N.M., Goto, A., Takahashi, S., Itai, T., Asante, K.A., Kunisue, T., Tanabe, S., 2016. Release of chlorinated, brominated and mixed halogenated dioxin-related compounds to soils from open burning of e-waste in Agbogbloshie (Accra, Ghana). J. Hazard. Mater. 302, 151–157.
Tue, N.M., Katsura, K., Suzuki, G., Tuyen le, H., Takasuga, T., Takahashi, S., Viet, P.H., Tanabe, S., 2014. Dioxin-related compounds in breast milk of women from Vietnamese e-waste recycling sites: levels, toxic equivalents and relevance of non-dietary exposure. Ecotoxicol. Environ. Saf. 106, 220–225.
Tue, N.M., Matsushita, T., Goto, A., Itai, T., Asante, K.A., Obiri, S., Mohammed, S., Tanabe, S., Kunisue, T., 2019. Complex mixtures of brominated/chlorinated diphenyl ethers and dibenzofurans in soils from the Agbogbloshie e-waste site (Ghana): occurrence, formation, and exposure implications. Environ. Sci. Technol. 53, 3010–3017.
Tue, N.M., Suzuki, G., Takahashi, S., Isobe, T., Trang, P.T.K., Viet, P.H., Tanabe, S., 2010. Evaluation of dioxin-like activities in settled house dust from Vietnamese E-waste recycling sites: relevance of polychlorinated/brominated dibenzo-p-dioxin/furans and dioxin-like PCBs. Environ. Sci. Technol. 44, 9195–9200.
Tue, N.M., Takahashi, S., Subramanian, A., Sakai, S., Tanabe, S., 2013. Environmental contamination and human exposure to dioxin-related compounds in e-waste recycling sites of developing countries. Environ. Sci. Process. Impacts. 15, 1326–1331.
Tuomisto, J., 2019. Dioxins and dioxin-like compounds: toxicity in humans and animals, sources, and behaviour in the environment. WikiJ. Medicine. 6, 8.
Uemura, H., Arisawa, K., Hiyoshi, M., Kitayama, A., Takami, H., Sawachika, F., Dakeshita, S., Nii, K., Satoh, H., Sumiyoshi, Y., 2009. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. Environ. Health Perspect. 117, 568–573.
Uemura, H., Arisawa, K., Hiyoshi, M., Satoh, H., Sumiyoshi, Y., Morinaga, K., Kodama, K., Suzuki, T., Nagai, M., Suzuki, T., 2008. Associations of environmental exposure to dioxins with prevalent diabetes among general inhabitants in Japan. Environ. Res. 108, 63–68.
United Nations Environment Programme (UNEP), 2016. The 2nd POPs Monitoring Report Asia-Pacific Region. chm.pops.int/implementation/globalmonitoringplan/

monitoringreports/ (accessed 10 October 2019).
Urban, P., Pelclová, D., Lukáš, E., Kupka, K., Preiss, J., Fenclová, Z., Šmerhovský, Z., 2007. Neurological and neurophysiological examinations on workers with chronic poisoning by 2,3,7,8-TCDD: follow-up 35 years after exposure. Eur. J. Neurol. 14, 213–218.
Vaccari, M., Vinti, G., Cesaro, A., Belgiorno, V., Salhofer, S., Dias, M.I., Jandric, A., 2019. WEEE Treatment in Developing Countries: Environmental Pollution and Health Consequences—An Overview. Int. J. Environ. Res. Public Health 16, 1595.
Vafeiadi, M., Roumeliotaki, T., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Fthenou, E., Kyrtopoulos, S.A., Kogevinas, M., Chatzi, L., 2017. Persistent organic pollutants in early pregnancy and risk of gestational diabetes mellitus. Environ. Int. 98, 89–95.
van den Berg, M., Birnbaum, L., Bosveld, A.T.C., Brunström, B., Cook, P., Feeley, M., Giesy, J.P., Hanberg, A., Hasegawa, R., Kennedy, S.W., Kubiak, T., Larsen, J.C., van Leeuwen, F.X.R., Liem, A.K.D., Nolt, C., Peterson, R.E., Poellinger, L., Safe, S., Schrenk, D., Tillitt, D., Tysklind, M., Younes, M., Waern, F., Zacharewski, T., 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ. Health Perspect. 106, 775–792.
van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A., Haws, L., Rose, M., Safe, S., Schrenk, D., Tohyama, C., Tritscher, A., Tuomisto, J., Tysklind, M., Walker, N., Peterson, R.E., 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol. Sci. 92, 223–241.
van den Berg, M., Denison, M.S., Birnbaum, L.S., DeVito, M.J., Fiedler, H., Falandysz, J., Rose, M., Schrenk, D., Safe, S., Tohyama, C., Tritscher, A., Tysklind, M., Peterson, R.E., 2013. Review polybrominated dibenzo-p-dioxins, dibenzofurans, and biphenyls: inclusion in the toxicity equivalency factor concept for dioxin-like compounds. Toxicol. Sci. 133, 197–208.
van den Berg, M., Kypke, K., Kotz, A., Tritscher, A., Lee, S.Y., Magulova, K., Fiedler, H., Malisch, R., 2017. WHO/UNEP global surveys of PCDDs, PCDFs, PCBs and DDTs in human milk and benefit–risk evaluation of breastfeeding. Arch. Toxicol. 91, 83–96.
van Leeuwen, F.X.R., Feeley, M., Schrenk, D., Larsen, J.C., Farland, W., Younes, M., 2000. Dioxins: WHO's tolerable daily intake (TDI) revisited. Chemosphere 40, 1095–1101.
Van Luong, H., Tai, P.T., Nishijo, M., Trung, D.M., Thao, P.N., Van Son, P., Van Long, N., Linh, N.T., Nishijo, H., 2018. Association of dioxin exposure and reproductive hormone levels in men living near the Bien Hoa airbase, Vietnam. Sci. Total Environ. 628–629, 484–489.
Vena, J., Boffetta, P., Becher, H., Benn, T., Bueno-de-Mesquita, H.B., Coggon, D., Colin, D., Flesch-Janys, D., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J.D., Neuberger, M., Pearce, N., Pesatori, A.C., Saracci, R., Steenland, K., Kogevinas, M., 1998. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environ. Health Perspect. 106 (Suppl 2), 645–653.
Viel, J.F., Daniau, C., Goria, S., Fabre, P., de Crouy-Chanel, P., Sauleau, E.A., Empereur-Bissonnet, P., 2008. Risk for non Hodgkin's lymphoma in the vicinity of French municipal solid waste incinerators. Environ. Health. 7, 51.
Vorderstrasse, B.A., Bohn, A.A., Lawrence, B.P., 2003. Examining the relationship between impaired host resistance and altered immune function in mice treated with TCDD. Toxicology 188, 15–28.
Vos, J.G., Moore, J.A., Zinkl, J.G., 1973. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. Environ. Health Perspect. 5, 149–162.
Vreugdenhil, H.J.I., Lanting, C.I., Mulder, P.G.H., Boersma, E.R., Weisglas-Kuperus, N., 2002. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J. Pediatr. 140, 48–56.
Wan, C., Liu, J., Nie, X., Zhao, J., Zhou, S., Duan, Z., Tang, C., Liang, L., Xu, G., 2014. 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) induces premature senescence in human and rodent neuronal cells via ROS-dependent mechanisms. PLoS One 9, e89811.
Wang, Y., Sun, X., Fang, L., Li, K., Yang, P., Du, L., Ji, K., Wang, J., Liu, Q., Xu, C., Li, G., Giesy, J.P., Hecker, M., 2018. Genomic instability in adult men involved in processing electronic waste in Northern China. Environ. Int. 117, 69–81.
Wang, S.L., Lin, C.Y., Guo, Y.L., Lin, L.Y., Chou, W.L., Chang, L.W., 2004. Infant exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (PCDD/Fs, PCBs)—correlation between prenatal and postnatal exposure. Chemosphere 54, 1459–1473.
Wang, S.L., Su, P.H., Jong, S.B., Guo, Y.L., Chou, W.L., Päpke, O., 2005. In utero exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ. Health Perspect. 113, 1645–1650.
Wang, S.L., Tsai, P.C., Yang, C.Y., Guo, Y.L., 2008. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 31, 1574–1579.
Wang, Z., Hang, J.G., Feng, H., Shi, L.L., Dong, J.J., Shen, B., Luo, T., Cai, R.M., Shen, L.J., Kido, T., Sun, X.L., 2019. Effects of perinatal dioxin exposure on development of children: a 3-year follow-up study of China cohort. Environ. Sci. Pollut. Res. 26, 20780–20786.
Warner, M., Eskenazi, B., Olive, D.L., Samuels, S., Quick-Miles, S., Vercellini, P., Gerthoux, P.M., Needham, L., Patterson Jr., D.G., Mocarelli, P., 2007. Serum dioxin concentrations and quality of ovarian function in women of Seveso. Environ. Health Perspect. 115, 336–340.
Warner, M., Eskenazi, B., Mocarelli, P., Gerthoux, P.M., Samuels, S., Needham, L., Patterson, D., Brambilla, P., 2002. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ. Health Perspect. 110, 625–628.
Warner, M., Mocarelli, P., Brambilla, P., Wesselink, A., Patterson Jr., D.G., Turner, W.E., Eskenazi, B., 2013a. Serum TCDD and TEQ concentrations among Seveso women, 20 years after the explosion. J. Expo. Sci. Environ. Epidemiol. 24, 588–594.
Warner, M., Mocarelli, P., Brambilla, P., Wesselink, A., Samuels, S., Signorini, S., Eskenazi, B., 2013b. Diabetes, metabolic syndrome, and obesity in relation to serum dioxin concentrations: the Seveso Women's Health Study. Environ. Health Perspect. 121, 906–911.
Warner, M., Mocarelli, P., Samuels, S., Needham, L., Brambilla, P., Eskenazi, B., 2011. Dioxin exposure and cancer risk in the Seveso Women's Health Study. Environ. Health Perspect. 119, 1700–1705.
Warner, M., Rauch, S., Ames, J., Mocarelli, P., Brambilla, P., Signorini, S., Eskenazi, B., 2019. In utero dioxin exposure and cardiometabolic risk in the Seveso Second Generation Study. Int. J. Obes. 43, 2233–2243.
Weber, R., Kuch, B., 2003. Relevance of BFRs and thermal conditions on the formation pathways of brominated and brominated-chlorinated dibenzodioxins and dibenzofurans. Environ. Int. 29, 699–710.
Weisglas-Kuperus, N., Sas, T.C.J., Koopman-Esseboom, C., Van Der Zwan, C.W., De Ridder, M.A.J., Beishuizen, A., Hooijkaas, H., Sauer, P.J.J., 1995. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. Pediatr. Res. 38, 404–410.
Weisglas-Kuperus, N., Patandin, S., Berbers, G.A., Sas, T.C., Mulder, P.G., Sauer, P.J., Hooijkaas, H., 2000. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. Environ. Health Perspect. 108, 1203–1207.
Weisglas-Kuperus, N., Vreugdenhil, H.J., Mulder, P.G., 2004. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. Toxicol. Lett. 149, 281–285.
Wen, S., Gong, Y., Li, J., Shi, T., Zhao, Y., Wu, Y., 2011. Particle-bound PCDD/Fs in the atmosphere of an electronic waste dismantling area in China. Biomed. Environ. Sci. 24, 102–111.
Wen, S., Yang, F.X., Gong, Y., Zhang, X.L., Hui, Y., Li, J.G., Liu, A.L., Wu, Y.N., Lu, W.Q., Xu, Y., 2008. Elevated levels of urinary 8-hydroxy-2′-deoxyguanosine in male electrical and electronic equipment dismantling workers exposed to high concentrations of polychlorinated dibenzo-p-dioxins and dibenzofurans, polybrominated diphenyl ethers, and polychlorinated biphenyls. Environ. Sci. Technol. 42, 4202–4207.
Wen, S., Yang, F., Li, J.G., Gong, Y., Zhang, X.L., Hui, Y., Wu, Y.N., Zhao, Y.F., Xu, Y., 2009. Polychlorinated dibenzo-p-dioxin and dibenzofurans (PCDD/Fs), polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs) monitored by tree bark in an E-waste recycling area. Chemosphere 74, 981–987.
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.
Wilhelm, M., Wittsiepe, J., Lemm, F., Ranft, U., Krämer, U., Fürst, P., Röseler, S.C., Greshake, M., Imöhl, M., Eberwein, G., Rauchfuss, K., Kraft, M., Winneke, G., 2008. The Duisburg birth cohort study: influence of the prenatal exposure to PCDD/Fs and dioxin-like PCBs on thyroid hormone status in newborns and neurodevelopment of infants until the age of 24 months. Mutat. Res. 659, 83–92.
Williamson, M.A., Gasiewicz, T.A., Opanashuk, L.A., 2005. Aryl hydrocarbon receptor expression and activity in cerebellar granule neuroblasts: implications for development and dioxin neurotoxicity. Toxicol. Sci. 83, 340–348.
Winneke, G., Ranft, U., Wittsiepe, J., Kasper-Sonnenberg, M., Furst, P., Kramer, U., Seitner, G., Wilhelm, M., 2014. Behavioral sexual dimorphism in school-age children and early developmental exposure to dioxins and PCBs: a follow-up study of the Duisburg Cohort. Environ. Health Perspect. 122, 292–298.
Wittsiepe, J., Fobil, J.N., Till, H., Burchard, G.D., Wilhelm, M., Feldt, T., 2015. Levels of polychlorinated dibenzo-p-dioxins, dibenzofurans (PCDD/Fs) and biphenyls (PCBs) in blood of informal e-waste recycling workers from Agbogbloshie, Ghana, and controls. Environ. Int. 79, 65–73.
Wittsiepe, J., Fürst, P., Schrey, P., Lemm, F., Kraft, M., Eberwein, G., Winneke, G., Wilhelm, M., 2007. PCDD/F and dioxin-like PCB in human blood and milk from German mothers. Chemosphere 67, S286–S294.
Wolfe, W.H., Michalek, J.E., Miner, J.C., Rahe, A., Silva, J., Thomas, W.F., Grubbs, W.D., Lustik, M.B., Karrison, T.G., Roegner, R.H., Williams, D.E., 1990. Health status of Air Force veterans occupationally exposed to herbicides in Vietnam: I. Physical health. JAMA 264, 1824–1831.
Wolfe, W.H., Michalek, J.E., Miner, J.C., Rahe, A.J., Moore, C.A., Needham, L.L., Patterson Jr., D.G., 1995. Paternal serum dioxin and reproductive outcomes among Veterans of Operation Ranch Hand. Epidemiology. 6, 17–22.
Wong, M.H., Wu, S.C., Deng, W.J., Yu, X.Z., Luo, Q., Leung, A.O.W., Wong, C.S.C., Luksemburg, W.J., Wong, A.S., 2007. Export of toxic chemicals – a review of the case of uncontrolled electronic-waste recycling. Environ. Pollut. 149, 131–140.
World Economic Forum (WEF), 2019. A New Circular Vision for Electronics, Time for a Global Reboot. http://www3.weforum.org/docs/WEF_A_New_Circular_Vision_for_Electronics.pdf/ (accessed 1 August 2019).
World Health Organization (WHO), 1998a. Polybrominated dibenzo-p-dioxins and dibenzofurans. Environmental Health Criteria. World Health Organization, Geneva. 205.
World Health Organization (WHO), 1998b. Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). WHO consultation, 25–29 May, 1998, Geneva, Switzerland. 22.
World Health Organization (WHO), 2016. Dioxins and their effects on human health. http://www.who.int/en/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health/ (accessed 16 July 2019).
World Health Organization (WHO), 2017. E-waste: Promoting responsible recycling. In: World Health Organization (Eds.), Inheriting a sustainable world: Atlas on children's health and the environment. Geneva, Switzerland, pp. 88–91.
World Health Organization & International Programme on Chemical Safety (WHO/IPCS), 1992. Polychlorinated biphenyls and terphenyls (2nd ed). International Programme on Chemical Safety, World Health Organization. http://www.inchem.org/documents/ehc/ehc/ehc140.htm/ (accessed 8 November 2019).
Wu, C.C., Bao, L.J., Tao, S., Zeng, E.Y., 2016. Dermal uptake from airborne organics as an

important route of human exposure to e-waste combustion fumes. Environ. Sci. Technol. 50, 6599–6605.
Xiao, X., Chen, D., Mei, J., 2012. Particle-bound PCDD/Fs, PBDD/Fs and TBBPA in the atmosphere around an electronic waste dismantling site in Guiyu, China. Acta Pedol. Sinic. (China) 32, 1142–1148.
Xiao, X., Hu, J., Chen, P., Chen, D., Huang, W., Peng, P., Ren, M., 2014. Spatial and temporal variation, source profile, and formation mechanisms of PCDD/Fs in the atmosphere of an e-waste recycling area, South China. Environ. Toxicol. Chem. 33, 500–507.
Xiao, X., Hu, J., Peng, P., Chen, D., Bi, X., 2016. Characterization of polybrominated dibenzo-p-dioxins and dibenzo-furans (PBDDs/Fs) in environmental matrices from an intensive electronic waste recycling site, South China. Environ. Pollut. 212, 464–471.
Xing, G.H., Chan, J.K.Y., Leung, A.O.W., Wu, S.C., Wong, M.H., 2009. Environmental impact and human exposure to PCBs in Guiyu, an electronic waste recycling site in China. Environ. Int. 35, 76–82.
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.
Xu, M.X., Yan, J.H., Lu, S.Y., Li, X.D., Chen, T., Ni, M.J., Dai, H.F., Wang, F., Cen, K.F., 2009. Concentrations, profiles, and sources of atmospheric PCDD/Fs near a municipal solid waste incinerator in Eastern China. Environ. Sci. Technol. 43, 1023–1029.
Xu, P., Lou, X., Ding, G., Shen, H., Wu, L., Chen, Z., Han, J., Han, G., Wang, X., 2014. Association of PCB, PBDE and PCDD/F body burdens with hormone levels for children in an e-waste dismantling area of Zhejiang Province. China. Sci. Total Environ. 499, 55–61.
Xu, P., Tao, B., Zhou, Z., Fan, S., Zhang, T., Liu, A., Dong, S., Yuan, J., Li, H., Chen, J., Huang, Y., 2017. Occurrence, composition, source, and regional distribution of halogenated flame retardants and polybrominated dibenzo-p-dioxin/dibenzofuran in the soils of Guiyu, China. Environ. Pollut. 228, 61–71.
Xu, X., Zeng, X., Boezen, H.M., Huo, X., 2015. E-waste environmental contamination and harm to public health in China. Front. Med. 9, 220–228.
Ye, M., Warner, M., Mocarelli, P., Brambilla, P., Eskenazi, B., 2018. Prenatal exposure to TCDD and atopic conditions in the Seveso second generation: a prospective cohort study. Environ. Health. 17, 22.
Yorifuji, T., Kashima, S., Tokinobu, A., Kato, T., Tsuda, T., 2013. Regional impact of exposure to a polychlorinated biphenyl and polychlorinated dibenzofuran mixture from contaminated rice oil on stillbirth rate and secondary sex ratio. Environ. Int. 59, 12–15.
Yu, X., Zennegg, M., Engwall, M., Rotander, A., Larsson, M., Wong, M.H., Weber, R., 2008. E-waste recycling heavily contaminates a Chinese city with chlorinated, brominated and mixed halogenated dioxins. Organohal. Compd. 70, 813–816.
Zeng, X., Gong, R., Chen, W.Q., Li, J., 2016. Uncovering the recycling potential of "New" WEEE in China. Environ. Sci. Technol. 50, 1347–1358.
Zennegg, M., Schluep, M., Streicher-Porte, M., Lienemann, P., Haag, R., Gerecke, A.C., 2014. Formation of PBDD/F from PBDE in electronic waste in recycling processes and under simulated extruding conditions. Chemosphere 116, 34–39.
Zhang, T., Huang, Y., Chen, S., Liu, A., Xu, P., Li, N., Qi, L., Ren, Y., Zhou, Z., Mai, X., 2012b. PCDD/Fs, PBDD/Fs, and PBDEs in the air of an e-waste recycling area (Taizhou) in China: current levels, composition profiles, and potential cancer risks. J. Environ. Monit. 14, 3156–3163.
Zhang, J., Jiang, Y., Zhou, J., Wu, B., Liang, Y., Peng, Z., Fang, D., Liu, B., Huang, H., He, C., Wang, C., Lu, F., 2010. Elevated body burdens of PBDEs, dioxins, and PCBs on thyroid hormone homeostasis at an electronic waste recycling site in China. Environ. Sci. Technol. 44, 3956–3962.
Zhang, M., Buekens, A., Li, X., 2016a. Brominated flame retardants and the formation of dioxins and furans in fires and combustion. J. Hazard. Mater. 304, 26–39.
Zhang, M., Buekens, A., Li, X., 2017a. Open burning as a source of dioxins. Crit. Rev. Env. Sci. Technol. 47, 543–620.
Zhang, M., Feng, G., Yin, W., Xie, B., Ren, M., Xu, Z., Zhang, S., Cai, Z., 2017b. Airborne PCDD/Fs in two e-waste recycling regions after stricter environmental regulations. J. Environ. Sci. 62, 3–10.
Zhang, Z., He, J., Shi, T., Tang, N., Zhang, S., Wen, S., Liu, X., Zhao, M., Wang, D., Chen, W., 2019. Associations between polychlorinated dibenzo-dioxins and polychlorinated dibenzo-furans exposure and oxidatively generated damage to DNA and lipid. Chemosphere 227, 237–246.
Zhang, K., Schnoor, J.L., Zeng, E.Y., 2012a. E-waste recycling: Where does it go from here? Environ. Sci. Technol. 46, 10861–10867.
Zhang, L., Yin, S., Li, J., Zhao, Y., Wu, Y., 2016b. Increase of polychlorinated dibenzo-p-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls in human milk from China in 2007–2011. Int. J. Hyg. Environ. Health 219, 843–849.
Zhao, G., Xu, Y., Li, W., Han, G., Ling, B., 2007. Prenatal exposures to persistent organic pollutants as measured in cord blood and meconium from three localities of Zhejiang China. Sci. Total Environ. 377, 179–191.
Zheng, G.J., Leung, A.O.W., Jiao, L.P., Wong, M.H., 2008. Polychlorinated dibenzo-p-dioxins and dibenzofurans pollution in China: sources, environmental levels and potential human health impacts. Environ. Int. 34, 1050–1061.
World Health Organization (WHO), 2010. Preventive disease through healthy environments. Exposure to dioxins and dioxin-like substances. http://www.who.int/ipcs/features/dioxins.pdf?ua=1/ (accessed 23 September 2019).
Zhou, L., 2011. A preliminary study on the pollution characteristics of chlorinated and brominated dioxins in the typical areas of China. Guangzhou Institute of Geochemistry, Chinese Academy of Science. https://www.docin.com/p-895196426.html/ (accessed 5 October 2019).
Zhu, J., Hirai, Y., Sakai, S., Zheng, M., 2008. Potential source and emission analysis of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in China. Chemosphere 73, 72–77.
Zober, A., Messerer, P., Ott, M.G., 1997. BASF studies: epidemiological and clinical investigations on dioxin-exposed chemical workers. Teratog. Carcinog. Mutagen. 17, 249–256.
Zober, A., Ott, M.G., Messerer, P., 1994. Morbidity follow up study of BASF employees exposed to 2,3,7, 8-tetrachlorodibenzo-p-dioxin (TCDD) after a 1953 chemical reactor incident. Occup. Environ. Med. 51, 479–486.
Zong, G., Valvi, D., Coull, B., Goen, T., Hu, F.B., Nielsen, F., Grandjean, P., Sun, Q., 2018. Persistent organic pollutants and risk of type 2 diabetes: a prospective investigation among middle-aged women in Nurses' Health Study II. Environ. Int. 114, 334–342.