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PCDD/Fs in human tissues: A review of global biomonitoring data

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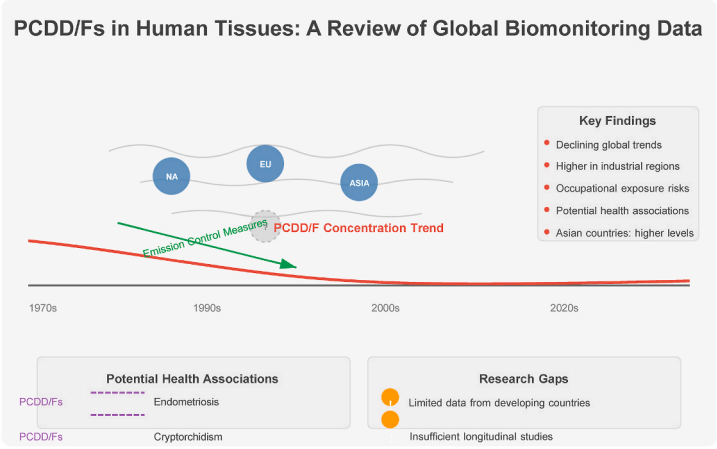
HIGHLIGHTS

- There is a global decline in PCDD/F levels in human adipose tissue.
- Limited data from developing countries and underrepresented regions.
- PBPK models estimate PCDD/F distribution in human tissues.
- Potential health links to endometriosis and cryptorchidism need further study.

GRAPHICAL ABSTRACT



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ABSTRACT

This review investigates the concentrations of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs) in internal human organs and tissues – excluding blood – with a particular focus on adipose tissue studies conducted worldwide up to January 2025. A thorough analysis of published literature highlights significant geographical and temporal trends in human PCDD/F exposure, including potential associations between PCDD/F levels and various health conditions. Several research gaps are identified, and proposals for future studies are given. Studies from Europe, Asia, and North America demonstrated a general decline in tissue PCDD/F concentrations over recent decades, particularly from the 1970s to early 2000s, attributed to successful emission control measures. Adipose tissue PCDD/F levels were typically higher in industrialized regions, with occupational exposure studies showing significantly elevated concentrations compared to the general population. Notable regional variations were observed, with some Asian countries continuing to show relatively high PCDD/F levels despite the overall declining trend. The review also highlighted potential associations between PCDD/F exposure and various health conditions, including endometriosis and cryptorchidism, though causal relationships remain unclear. Physiologically Based Pharmacokinetic (PBPK) modeling studies estimate valuable insights into the distribution and accumulation of these compounds in human tissues. Research gaps identified include limited data from developing countries and other underrepresented regions. It is also important to acknowledge the variability in analytical methods and reporting units across the reviewed studies, which may complicate direct

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comparisons of results. This review emphasizes the importance of continued biomonitoring efforts, particularly in underrepresented regions, to track exposure trends and protect vulnerable populations.

1. Introduction

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans (PCDD/Fs), commonly known as dioxins, are persistent organic pollutants (POPs) of significant environmental and public health concern. PCDD/Fs are primarily by-products of industrial processes, such as waste incineration, chemical manufacturing, and metal smelting, as well as uncontrolled combustion events (Schuhmacher and Domingo, 2006; Zhan et al., 2021; Zhang et al., 2022; Song et al., 2023; Domingo et al., 2024). The chemical stability and lipophilicity of these compounds result in bioaccumulation and biomagnification in food chains, making human exposure largely dietary through the consumption of animal-derived products such as meat, fish, and dairy (González and Domingo, 2021). Due to their persistence, PCDD/Fs are ubiquitously present in the environment, even in regions remote from emission sources. Human exposure to dioxins has been linked to a range of adverse health outcomes, including carcinogenicity, endocrine disruption, immunotoxicity, and reproductive impairments (ATSDR, 2024). The World Health Organization (WHO) and other regulatory organizations have established stringent guidelines for tolerable daily intake levels to minimize risks associated with these environmental pollutants (WHO, 2023).

Monitoring human exposure levels is essential for understanding population-wide exposure trends, identifying vulnerable subgroups, and evaluating the effectiveness of regulatory interventions aimed at reducing environmental emissions of PCDD/Fs, a reduction that has become very notable in recent decades (EEA, 2024). National and regional regulations have also been put in place to control PCDD/F emissions from industrial sources and to reduce human exposure through food, air, and water. However, despite these efforts, PCDD/Fs continue being a significant challenge to public health, particularly in regions with high levels of industrial activity or where historical contamination has occurred (EEA, 2024).

Human biomonitoring (HBM) serves as a critical tool for assessing exposure to PCDD/Fs. Biological matrices such as blood and breast milk have been commonly used for non-invasive or minimally invasive HBM of PCDD/Fs (Esteban and Castaño, 2009; Marquès and Domingo, 2019; González and Domingo, 2025). It provides a direct measure of internal chemical burden and reflects cumulative exposure of these compounds over time. Moreover, the measurement of PCDD/F levels in breast milk has been widely utilized to assess maternal and infant exposure, as these compounds readily transfer during lactation (LaKind et al., 2023; González and Domingo, 2025). However, information on the levels PCDD/Fs in other biological tissues and internal organs remain limited. Because of the lipophilic nature of PCDD/Fs, most studies investigating their concentrations in internal tissues have focused on adipose tissue. This paper was aimed at providing a comprehensive overview of the levels of PCDD/Fs in human internal organs and tissues, excluding blood. Patterns of human exposure, geographic and temporal trends, and other factors that may influence individual and population-level variability in PCDD/F body burdens are discussed.

2. Search strategy

A comprehensive literature review was conducted to evaluate the current state of knowledge regarding PCDD/Fs concentrations in human organs and tissues, excluding blood samples. The systematic search was performed across three major scientific databases: Scopus, Web of Science, and PubMed, covering literature published through January 20, 2025. The search strategy employed the following keyword combinations: “dioxins” or “PCDDs”, or “furans” or “PCDFs”, “human tissues”, “autopsy tissues”, “adipose tissue” AND “human biomonitoring of PCDD/Fs. To broaden the search and include relevant studies, we also used the following search string: (PCDD or PCDF or Dioxin or Furan) AND (human or adipose or tissue). English-language publications were prioritized for inclusion. Although the initial database searches generated a broad range of results, the selection was refined to focus exclusively on studies directly addressing PCDD/F concentrations in human tissues other than blood. Publications that did not specifically investigate tissue concentrations of PCDD/Fs or fell outside the scope of this review were excluded. The inclusion criteria involved studies measuring PCDD/Fs in human tissues other than blood. Exclusion criteria were studies not specific to PCDD/Fs in tissues or outside the scope of the review.

3. Results

3.1. Concentrations of PCDD/Fs in human adipose tissue

A comprehensive database search for this review found that most studies measuring PCDD/F concentrations in human internal organs and tissues – excluding blood – primarily used adipose tissue samples. The results are summarized in Table 1 and ordered according to the continent. It should be noted that studies with smaller sample sizes have limited statistical power, and their findings should be interpreted with caution.

3.1.1. European studies

Spain is the European country with the most information available on this topic. In a study conducted by González et al. (1993), the concentrations of PCDD/Fs were measured in samples of adipose tissue from the general population of Madrid. The mean (range) for the ∑PCCD/Fs was 1811.7 (963.7–3604.2) pg/g fat, being the levels of PCDFs lower than those of PCDDs. The distribution among groups of congeners was found to be more uniform for PCDFs than for PCDDs. One of the places where information is particularly abundant is Tarragona County (Catalonia), where in 1999 started the regular operations the first (and to date only) hazardous waste incinerator (HWI) existing in Spain. A monitoring program to know the impact of the emissions of PCDD/Fs and heavy metals on the environment and health of the surrounding population was designed. Measurements were initiated during the construction period of the plant, and the monitoring program is still active. One of the points of the program involved periodic measurements of PCDD/Fs in human samples of blood, breast milk, and adipose tissue (Schuhmacher et al., 1999a, 1999b, 1999c). Regarding adipose tissue, during the period of construction of the facility, a baseline/background study was carried out by Schuhmacher et al. (1999c). PCDD/Fs levels were determined in samples of 15 autopsied subjects. The mean and median PCDD/F values were 30.98 and 26.30 pg I-TEQ/g fat, respectively, with a range of concentrations from 3.37 to 69.37 pg I-TEQ/g fat. The levels of PCDD/F concentrations were higher in women (mean: 44.95 pg I-TEQ/g fat) than in men (mean: 24.00 pg I-TEQ/g fat). Three years after regular operations in the HWI, Schuhmacher et al. (2004) performed the first follow-up study on the concentrations of PCDD/Fs in human adipose tissue. Fifteen samples of adipose tissue from autopsied persons were again collected. The mean and median PCDD/F concentrations were 11 and 7.4 pg WHO-TEQ/g fat, respectively, with a range between 1.5 and 41 pg WHO-TEQ/g fat. The results meant a reduction of 70 % with respect to those of the baseline study, reduction that was in accordance with the notable decrease also observed in the dietary intake of PCDD/Fs in the area (Bocio and Domingo, 2005). A second follow-up study was carried out in 2007 in

the same geographical area (Nadal et al., 2009). Once again, the concentrations of PCDD/Fs were measured in samples of adipose tissue of 15 autopsied individuals living in the vicinity of the HWI. The mean level of PCDD/Fs was 14.6 pg WHO-TEQ/g of fat (range: 3.3–55.4 pg WHO-TEQ/g of fat), which meant remarkable differences with respect to the mean concentrations found in the baseline (Schuhmacher et al., 1999c) and previous survey (Schuhmacher et al., 2004), with a reduction of 64 %, and an increase of 47 %, respectively. Within the monitoring program of the HWI, another study was conducted in 2013, when 15 samples of adipose tissue of autopsied subjects were again collected

Table 1
PCDD/F levels in human adipose tissue according to different studies from the scientific literature.

Country/Region	Number of samples	Sampling Period	Mean TEQ (pg TEQ/g fat)	Range TEQ (pg TEQ/g fat)	Main Contributor	TEF Scheme	Highlight	Reference
Madrid, Spain	17	n.a.	41.8	4.09–82.89	OCDD	I-TEF	Autopsy abdominal subcutaneous adipose tissue from subjects who died from natural causes	González et al. (1993)
Tarragona, Spain	15	1998	30.98	13.37–69.37	OCDD	I-TEF	Baseline study in an area near a hazardous waste incinerator (HWI) under construction	Schuhmacher et al. (1999c)
Tarragona, Spain	15	2002	11.0	1.5–41.0	OCDD	WHO-TEF	First follow-up of a HWI running since 1999	Schumacher et al. (2004)
Tarragona, Spain	15	2007	14.6	3.3–55.4	OCDD	WHO-TEF	Second follow-up of a HWI running since 1999	Nadal et al. (2009)
Tarragona, Spain	15	2013	11.5	2.8–46.3	OCDD	WHO-TEF	Third follow-up of a HWI running since 1999	Schuhmacher et al. (2014)
Tarragona, Spain	15	2019	6.63	0.95–12.95	OCDD	WHO-TEF	Fourth follow-up of a HWI running since 1999	García et al. (2021)
Granada, Spain	20	2003	19.6	6.4–37.6	OCDD	WHO-TEF	Samples collected from women undergoing surgery for malignant and benign diseases	López-Espinosa et al. (2008)
Helsinki, Finland	3	1984	76, 65, 84	n.a.	OCDD	TEF proposed by Safe (1992)	Post-mortem examinations	Koistinen et al. (1995)
Kärkölä and Kuopio, Finland	7 + 7	n.a.	58.5; 40.9	37.6–94.3; 21.7–63.1	OCDD	I-TEF	Population exposed to chlorophenols via their drinking water for 20 y	Vartiainen et al. (1995)
Southern Finland	420	1997–1999	29.0	3.64–153	OCDD	WHO-TEF	Appendicitis patients chosen as controls in a case-control study of soft tissue sarcoma	Kiviranta et al. (2005)
Paris, France	16	1999	35.63	18.5–76.9	OCDD	I-TEF	Surgical ablation of lipomas	Arfi et al. (2001)
Italy	9	n.a.	9.6	3.4–13.3	OCDD	WHO-TEF	Bariatric surgery patients	La Rocca et al. (2008)
Ankara, Turkey	23	?	9.2	3.2–19.7	–	WHO-TEF	Voluntary men	Cok et al. (2007)
Ankara, Turkey	23 + 22	?	7.2; 7.0	3.0–15.8; 2.8–17.2	–	WHO-TEF	Fertile vs. infertile men	Cok et al. (2008)
Fukuoka, Japan	8	1989	14	3.0–25	OCDD	n.a.	Autopsies	Iida et al., 1999
Tokyo, Japan	20 + 15 + 10	1970–1971; 1994–1996; 2000	31.6; 31.5; 11.9	n.a.	OCDD	WHO-TEF	Temporal trend study	Choi et al. (2002)
Japan	28	1998–1999	49	n.a.	OCDD	n.a.	Paired livers and mesenteric adipose tissues of patients with various illnesses	Takenaka et al. (2002)
Jinju, South Korea	32	1994–1995	18	1.0–44	n.a.	I-TEF	Samples collected randomly from Kyungsang University Hospital	Kang et al. (1997)
Daegu, South Korea	53	2007–2008	7.0	0.72–22	OCDD	WHO-TEF	Female myoma patients undergoing a laparoscopy-assisted surgery	Moon et al. (2011)
Zhejiang Province, China	24	2006	7.73	1.33–16.4	OCDD	WHO-TEF	Liposuction/surgical procedures	Shen et al. (2009)
Coimbatore, India	21	2000	n.a.	14-46; 16-56	OCDD	WHO-TEF	Biopsies	Kumar et al. (2001)
Five Ontario municipalities, Canada	76	1984	65.9	10.9–184	OCDD	I-TEF	Samples obtained from unembalmed cadavers during autopsies	LeBel et al. (1990)
USA	865	1987	27.9	n.a.	OCDD	I-TEF	National Human Adipose Tissue Survey	Orban et al. (1994)
Atlanta, GA, USA	28	1984–1986	8.9	n.a.	OCDD	I-TEF	Samples at autopsy from the abdominal wall of men and women who died suddenly	Patterson et al. (1994)
New York, USA	5	1995–1996	8.42	n.a.	OCDD	I-TEF	6 tissue samples each from 5 women to study partitioning of PCDD/Fs	Schecter et al. (1998)
Germany	28	n.a.	56	18–122	OCDD	I-TEF	Non-occupationally exposed population	Beck et al. (1989)

n.a.: not available.

to measure the levels of PCDD/Fs (Schuhmacher et al., 2014). The mean concentration was 11.5 pg WHO-TEQ/g fat, with a range between 2.8 and 46.3 pg WHO-TEQ/g fat. There were no significant differences in the mean PCDD/F levels found in the period 2002–2013, although the mean level was notably lower (64 %) than that corresponding to the baseline study. Interestingly, that important decrease was also noted in other human biological monitors (plasma and breast milk) included in the surveillance program of the facility, agreeing with the reduction in the dietary intake of PCDD/Fs found in the same area of study. In 2019, García et al. (2021) carried out the last (until today) collection of samples of adipose tissue from 15 autopsied subjects who had been living near the HWI. The mean level of PCDD/Fs was 6.63 pg WHO-TEQ/g fat with a range between 0.95 and 12.95 pg WHO-TEQ/g fat. OCDD was the predominant congener, followed by 1,2,3,6,7,8-HxCDD and 1,2,3,4,6,7,8-HpCDD. The comparison of the profiles found in that study with those of the baseline and previous surveys showed that despite the differences in the respective levels, the profiles were generally very similar, with PCDFs showing lower concentrations than PCDDs. In another Spanish region, López-Espinosa et al. (2008) measured the levels of PCDD/Fs in 20 samples of adipose tissue collected from women undergoing surgery for malignant and benign diseases in a Hospital of Granada (Southern, Spain). A geometric mean of 410 pg/g fat was found for the sum of congeners (17.9 pg/g fat for WHO-TEQ). To improve comparability with other studies, the arithmetic mean would ideally be used if provided. OCDD showed the highest concentration (265 pg/g fat), followed by 1,2,3,6,7,8-HxCDD and 1,2,3,4,6,7,8-HpCDD, while for PCDFs, 2,3,4,7,8-PeCDF had the highest level. The main contributors to WHO-TEQ were 1,2,3,7,8-PeCDD (31.6 %), 1,2,3,6,7,8-HxCDD (28.3 %), and 2,3,4,7,8-PeCDF (14.6 %), with levels increasing with age.

In Finland, Koistinen et al. (1995) determined the concentrations of PCDD/Fs in three samples of adipose tissue obtained from the Department of Forensic Medicine, Helsinki, during routine post-mortem examinations carried out in 1984. I-TEQ values of 76, 65 and 84 pg/g fat were found. The highest concentrations corresponded to the congener OCDD (800, 790, and 820 pg/g fat). In turn, Vartiainen et al. (1995) measured the levels of PCDD/Fs in seven fat samples from individual living in the village of Kärkölä, samples taken during non-acute abdominal operations. Seven samples of matched controls were collected from Kuopio University Hospital. Kärkölä (Eastern Finland) was selected because in that village there was an episode of pollution of drinking water with chlorophenols. Although there were no significant differences in the concentrations of PCDD/Fs between the residents in Kärkölä (∑PCDD/Fs: 344–958 pg/g fat) and Kuopio (∑PCDD/Fs: 298–1106 pg/g fat), the levels tended to be higher in Kärkölä. The mean PCDD/F concentration (I-TEQ value) in Kärkölä was 58.5 pg/g fat (range: 37.6–94.3 pg/g fat), while in Kuopio was 40.9 pg/g fat (range: 21.7–63.1 pg/g fat). On the other hand, Kiviranta et al. (2005) determined the levels of PCDD/Fs in adipose tissue samples of 420 individuals (appendicitis patients), who lived in 14 different municipalities of southern Finland. The mean and median ∑PCDD/Fs were 413 and 364 pg/g fat, respectively (range: 78.0–2080 pg/g fat), while the mean (range: 3.64–153 pg/g fat) and median WHO-TEQ were 29.0 and 24.1 pg/g fat, respectively. OCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,6,7,8-HxCDD, and 2,3,4,7,8-PeCDF were the congeners showing the highest contribution to the mean and median ∑PCDD/Fs.

A few studies corresponding to other European countries are also available in the scientific databases. Duarte-Davidson et al. (1993) measured the levels of PCDD/Fs in five adipose tissue samples of donors of various localities from Wales, UK. The mean ΣPCDD/F concentration was 1220 pg/g adipose tissue. No clear relationships were found between sampling location and the levels of PCDD/F and patterns. The major contributors to the total toxic equivalent (ΣTEQ) were 1,2,3,6,7,8-HxCDD (18.2 pg/g), 2,3,4,7,8-P5CDF (12 pg/g), and 1,2,3,7,8-P5CDD (11.5 pg/g). In France, Arfi et al. (2001) determined the levels of PCDD/Fs in adipose tissue samples of adult patients undergoing a surgical ablation of benign subcutaneous lipomas in a hospital of Paris. The correlation with the dietary intake of PCDD/Fs was also examined. Adipose tissue PCDD/Fs levels ranged from 18.5 to 76.9 pg I-TEQ/g fat, with mean and median (values of 35.63 and 32.84 pg I-TEQ/g fat, respectively. The predominant congener was OCDD, followed by 1,2,3,4,6,7,8-HpCDD and 1,2,3,6,7,8-HxCDD. No significant correlation was observed between the dietary intake of PCDD/Fs and the concentrations of these pollutants in adipose tissue, values that, according to the author, were comparable to those found in other industrialized countries. In Italy, La Rocca et al. (2008) measured the concentrations of PCDD/Fs in nine samples of abdominal adipose tissue of obese patients, samples that were collected during bariatric surgery in a hospital of Rome. The mean concentration of ∑PCDD/Fs was 195 pg/g fat (range: 68–316 pg/g fat), while the total WHO-TEQ levels ranged between 3.4 and 13.3 pg TEQ/g fat for ∑PCDD/Fs. The congeners 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 2,3,4,7,8-PeCDF were the main contributors to total TEQs. Interestingly, it was highlighted that in obese patients, a considerable loss of weight occurs within six months after bariatric surgery. It could explain a reduction of the body fat content of about 16 %, which would mean an exposure of internal organs to PCDD/Fs that were released into the blood circulation. In Turkey, Cok et al. (2007) conducted the first study in that country aimed at determining the concentrations of PCDD/F in human adipose tissue. Samples of 23 Turkish voluntary men living in Ankara were collected during appendectomies or sarcoma operations. PCDD/F concentrations ranged from 3.2 to 19.7 pg WHO-TEQ/g fat, with a mean WHO-TEQ concentration of 9.2 pg/g fat. In a subsequent study performed by the same research group (Cok et al., 2008), PCDD/F levels were determined in adipose tissue samples (collected during surgical operations) of infertile men living in Ankara, being the results compared with those of the previous survey (Cok et al., 2007). Mean concentrations of PCDD/Fs were similar for fertile and infertile men: 7.2 pg WHO-TEQ/g fat(range: 3.0–15.8) and 7.0 (range: 2.8–17.2) pg WHO-TEQ/g fat, respectively. ΣPCDD concentrations were 46.9 pg/g fat for fertile men, and 57.3 pg/g fat for infertile men, while ΣPCDF concentrations were 26.2 pg/g fat for fertile men, and 25.1 pg/g fat for infertile men. No significant differences were observed between both groups.

3.1.2. *Asian studies*

Japan is the Asian country with the most information available on the topic of this review. Ogaki et al. (1987) measured the concentrations of PCDD/Fs in human samples of adipose tissue (and liver), which were collected in 1985 in three different areas of Japan by justice dissection, and/or a pathological anatomy, from autopsied individuals. Regarding adipose tissue, the levels of total PCDDs and PCDFs were 1397 and 124 pg/g fat, respectively, with ranges between 5 (TCDD) and 1213 (OCDD) pg/g fat for PCDDs, and 20 (TCDF) and 39 (HxCDFs) pg/g fat for PCDFs. Twelve years after, Iida et al., 1999 reported the results of a survey in which the concentrations of PCDD/Fs were determined in samples of human blood and various internal tissues, including adipose tissue. Samples were collected in 1989 during the autopsies of eight subjects in Fukuoka, Japan. For adipose tissue, the mean total TEQ was 14 pg/g fat (range: 3.0–25 pg/g fat), being OCDD the congener with the highest contribution, 2500 pg/g fat. The congener concentrations in adipose tissue (as well as those found in liver, kidney and spleen) were correlated to those found in blood. It was concluded that the congener levels in blood could be useful to estimate the congener concentrations in the analyzed internal organs/tissues. Already in the present century, Choi et al. (2002) reported the results of a study focused on measuring the levels of PCDD/Fs (and coplanar PCBs) in samples of adipose tissue taken from the abdomens of cadavers of Japanese adults, which were collected in Tokyo in 1970–1971, 1994–1996 and 2000. The temporal trend of the PCDD/Fs levels was also assessed. The mean levels of PCDD/Fs were 4850, 430 and 171 pg/g fat, for the periods 1970–1971, 1994–1996, and 2000, respectively, showing a considerable decrease (about 30 times) in the samples collected in 1970–1971 and 2000. Although the levels of some congeners fluctuated with time, between

1970 and 2000 the dominant congeners were OCDD, 1,2,3,6,7,8-HxCDD and 2,3,4,7,8-PeCDF. A decreasing trend was also noted for the TEQ values: 31.6, 31.5 and 11.9, for the periods 1970–1971, 1994–1996, and 2000, respectively. In turn, Takenaka et al. (2002) determined the concentrations of PCDD/Fs (and various PCBs) in samples of liver and adipose collected in autopsies of 28 Japanese patients affected by various diseases. In adipose tissue, the mean level was 49 pg TEQ/g fat, being the value of total PCDDs 741 pg/g fat (range: 63–3362 pg/g fat), while that of total PCDFs was 7.1 pg/g fat (range: ND-21 pg/g fat).

In South Korea, Kang et al. (1997) conducted the first study in that country on PCDD/Fs accumulation in human adipose tissue. The levels of PCDD/Fs, as well as other POPs, were measured in samples collected in1994 and early 1995 from 32 subjects from Jinju (western Kyungnam). On a fat basis, the mean I-TEQ values were 8 pg/g (range: 0.2–19 pg/g) and 10 pg/g (range: 0.8–25 pg/g), for PCDDs and PCDFs, respectively. In a subsequent study, Moon et al. (2011) determined the concentrations of PCDD/Fs (and dioxin-like PCBs) in samples of adipose (omental fat) tissue of 53 female myoma patients undergoing a laparoscopy-assisted surgery in the Kyungpook National University Hospital (Daegu, South Korea). The levels of PCDDs and PCDFs ranged between 30 and 530 pg/g fat, and between 6.5 and 50 pg/g fat, respectively. In turn, the TEQ concentrations of PCDDs and PCDFs ranged between 0.02 and 11 pg/g, and from 0.7 to 11 pg/g, respectively. Each homologue group of PCDD/Fs was found in all analyzed samples, being OCDD the highest contributor (>70 %) to total PCDD/F concentrations. No significant correlation between body mass index (BMI) and the levels of PCDD/Fs was found. In China, the first study of PCDD/F accumulation in human adipose tissue was conducted in Zhejiang Province by Shen et al. (2009), who used 24 samples obtained in 2006 during liposuction or other surgical procedures. Total PCDD/F concentrations ranged from 33.9 to 504 pg/g fat, with a mean of 108 pg/g fat. The mean.

3.1.3. North American studies

In a study conducted in the early 1980s, Ryan et al. (1985) measured the levels of PCDD/Fs in 72 human adipose tissue samples (mostly from Canada) taken from the abdominal region during autopsies carried out in 1972, 1976, 1980 and 1983–1984. Only 2,3,7,8-chlorine substituted dioxins and furans were detected. Concentrations of PCDDS increased with chlorination level, from 5 to 10 pg/g fat for 2,3,7,8-TCDD to 600–800 pg/g fat for OCDD, while the levels of PCDFs were lower, with average values of 17, 17, and 33 pg/g fat for penta-, hexa-, and hepta-congeners, respectively. The authors concluded that PCDD/F concentrations were 2–3 orders of magnitude lower than the levels known at that time to cause adverse effects in humans. In another study performed in Canada, LeBel et al. (1990) measured the concentrations of PCDD/Fs in samples of human adipose tissue obtained in 1984 from autopsies carried out in five municipalities in the Great Lakes Basin, Ontario. Only 12 of the 17 possible 2,3,7,8-substituted congeners were detected. The mean I-TEQ value was 66 pg/g. The PCDD/F concentrations found in that study were somewhat higher but consistent with the levels of PCDD/Fs previously reported by Ryan et al. (1985). In the USA, studies conducted during the 1980s and early 1990s provided comprehensive insights into PCDD/Fs concentrations in human tissues across various populations. The US EPA's National Human Adipose Tissue Survey (1987) established baseline levels in the USA population (Orban et al., 1994), finding average 2,3,7,8-TCDD concentrations of 5.38 pg/g corresponding to 865 subjects, with significant age-related variations ranging from 1.98 pg/g in children under 14 years, to 9.40 pg/g in adults over 45 years. Regional differences were observed in specific compounds, particularly 2,3,4,7,8-PeCDFs. Notwithstanding, no significant variations were found between sexes or races. On the other hand, Patterson et al. (1994) measured the concentrations of PCDD/Fs (and PCBs) in samples of human blood and adipose tissue collected in Atlanta (GA). The results revealed consistent PCDD and PCDF patterns across individuals, with age significantly correlating with 2,3,7,8-TCDD concentrations. Total PCDDs and PCDFs were 634 and 26.3 pg/g fat, respectively. OCDD (446 pg/g fat) and 1,2,3,4,6,7,8-HpCDF were the congeners with the highest values for PCCDs and PCDFs, respectively.

3.1.4. TEFs, analytical methods, dietary intake, and age correlation

It is important to consider the different Toxic Equivalency Factors (TEFs) used in the studies included in this review, as these impact the comparability of TEQ values. The initial I-TEF system was published in 1988, followed by updates from the World Health Organization (WHO) in 1998, 2005 and 2022 (van den Berg et al., 2006; DeVito et al., 2024). These revisions reflect advances in understanding the relative toxicity of different PCDD/F congeners and, more recently, the inclusion of dioxin-like PCBs (dl-PCBs) in the TEQ calculation. It is important to note if studies included dl-PCBs and what TEF values were used. For example, the study by Patterson et al. (1994) likely did not include dl-PCBs, as they were not commonly included in TEQ calculations at that time. Future studies should standardize reporting and include all relevant compounds to enhance data comparability.

Analytical methods also vary across studies. Most studies utilized high-resolution gas chromatography/high-resolution mass spectrometry (HRGC/HRMS), which is considered the gold standard for PCDD/F analysis due to its high sensitivity and specificity. However, variations in sample preparation, cleanup procedures, and quantification methods can still contribute to variability between studies. These differences are not always fully reported making comparison difficult.

On the other hand, it is very important to highlight that dietary intake is a major source of exposure to PCDD/Fs for the general population, with the main contributions coming from food of animal origin such as fatty fish, meat, and dairy products (González and Domingo, 2021). The reviewed studies often did not include detailed dietary information, making it difficult to assess the relationship between dietary exposure and adipose tissue concentrations. Thus, further research should incorporate dietary assessments to better understand the sources of human exposure.

Several studies, including Orban et al. (1994) and López-Espinosa et al. (2008), reported that PCDD/F concentrations in adipose tissue tend to increase with age. This is likely due to the bioaccumulative nature of these compounds and the long-term exposure from dietary and other sources. However, this correlation was not consistently observed across all studies. Therefore, further research is needed to clarify the relationship between age and PCDD/F levels in human tissues.

3.2. Concentrations of PCDD/Fs in other human tissues

In addition to measuring the levels of PCDD/Fs in samples of human adipose tissue, Ogaki et al. (1987) also determined the concentrations of PCDDs in samples of human liver, which were collected from the same autopsied individuals in one area (a big city) of the three zones into which was divided the sampling for gathering adipose tissue. For some undiscussed reason, the authors did not report data regarding PCDFs. The total mean level of PCDDs was 1270 pg/g wet weight (range: 88–2300 pg/g ww). In comparison to adipose tissue, from TCDD to HepCDD, the absolute amount (for adipose tissue, results were given on a fat basis) was rather similar. However, the OCCD content in human liver was significantly higher. This is in addition to the concentrations (above reported) in human adipose tissue. The main goal of the study was to establish the correlations between the concentrations of PCDD/Fs in blood and other human tissues. The TEQ values (in pg/g fat) for the PCDD/Fs congeners plus 3,3′,4.4′-TeCB, 3,3′,4.4′,5-PeCB and 3,3′,4.4′,5,5′-HxCB were the following: liver, 270; brain, 11; spleen, 43; muscle, 68; kidney, 29; and lung, 77. It was found that congener concentrations in liver, adipose tissue, kidney and spleen correlated to those in human blood, being concluded that the blood concentrations could be useful to estimate the respective congener concentrations in human tissues. In another study also conducted in Japan, Muto et al. (1991) assessed the distribution of 2,3,7,8-chlorine-substituted dibenzo-p-dioxins across

various organs and tissues in 11 cancer patients from Akita. OCDD (pg/g fat) was the most abundant congener (10.0 in liver, 5.0 in lung, 3.0 in kidney, 2.0 in spleen, 1.0 in gonad, 0.5 in adrenal gland, 0.2 in heart, 0.1 in brain, 0.05 in muscle, 0.01 in fat, and 0.005 in blood), followed by HpCDD (pg/g fat) (5.0 in liver, 2.5 in lung, 1.5 in kidney, 1.0 in spleen, 0.5 in gonad, 0.25 in adrenal gland, 0.1 in heart, 0.05 in brain, 0.025 in muscle, 0.005 in fat, and 0.0025 in blood). The highest TEQ was found in a female with cancerous goiter, who also had the highest levels of penta- and hexaCDDs. In turn, Kitamura et al. (2001) analyzed 20 dioxin congeners in bile, blood, and liver from 27 autopsy cases in Tokyo, Japan. The liver showed the highest total-TEQ values (127.8 pg TEQ/g fat), which was three times higher than those found in bile and blood. Highly chlorinated PCDDs and PCDFs showed preferential accumulation in the liver compared to bile and blood, with 1,2,3,4,6,7,8-HpCDF showing the strongest accumulation tendency. The accumulation of PCDD/Fs (pg TEQ/g fat) in liver (1.91) was found to be notably higher than those in bile (0.99) and blood (0.70). On the other hand, in addition to samples of human adipose tissue, Takenaka et al. (2002) also analyzed the concentrations of PCDD/Fs in human liver. The mean total PCDD/Fs levels in that organ was 57 pg TEQ/g fat. While PCDDs showed similar behavior between liver and adipose tissue, what means they presented isomers with similar distribution across both tissue samples, most PCDFs isomers had different distribution patterns between these tissues.

4. Special population studies

4.1. Occupational studies

In Germany, Beck et al. (1994) determined the concentrations of PCDD/Fs in samples of adipose tissue from non-occupationally exposed individuals and occupationally exposed workers (study design: cross-sectional). The TEQ values (mean and range in pg/g fat) were the following: for non-occupationally exposed subjects, the mean of 28 adults was 56 pg/g fat (range: 18–122), while for infants (six samples) the range was between 2.1 and 22 pg/g fat. In occupationally exposed individuals, the mean increased to 502 pg/g fat (range: 37–2928), which showed that persons working in certain chemical plants or specific industrial processes had significantly elevated or high PCDD/F levels, their exposure far exceeds that of the general population.

4.2. Disease related studies

Tuomisto et al. (2004) investigated the association between exposure to PCDD/Fs and soft-tissue sarcoma (STS) in a case-control study conducted in Finland. The study included 110 STS, analyzing individual PCDD/F concentrations from subcutaneous fat samples. The mean PCCD/F concentration (WHO-TEQ) was 33.4 pg/g fat, with a range of 4.4–145.5 pg/g fat. No increased risk of STS was found with respect to a higher exposure to PCDD/Fs. In fact, the highest risk was observed at low PCDD/F levels. The odds ratios for different quintiles, compared to the lowest quintile (median: 11.5 ng/kg), ranged from 0.43 (95 % CI: 0.18–1.05) to 0.65 (95 % CI: 0.22–1.95), suggesting no positive association between PCDD/Fs and STS risk. Martínez-Zamora et al. (2015) performed a study (design: case control) aimed at providing the levels of the most toxic PCDD/Fs and dioxin like PCBs (dl-PCBs) in adipose tissue samples of patients (30 women undergoing laparoscopic surgery) with deep infiltrating endometriosis (DIE group), which were collected in a hospital of Catalonia, Spain. PCDD/Fs were also analyzed in adipose tissue of control individuals without endometriosis. The total concentration of PCDD/Fs in adipose tissue was significantly higher in the DIE group than in controls, with median values of 6.90 and 6.10 pg/g fat, respectively. The TEQ values and levels of 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD were also significantly higher in patients with DIE. It was suggested that PCDD/Fs could have a potential role in the pathogenesis of DIE. In Amman, Jordan, Alawi et al. (2018) measured the concentrations of three groups of POPs (OCPs, PCBs, and PCDDs/Fs) in human adipose tissue samples from 33 cancer-affected patients and 46 non-cancer affected healthy subjects. Regarding PCDD/Fs, the highest TEQ value in healthy individuals corresponded to 2,3,4,7,8-PeCDFs (5.93 pg TEQ/g fat), while in cancer patients, the highest TEQ value corresponded to 1,2,3,7,8-PeCDDs (20.64 pg TEQ/g fat). The TEQ values for PCDDs/Fs in samples of cancer patients were about three times higher than those in samples of healthy individuals. Although the PCDD/F levels were higher in cancer patients, a clear relationship between these elevated PCDD/Fs levels and cancer development could not be established only with the results of that study. It is well known that to develop cancer, many factors other than exposure to carcinogenic pollutants are involved.

On the other hand, Koskenniemi et al. (2015) investigated (study design: case control). the association between concentrations of various POPs (PCDD/Fs, PCBs and PBDEs) in adipose tissue and cryptorchidism in early childhood. Subcutaneous adipose tissue biopsy samples of 44 cryptorchid cases and 38 controls were collected at Hospitals of Turku, Finland, and Copenhagen, Denmark. The median $\sum$PCDD/F concentrations were 103 pg/g fat (range: 21.7–320 pg/g fat) and 79.1 pg/g fat (range: 21.7–1290 pg/g fat), for cryptorchid cases and controls, respectively. It was found that PCDD/Fs were significantly associated with increased risk of cryptorchidism, with an odds ratio of 3.69, after adjusting for key factors.

In France, Ploteau et al. (2016) examined (study design: cross-sectional) the distribution of PCDD/Fs in serum, omental, and parietal adipose tissue of 68 French women with DIE and 45 controls. Significant associations were found between DIE and adipose tissue levels, mainly for 1,2,3,7,8-PeCDD and OCDF, which showed the strongest association. The WHO-TEQ PCDD/F values ranged between 2.4 and 20.7 pg/g fat, (median: 7.4 pg/g fat), and between 2.2 and 22.3 pg/g fat (median: 6.4 pg/g fat) in omental and parietal adipose tissue, respectively. In agreement with the results of Martínez-Zamora et al. (2015), these findings suggested a potential link between PCDD/F exposure and DIE, particularly in cases concurrent with ovarian endometrioma. In a subsequent study (design: cross-sectional). conducted by the same research group (Ploteau et al., 2017), the potential association between DIE (with or without endometrioma) and the internal concentrations of various POPs in adipose tissue of French women was assessed. Samples of adipose tissue were collected from surgically confirmed DIE cases. Significantly higher levels were only observed for 1,2,3,7,8-PCDD (2.05 pg/g fat in controls vs. 2.28 and 3.79 pg/g fat in cases of DIE without ovarian endometrioma, and DIE with ovarian endometrioma, respectively) and OCDF (0.42 pg/g fat in controls, and 0.59 and 0.77 pg/g fat in DIE cases with or without ovarian endometrioma, respectively). WHO-TEQ values were found to be 5.53 pg/g fat for controls, 5.80 pg/g fat and 8.75 pg/g fat for DIE cases with or without ovarian endometrioma.

5. PBPK modeling of exposure to PCDD/Fs

Physiologically Based Pharmacokinetic (PBPK) modeling has been extensively used to study the distribution and accumulation of PCDD/Fs in human tissues. Several key studies have contributed to understanding these processes and their implications for exposure assessment and risk evaluation. Maruyama et al. (2002) investigated interindividual variability in PCDD/Fs concentrations using PBPK modeling. Their simulations, spanning four decades, examined compound distribution in tissues such as liver, kidneys, fat, blood, muscle, and richly perfused organs. The findings showed tissue concentrations ranging from 0.17 to 4.1 times the standard level due to variations in body weight, gastrointestinal absorption, and dietary habits. The model effectively captured over 80 % of the observed anatomical data for several PCDD/Fs in liver, fat, and blood, highlighting the influence of physiological factors on individual differences. In a subsequent study, Maruyama et al. (2003) applied PBPK modeling to assess fetal exposure to PCDD/Fs among the

Japanese population. Simulations of maternal accumulation over 40 years demonstrated that PBPK models provided a better fit to measured concentrations in richly perfused tissues than simpler one-compartment models. Assuming fetal exposure mirrored maternal richly perfused tissue concentrations, the study estimated that daily intake of 2,3,7, 8-TCDD was approximately 1/50 of the threshold linked to reproductive toxicity. However, considering the cumulative effects of 29 dioxin congeners, that intake level rose to about 1/5 of the hazardous threshold.

On the other hand, Emond et al. (2017) developed a revised version of the US EPA's human PBPK model for dioxins using Berkeley Madonna software. Their approach integrated CYP1A2 induction as a critical factor influencing dioxin metabolism and implemented a body burden-dependent elimination half-life. The recoded model successfully replicated the original US EPA predictions and effectively simulated both acute and chronic exposure scenarios. The authors emphasized its utility in interpreting human biomonitoring data for dioxin risk assessment. In turn, Schuhmacher et al. (2014) employed a multi-compartmental PBPK model to estimate PCDD/F levels in adipose tissue near a hazardous waste incinerator in Tarragona (Catalonia, Spain). Comparing model predictions with data from four environmental surveys (1998–2013), a strong concordance was found, confirming the model's reliability for assessing internal PCDD/F doses. These results again underscored PBPK modeling as a valuable tool for environmental exposure assessments. Overall, these studies illustrate the effectiveness of PBPK models in characterizing PCDD/F pharmacokinetics and exposure dynamics. By incorporating physiological parameters, these models enhance the accuracy of tissue concentration predictions across different exposure scenarios. Their application in risk assessment helps to explain interindividual variability in PCDD/F accumulation and supports more precise evaluations of potential health risks.

6. Discussion

This comprehensive review of PCDD/F concentrations in human tissues, with a primary focus on adipose tissue due to its greater data availability, identifies significant trends and patterns that offer critical insights into human exposure to these POPs. The lipophilic nature of PCDD/Fs causes their accumulation in fatty tissues, making adipose tissue the primary matrix for biomonitoring these compounds (Jackson et al., 2017). Most studies reviewed here indicate that PCDD/Fs levels in adipose tissue are higher in industrialized regions, where these pollutants are more likely to be present due to emissions from waste incineration and industrial processes (Schuhmacher et al., 2004; Nadal et al., 2009).

The analysis highlights a global pattern of declining PCDD/Fs levels over time, especially from the 1970s to the early 2000s. This trend is largely attributed to the successful implementation of emission control measures, particularly in Europe and North America (Choi et al., 2002; Kiviranta et al., 2004; García et al., 2021). For instance, data from Spain show clear decreasing trends (García et al., 2021), with older studies from USA and Japan also corroborating a decline. The decreasing trend is not uniform across all regions. Thus, some studies, particularly in Asian countries, reported high PCDD/F levels, although generally lower than those found in Europe. For example, studies carried out in Japan, Korea, and China illustrated regional variations in exposure levels, with some areas exhibiting relatively high PCDD/F concentrations, which is probably due to localized industrial activities or the use of contaminated resources like food and water (Shen et al., 2009; Moon et al., 2011). Conversely, India presented lower levels of exposure, potentially reflecting differences in industrialization and regulatory measures. However, it must be noted that the most recent available data for India were reported more than two decades ago (Kumar et al., 2001).

Furthermore, geographical disparities in PCDD/F concentrations underscore the critical role of localized environmental sources. Industrial activities, waste management, and agricultural practices significantly influence POP levels in human tissues (Mustieles et al., 2017; Reina-Pérez et al., 2023), with PCDD/Fs being no exception (Domingo et al., 2017; Marquès and Domingo, 2019). For PCDD/Fs, urban-rural comparisons reveal that urban populations, typically in the proximity to industries, show higher exposure levels compared to rural populations, which are generally less exposed to industrial emissions (Marquès and Domingo, 2019; Ssebugere et al., 2019). This is especially evident in countries like Canada, where urban areas showed higher levels than rural settings (LeBel et al., 1990), and in China, where industrial activities in urban centers contributed to elevated body burdens (Shen et al., 2009).

The review also highlights the importance of special population studies. Thus, workers in industries such as waste incineration and e-waste recycling are at heightened risk for elevated exposure to PCDD/Fs (Beck et al., 1994; Chan and Wong, 2013). Moreover, certain health conditions, including endometriosis and cryptorchidism, have been linked to higher PCDD/F levels, indicating potential associations between these pollutants and reproductive health outcomes (Martínez-Zamora et al., 2015; Ploteau et al., 2017). While these findings are compelling, the evidence remains inconclusive. Therefore, more research is needed to establish direct cause-effect relationships. Methodological considerations are crucial in interpreting the results. The diversity in analytical methods and reporting units across the studies reviewed complicates the comparison of results. Variations in sampling protocols, tissue selection, and detection methods highlight the need for standardization in future research to ensure consistency and comparability of findings. The selection of appropriate matrices for biomonitoring PCDD/Fs, particularly in the context of emerging non-invasive sampling methods, is another area for improvement (Alves et al., 2014; Pollock et al., 2021). Future studies should focus on refining these methodologies to enhance exposure assessments. Additionally, the emerging effects of climate change on exposure patterns and the potential for increased exposure in certain regions warrant special attention.

One notable research gap is the lack of sufficient data from developing countries and other underrepresented regions. Many studies have focused on industrialized nations, and the lack of data from many countries of various continents limits the understanding of global exposure patterns. Longitudinal studies that track exposure levels over extended periods are also lacking, hindering the ability to evaluate the long-term health impacts of PCDD/Fs exposure. It must be highlighted that PCDD/F exposure is linked to various health effects, including increased cancer risk, metabolic disorders, and reproductive issues due to its interaction with the aryl hydrocarbon receptor (AhR) (Furue et al., 2021; Aldeli et al., 2024; Zhong et al., 2024). Studies suggest associations with conditions like endometriosis and neurodevelopmental deficits, particularly in vulnerable populations. However, direct causal mechanisms remain unclear, highlighting the need for further research on toxicokinetics and the potential synergistic effects of PCDD/Fs with other pollutants.

In conclusion, while the available data show a general decline in PCDD/F levels in human tissues over recent decades in some regions such as North America and Europe, significant regional and population-specific disparities persist. Integrating biomonitoring data with exposure modeling, advancing non-invasive sampling methods, and investigating mixture effects will be crucial for refining risk assessment strategies, significant regional and population-specific disparities persist. Integrating biomonitoring data with exposure modeling, advancing non-invasive sampling methods, and investigating mixture effects will be crucial for refining risk assessment strategies. Biomonitoring efforts, particularly in underrepresented regions, are essential to track exposure trends and protect vulnerable populations. Future research priorities should include standardizing analytical methods and understanding the health implications of current exposure levels to PCDD/Fs.

CRediT authorship contribution statement

Jose L. Domingo: Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Martí Nadal:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization.

Declaration of competing interest

The author declares the following financial interests/personal relationships which may be considered as potential competing interests.

Jose L Domingo and Marti Nadal, co-authors of the current submission to CHEMOSPHERE declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

This is a REVIEW-manuscript that does not contain original data. All data included in the paper belong to studies referenced in the list of studies used to write the manuscript

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