International Journal of Dairy Technology

SDT Society of Dairy Technology

doi: 10.1111/1471-0307.12917

REVIEW

Dioxins and furans in cow milk and dairy products: A review of the scientific literature

JOSE L DOMINGO*

School of Medicine, Laboratory of Toxicology and Environmental Health, Universitat Rovira i Virgili, San Llorenç 21, Reus, Catalonia 43201 Spain

Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) are a group of persistent organic pollutants with well-known toxic effects and potential carcinogenicity. Human exposure to PCDD/Fs is mainly through food, including dairy products. The scientific information on the concentrations of PCDD/Fs in milk and dairy products is here reviewed. It also includes the intake of PCDD/Fs through the consumption of these products. PCDD/Fs concentrations in milk and dairy products are currently decreasing. A similar trend is also noted for their contributions to the total dietary intake of PCDD/Fs. No significant health risks due to exposure to PCDD/Fs through the consumption of dairy products are expected.

Keywords Polychlorinated dibenzo-p-dioxins and dibenzofurans, Milk and dairy products, Human consumption, Health risks.

*Author for correspondence. E-mail: joseluis.domingo@urv.cat

INTRODUCTION

Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs), generally known as dioxins and furans, are unintentionally produced organic compounds, which belong to the called 'dirty dozen', a group of dangerous persistent organic pollutants (POPs). PCDD/Fs are of notable concern given their important adverse effects in mammals (USEPA 2022). Their toxic effects include among others, reproductive and developmental problems, interferences with hormones, damage to the immune system, and being also potential carcinogenic agents (WHO 2016). With respect to potential human exposure to PCDD/Fs, it is well established that more than 90% of PCDD/Fs exposure is through food, mainly meat, milk and dairy products, and fish and shellfish (González and Domingo 2021).

For most population over the world, milk is an essential component of their diets. Milk is considered as the only foodstuff that contains all different substances that are known to be essential for an adequate human nutrition (Davoodi *et al*. 2013; Scholz-Ahrens *et al*. 2020; Lin *et al*. 2021). Therefore, the consumption of milk and milk products is usually recommended for a healthy and balanced human diet (Pereira 2014; Rumbold *et al*. 2022). Regarding the health benefits, a number of epidemiological studies have shown the importance of consuming milk and dairy products (low-fat and fermented) in preventing various potential adverse health effects such as bone problems and osteoporosis (Rozenberg *et al*. 2016; Fardellone *et al*. 2017; Fardellone 2019; Ratajczak *et al*. 2021), risk of childhood obesity (Thorning *et al*. 2016) and type 2 diabetes mellitus (Alvarez-Bueno *et al*. 2019; Awwad *et al*. 2022). With respect to cardiovascular diseases, since milk and milk products can be a source of saturated fatty acids, their regular consumption could be linked to increased risks of these diseases. However, it has been shown that the consumption of dairy products with a low-fat content does not mean additional risks of cardiovascular diseases (Drouin-Chartier *et al*. 2016; Fontecha *et al*. 2019; Sellem *et al*. 2022).

In addition to significantly contribute to reach the requirements of a number of micronutrients (Ca, Mg, K, Se, Zn, phosphorus, riboflavin, vitamins A and B12, *etc*.), milk and dairy products contain also various bioactive constituents, which can influence positively on the risks of certain cancers (Lampe 2011; Ferraz *et al*. 2012; Davoodi *et al*. 2013; Thorning *et al*. 2016; Gil and Ortega 2019; Scholz-Ahrens *et al*. 2020). With respect to the relationship between the consumption of dairy products and benefits/risks on cancer prevention, the debate remains open. While there are studies showing decreases in certain types of cancer (e.g. colorectal and bladder cancers) (Lampe 2011; Thorning *et al*. 2016: Bermejo *et al*. 2019; Leischner *et al*. 2021), other investigations have reported increases in some cancers such as the non-Hodgkin lymphoma (Wang *et al*. 2016) and prostate (Zhao *et al*. 2022). In relation to the factors that can increase the risks of certain cancers, various exogenous milk compounds should be taken into account. Thus, pesticides and several environmental pollutants, together with veterinary drugs and melamine, which can be contained in milk and dairy products, may contribute to develop some forms of cancer (Davoodi *et al*. 2013; Urseler *et al*. 2022). This has been already suggested for red meat, for example, as a result of the International Agency for Research on Cancer (IARC) statement on the potential carcinogenicity of the consumption of red meat and processed meats (Domingo and Nadal 2016; Domingo 2017; González *et al*. 2020). Anyhow, making a balance on the potential health risks and benefits of a regular daily consumption of milk and dairy products, the benefits are more significant. In general, it seems to be well demonstrated that those subjects consuming higher quantities of milk and milk products have health advantages in comparison to those who do not consume these foodstuffs, or their consumption is lower (Kliem and Givens 2011; Poppitt 2020; Bruno *et al*. 2021).

Recently, the available scientific literature on the concentrations in cow milk of four toxic elements, arsenic, cadmium, mercury and lead, was reviewed (Domingo 2021). It was concluded that human exposure to those elements through a frequent consumption of cow milk should not mean significant health risks for the consumers. Given the importance of the potential human health risks due to the exposure to PCDD/Fs through the diet, including dairy products, the current paper was aimed at reviewing the recent literature on the human exposure to PCDD/Fs through the consumption of cow milk and milk products. The databases Scopus (https://www.scopus.com) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) were used for searching the scientific information on the topic of this review. The following search terms were included: 'cow milk', 'human consumption', 'human dietary intake', 'PCDD/Fs' and 'dioxins'. The present review has been focussed only on articles published in the current century.

CONCENTRATIONS OF PCDD/FS IN MILK AND DAIRY PRODUCTS

Asian countries

China

Zhang *et al*. (2013) determined the levels of PCDD/Fs in 96 composite samples from eight food groups from the Chinese total diet study (TDS) conducted in 2007 in 12 provinces of the country. Milk and dairy products were one of the selected groups. PCDD/F concentrations ranged between 0.07 and 0.013 pg TEQ/g fresh weight (fw). Dairy products (and eggs) showed the highest contribution to the estimated daily dietary intake of PCDD/Fs in two of the 12 provinces. For the various subgroups of population, all intakes were below those recommended by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA). In a subsequent study, Zhang *et al*. (2015) measured the concentrations of PCDD/Fs in Chinese foodstuffs from the latest Chinese TDS carried out in 2011. The dietary intake of PCDD/Fs, as well as the human health risks, was also determined. The mean (±SD) concentration of PCDD/Fs in 19 composite samples of milk and dairy products was 0.10 (0.08) pg TEQ/g fw, very similar to the levels found in the previous survey (Zhang *et al*. 2013). In general, the highest contribution to the dietary intake corresponded to meat and meat products (29.1%), followed by aquatic foods (24.1%), and milk and dairy products (14.7%). The consumption of milk and dairy products in a typical Chinese diet is low, being the relative contribution in most Chinese regions between 0.7 and 27.2%. Notwithstanding, milk and dairy products showed the highest contribution in two regions (Beijing and Neimenggu: 44.7 and 33.6%, respectively), because of the relatively higher contamination levels, as well as the consumption of milk and dairy products in both regions. In turn, van leeuwen *et al*. (2000) determined the concentrations of PCDD/Fs in Zhejiang (a typical large E-waste disassembling area) and estimated the dietary intake from foodstuffs obtained from market basket and from polluted sites in the area (not available for fresh/powder milk). Among the 13 categories of market basket foods, 83 fresh milk samples and 35 milk powder samples were analysed. The median levels of PCDD/Fs were found to be 0.05 and 0.22 pg WHO-TEQ/g fw, for fresh milk and milk powder, respectively. These values were lower than the maximum limit (ML) set by the EU. On the contrary, Wang *et al*. (2017) assessed also the dietary exposure to PCDD/Fs of the Chinese population. Food samples (634) belonging to 11 food groups, including 55 samples of milk and dairy products, were analysed. The mean level of total PCDD/Fs in this food group was 0.255 pg WHO-TEQ/g fw. If expressed according to the fat content, the concentrations of PCDD/Fs ranged from 0.023 to 2.840 pg TEQ/g fat, with an average of 0.411 pg TEQ/g fat. The estimated percentages of contribution to the total daily intake of PCDD/Fs for Chinese people through the consumption of milk and dairy products were 2.15 and 14.27%, for rural and urban areas, respectively. It was concluded that there were little health risks from PCDD/Fs in food in general, and in milk and dairy products specifically. In order to assess the exposure to PCDD/Fs by the population living in the vicinity of municipal solid waste incinerators (MSWIs), Ben *et al*. (2017) measured the PCDD/F concentrations in local vegetables collected near an MSWI located in Shenzhen (South China), as well as commercial vegetables purchased from a market. The concentrations of PCDD/Fs were also analysed in samples of meat, fish and shrimp, cereals, eggs, fruits and milk. The human dietary exposure to PCDD/Fs near the MSWI was subsequently assessed. Regarding milk, eight commercial samples were analysed, being the average concentration 0.050 ± 0.046 pg TEQ/g fw. The percentage of contribution of milk consumption to the total dietary intake – which for a general adult was 0.94 ± 0.41 pg TEQ/kg bw/day – was 4.2%, while the contribution of local vegetables was 52.3% of the total, which is especially relevant for the population living in the vicinity of MSWIs. Based on the information summarised in a large database from China (Dong *et al*. 2021), recently Fan *et al*. (2021) assessed the dietary exposure to various POPs in that country. PCDD/Fs were among the analysed POPs. For dairy products (most studies focussed on yoghurt and butter), the mean concentration (standard deviation) of PCDD/Fs was 0.084 (0.065) pg TEQ/g fw. Temporal decreasing trends were found for some POPs (DDTs, HCHs, PBDEs and PFOA), including PCDD/Fs, but without significant changes for other POPs. The estimated daily intake for adults was 0.37 ± 0.17 pg TEQ/kg/day for PCDD/Fs, not being indicated the specific contribution of milk and dairy products. Based on data from the first Hong Kong TDS, Wong *et al*. (2013) assessed the dietary exposure to PCDD/Fs for various age-gender groups. A total of 142 composite samples belonging to nine food groups – including dairy products – were analysed for the concentrations of PCDD/Fs. Exposure to these pollutants through the consumption of dairy products was 0.28 pg TEQ/kg bw/month, being the total intake 21.92 pg TEQ/kg bw/month. Thus, the contribution of dairy products to the total dietary intake of PCDD/Fs was 1.3%.

Japan

In order to estimate the daily intake of PCDD/Fs, Tsutsumi *et al*. (2001) analysed the concentrations of these environmental contaminants in individual samples of 14 food groups from 16 Japanese locations, being milk and dairy products one of these groups. The estimated intakes (mean ± SD) for an adult of 50 kg bw were 3.33 ± 2.28 and 5.05 ± 1.86 pg TEQ/person/day. These intakes correspond to calculations done assuming that ND values were equal to 0 or to 1/2 LOD, respectively. On the contrary, from 1999 to 2004, Sasamoto *et al*. (2006) conducted in the Tokyo region a TDS to estimate the daily intake of PCDD/Fs using data on food consumption obtained from the Japanese Nutrition Survey. Milk and dairy products were among the 14 food groups involved in that study. The daily intakes of PCDD/Fs (TEQs) through the consumption of milk and dairy products in Tokyo metropolitan area decreased yearly between 1999 and 2004, diminishing from 8.81 pg TEQ/day (1999) to 2.77 pg TEQ/day (2004). The ratio of milk and dairy products to total dietary intake of PCDD/Fs also decreased from 8.07% (1999) to 3.58% (2004). Anyway, these percentages were lower than the contributions corresponding to the groups of fish and shellfish, meat and eggs. In another survey with similar objectives conducted during 2000–2002, Nakatani *et al*. (2011) estimated the human intake of PCDD/Fs from foods in Osaka City. The design of the TDS samples was based on official food classifications (14 groups), while data regarding food consumption were obtained from the Japanese Nutrition Survey. Milk and dairy products were again one of the 14 food groups. For an adult of 50 kg bw, the intakes of PCDD/Fs through the consumption of milk and dairy products were 4.37, 1.88 and 0.025 pg TEQ/person/day in 2000, 2001 and 2002, respectively. More recently, Tsutsumi *et al*. (2018) reported the results of a TDS focussed on establishing the dietary intake of PCDD/Fs by the general Japanese population ≥1 year old. The authors also discussed how the intakes of these pollutants changed in the last two decades. For a person of 50 kg bw, the group of milk and dairy products contributed to the total dietary intake of PCDD/Fs with 0.027 or 1.4 pg TEQ/person/day depending on whether the values were calculated at ND = 0 or at ND = ½ LOD. The groups of fish and shellfish, meat and eggs contributed with more than 99% to the total intake of PCDD/Fs (0.54 pg TEQ/kg bw/day), while the contribution of all the remaining groups (including milk and dairy products) was lower than 1% of the total.

Other Asian countries

Chang *et al*. (2012) reported the results of a survey conducted in Taiwan aimed at evaluating the human dietary intake of PCDD/Fs (plus DL-PCBs) from fresh foods. The foodstuffs analysed included 108 milk (whole-fat milk and whole-fat milk powdered) samples and 21 samples of dairy products (cream, butter, cheese, fermented milk and condensed milk). The highest levels of PCDD/Fs in milk and dairy products corresponded to fermented milk (1.089 pg WHO-TEQ/g fat) and whole-fat milk (0.889 pg WHO-TEQ/g fat), while the lowest concentrations were found in samples of cream (0.310 pg WHO-TEQ/g fat) and whole-fat milk powder (0.163 pg WHO-TEQ/g fat). Based on age-gender groups, the highest average daily intake of PCDD/Fs (plus DL-PCBs) through the consumption of milk and dairy products corresponded to children (males, 6–12 years old): 0.155 pg WHO-TEQ/kg bw, while the lowest intake, 0.025 pg WHO-TEQ/kg bw, corresponded to males, 19–64 years old. In Malaysia, Leong *et al*. (2014) determined the concentrations of PCDD/Fs in 126 food samples belonging to these three groups: seafood and seafood products, meat and meat products, and milk and dairy products (formula milk, full cream milk powder, fresh milk, butter and flavoured milk). The mean concentration of PCDD/Fs in milk and dairy products, 0.168 pg WHO-TEQ/g fw, was only very slightly higher than the levels found in seafood/seafood products and meat/meat products (0.167 and 0.162 pg WHO-TEQ/g fw, respectively). However, the highest exposure to PCDD/Fs corresponded to seafood and seafood products, 0.415 pg WHO-TEQ/kg bw/day, with an estimation of 0.365 pg WHO-TEQ/kg bw/day for milk and dairy products, values obtained using the Malaysian food consumption statistics. Anyhow, these exposures were much lower than the TDI recommended by the WHO. Recently, Sharma *et al*. (2021) reported the results of survey carried out in India aimed at delivering the first comprehensive quality-assured assessment of human dietary exposure to POPs, which are considered as endocrine-disrupting chemicals (EDCs). PCDD/Fs were selected among the EDCs, being food samples collected in an urban (Delhi) and a rural (Dehradun) area of India. The dairy products in that survey included milk (packaged), Indian cottage cheese and yoghurt. As expected, the concentrations of the targeted POPs in food products of animal origin were higher than those found in plant-based food items. In total, up to 55 compounds were detected in milk, yoghurt and Indian cottage cheese, with similar levels and profiles among these products. The comparison with European data suggests a higher dietary exposure in Europe, especially of nonpesticidal POPs such as PCDDs (and also PCBs). It could be explained by a higher consumption of animal-based products in Europe.

American countries

In a recent review on the concentrations of PCDD/Fs in human dietary exposure to these pollutants (González and Domingo 2021), we already remarked the absence of data corresponding to studies – conducted in recent years – aimed at estimating the dietary intake of PCDD/Fs in the USA. Most studies on the topic were conducted in the 1990s and only some of them at the beginning of this century (Jensen and Bolger 2001; Schecter *et al*. 2001). The USA data on the dietary intake of PCDD/Fs (and related compounds) in the 1990s and the 2000s were summarised and discussed by Lorber *et al*. (2009). To the best of our knowledge, since then, there have been no available studies on the dietary intake of PCDD/Fs by the population of the USA, which logically includes also the lack of data on exposure to these pollutants through the consumption of milk and dairy products.

In Brazil, Rocha *et al*. (2016) performed a study aimed at determining the PCDD/Fs levels in cow milk collected in 34 selected sites of eight Brazilian states with an important milk production. The mean and median $\sum$ PCDD/Fs were 27.68 and 24.39 pg/g fat, respectively. The concentration profiles seemed to vary according to the characteristics of each region and state, being OCDD and OCDF the most predominant congeners, which were found in 100% of samples. Total TEQ value was 1.66 (range: 0.47–4.13) pg WHO-TEQ/g fat. Although all samples showed some levels of contamination by PCDD/Fs, all values were (at the time of the measurements) below the limit established by the EU. In Colombia, Pemberthy *et al*. (2016) determined the concentrations of PCDD/Fs in samples of various foods including oils (soybean, olive and fish), butter and shrimp, which were purchased from a local supermarket of Medellín. These products were selected because oils, fats and fishery products are foods controlled and regulated by the Colombian legislation. The mean level of PCDD/Fs in butter samples was 12.90 pg/g fat, being 1.03 pg WHO-TEQ/g fat, the corresponding TEQ. These values were intermediate among those found in the various food items analysed. In turn, for the first time in Chile, Pizarro-Aránguiz *et al*. (2015) reported the results of a survey in which the levels and congener profiles of PCDD/Fs (and DL-PCBs) were determined in 104 samples of cow milk (raw) and 12 butter samples collected in 2011–2013. For milk samples, the results showed that the 2012 average value was higher (0.24 pg WHO-TEQ/g fat) than the mean average level of 2011 (0.18 pg WHO-TEQ/g fat). The mean concentration of PCDD/Fs in butter samples was 0.5 pg/g fat (0.06 pg WHO-TEQ/g fat), with a range of 0.3–0.7 pg/g fat (0.02–0.1 pg WHO-TEQ/g fat). Both, concentrations of PCDD/Fs and dietary intake of cow milk and butter were below international and national regulations. In a subsequent study conducted by the same research group (Pizarro-Aránguiz *et al*. 2018), the potential relationships between PCDD/Fs levels in raw cow milk, with various meteorological and geographical factors within Chile's central valley regions, were assessed. The most relevant and significant ($P < 0.05$) factors were the year (mainly a negative coefficient), the season, as well as the hectares affected by forest fires.

European countries

Italy

Ingelido *et al*. (2009) investigated the levels and patterns of PCDD/Fs in feedstuffs and milk (bovine and ovine) from six farms near two incineration plants in Tuscany, as well as from two farms located in nearby background areas (control areas). In a previous study, Fattore *et al*. (2006) reported that fish and fish products, followed by milk and dairy products, were the main contributors to the dietary exposure to PCDD/Fs in Italy, with 44 and 27% of the total intake of these pollutants, respectively. The mean PCDD/F concentration of bovine milk in potentially contaminated areas was 0.076 pg WHO-TEQ/g lipid, being very similar to that found in control areas 0.073 pg WHO-TEQ/g lipid. No significant correlation was found between milk and feedstuffs (Spearman correlation coefficient $P > 0.05$) with respect to total TEQs and the cumulative concentrations of PCDD/Fs.

In order to draw a map of environmental diffusion of PCDD/Fs (and DL-PCBs) in Campania, Esposito *et al*. (2009) conducted in 2008 a survey in which 75 cow milk samples were collected from 63 farms and analysed for these environmental contaminants. PCDD/Fs concentrations in milk were between 0.05 and 16.4 pg TEQ/g fat (mean: 1.67 and median: 1.03). In samples with PCDD/F levels above 3 pg/g fat, a prevalence of furans (PCDD/PCDF ratio: 0.7) was observed. Although in general terms, PCDD/Fs in cow farms of Campania showed a situation of global low contamination, it was concluded that this could be critical in restricted areas of the region.

Bertocchi *et al*. (2015) measured the concentrations of PCDD/Fs in milk produced in 14 dairy farms in the Brescia area, while the safety of the food produced in this high industrialised area was also assessed. The mean concentration of total PCDD/Fs was 5.27 pg/g fat. In turn, for the 14 farms, WHO-TEQ levels ranged between 0.46 and 1.39 pg/g fat. The ratio PCDFs/PCDDs was between 1.17 and 2.08 pg TEQ/g fat. Interestingly, in three of the four most polluted farms, cow ration was replaced by feed coming from uncontaminated areas. In the three farms, contamination levels dropped below the EU legal limit for the sum of PCDD/Fs (and DL-PCBs) after 1 month from the removal of the pollution source. On the contrary, during the period 2012–2014, Lorenzi *et al*. (2016) analysed the concentrations of PCDD/Fs (and PCBs) in 160 bovine milk samples obtained from 151 dairy farms located in Lombardy and Emilia Romagna regions. The mean upper bound (UB) and lower bound (LB) (in parentheses) levels of PCDD/Fs in the 160 milk samples collected in Lombardy and Emilia Romagna regions were 3.26 (2.29) pg WHO-TEQ/g fat and 0.34 (0.23) pg WHO-TEQ/g fat. Lorenzi *et al*. (2016) also estimated the human exposure assessment to PCDD/Fs (plus DL-PCBs and NDL-PCBs), being PCB-126 the main contributor to the total intake of these pollutants through milk consumption. Recently, the same research group (Lorenzi *et al*. 2020) conducted a feeding study aimed at investigating the kinetics in cow milk of PCDD/Fs (plus 12 DL-PCBS and 6 NDL-PCBs regulated by the European Union legislation). Although it is well established that feed-to-milk transfer of PCDD/Fs is fast due to their relatively high carryover rate, the authors demonstrated that the removal of the contaminated feed succeeded in restoring after only 1 week. In turn, Diletti *et al*. (2018) estimated the PCDD/F dietary intake in Italy in order to be compared with the results obtained from other surveys recently carried out in other European countries. During 2013–2015, a total of 2116 food samples of animal and vegetable origin were collected. Milks of cow, buffalo, sheep and goat were included in that study. For cow milk, 303 samples were analysed, being 0.271 pg WHO-TEQ/g lipid, the mean concentration. Their groups of population were considered for estimating the dietary intake of PCDD/Fs: children, adults and seniors. In these groups, the relative mean contributions (%) to the cumulative intake from the contamination recorded for cow milk and dairy products were the following: 3.3–10.0 for whole milk, 0.1–0.2 for yoghurt (cow milk) and 1.7–2.0 for cheese (of different kinds) (Diletti *et al*. 2018).

France

Between 2001 and 2004, Tard *et al*. (2007) determined the concentrations of PCDD/Fs in a number of foods products included in the French diet, among these, milk and butter samples. To estimate the dietary intake of PCDD/Fs by French children and adults, the calculations regarding dairy products took into account the following: for the nonanalysed dairy products (cheese and yoghurts, for example), the intake was estimated by multiplying the milk contamination (pg TEQ/g fat) by their lipid percentage, as recorded in the French composition tables. The mean concentrations of PCDD/Fs in milk samples were 0.36 (ND = 0) and 0.38 (ND = ½ LOD) pg TEQ/g lipid, while in butter it was 0.29 pg TEQ/g lipid (for both scenarios). The main contributors to total intake of PCDD/Fs were fish, and milk and dairy products: 48 and 31% for adults and 34 and 43% for children, respectively. During 2006–2010, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) carried out the second French TDS, focussed on evaluating the exposure of the general French population to chemicals of public concern, among which PCDD/Fs (and PCBs) (Sirot *et al*. 2012). A total of 1319 samples were collected and analysed. Regarding milk and dairy products, these items were analysed: cheese, butter and margarines, yoghurts and milk. The mean levels (pg TEQ-WHO/g fw) of PCDD/Fs were the following: milk, 0.005; cheese, 0.046; butter, 0.817; margarines, 0.072 and yoghurts, 0.015, being butter one of the analysed food items showing the highest concentrations of PCDD/Fs. Based on these results, the intake (pg WHO-TEQ/kg bw/day) of PCDD/Fs by the French population was the following: milk, 0.07; cheese, 0.023; butter, 0.036; margarines, 0.002 and yoghurts, 0.015. It is on a total intake of PCDD/Fs of 0.192 pg WHO-TEQ/kg bw/day. More recently, the ANSES reported the results of a new TDS carried out in the period 2010–2016, which was aimed at assessing the health risk assessment to PCDD/Fs in infants under 3 years of age (Hulin *et al*. 2020). A total of 178 samples were analysed. Of these, 169 infant foods (*i.e.* products commercialised especially for infants and young children) and nine common foods. The mean levels (LB) of PCDD/Fs (pg WHO-TEQ/g fat) in food consumed by French infants and toddlers were the following: growing up milk, 0.150; milk-based beverages, 0.06; and milk-based desserts, 0.146. It was concluded that dietary exposure to PCDD/Fs was a concern for children above 6 months. Therefore, the major contribution to exposure of the most exposed children should be reduced, including not only fish, but also milk and ultra-fresh dairy products.

United Kingdom

In 2009, Lake *et al*. (2013) conducted the first detailed investigation in the UK on the seasonal variation of PCDD/Fs in cows' milk from individual farms. In fact, the main purpose of that study was to establish how the levels of PCDD/Fs in milk vary over the period of a year. A total of 58 samples (milk 18, soil 6, grass 10, silage 8, commercial feed 12 and bedding 4) were analysed. The concentrations of PCDD/Fs in cow milk ranged between 0.70 and 1.55 pg TEQ/g fat. Periodical fluctuations were found over time periods as short as 6 weeks. According to the authors, some variations could be explained by changes in the contaminant concentrations of dietary inputs consumed by the cattle. However, the changes in the contaminant inputs from grass and silage would be the main sources to explain these fluctuations. In another survey conducted in 2011–2012 by the same research group (Bramwell *et al*. 2017), two different methods for estimating human dietary exposure to various lipophilic POPs (including PCDD/Fs) were compared. These methods were as follows: (i) the 2012-TDS conducted by the UK Food Standards Agency (FSA), and (ii) a 24-h duplicate diet (DD) study of 20 adults from the North East of England. In the TDS, the concentrations of PCDD/Fs (plus DL-PCBs) were shown as a whole, being the mean for the 44 analysed milk samples, 8.2 pg WHO-TEQ/kg fw, while 105 pg WHO-TEQ/kg fw was the mean for the 105 samples of dairy products. Obviously, no specific data for milk and dairy products (or any other food group) were obtained by means of the DD study. The average adult dietary exposure to PCDD/Fs plus DL-PCBs was estimated to be 0.52 WHO-TEQ pg/kg bw/day using data from the TDS, while it was 0.27 WHO-TEQ/pg kg bw/day when using the DD data.

Sweden

Darnerud *et al*. (2006) analysed the concentrations of various organohalogen contaminants – including PCDD/Fs – in food samples obtained in 1999 in the four major Swedish cities. The samples belonged to these six food groups: fish/-fish products, meat/meat products, dairy products, eggs, fats and oils, and pastries. For dairy products, the analysed food items were as follows: milk, sour milk, yoghurt, cream, hard cheese, processed cheese and cottage cheese. The mean concentration of PCDD/Fs in dairy products was 0.028 pg WHO-TEQ/g fw (range between 0.020 in Uppsala and 0.030 pg WHO-TEQ/g fw in Gothenburg). The estimated intake of PCDD/Fs through the consumption of dairy products was 12.8 pg WHO-TEQ/day on a total daily intake from the six food groups of 54.4 pg WHO-TEQ/day. In a subsequent survey, Törnkvist *et al*. (2011) analysed the concentrations of selected POPs (including again PCDD/Fs) in a Swedish market basket and estimated the mean Swedish *per capita* intake. These results were compared with those of the earlier Swedish market basket study (Darnerud *et al*. 2006). For dairy products, samples of the following items were collected: milk, sour milk, yoghurt, cream and sour cream, cheese and cottage cheese. The mean concentration of PCDD/Fs in dairy products was 0.011 pg WHO-TEQ/g fw (calculated with 2005-TEFs, or 0.012 pg WHO-TEQ/g fw, calculated with 1998-TEFs). The range was between 0.008 in Gothenburg and 0.013 pg WHO-TEQ/g fw in Uppsala and Malmoe. These values were lower than those previously reported by Darnerud *et al*. (2006).

Switzerland

In order to assess the extent of PCDD/F contamination and to establish the efficiency of the measures taken in previous years to ensure the decontamination of the food supply in Switzerland, Schmid *et al*. (2002) measured the levels of PCDD/Fs in food samples of animal origin (cow milk, eggs, chicken meat, pork, veal and beef) collected during 1999 and 2000. The mean concentration of PCDD/Fs in the 44 samples of milk was 0.63 pg TEQ/g fat (range: 0.35–1.10). A subsequent survey was carried out to determine the average PCDD/F levels in milk from different Swiss regions. Schmid *et al*. (2003) analysed the levels of PCDD/Fs in pooled cow milk samples from (i) large industrial milk processing plants of the country, (ii) locations with nearby sources of pollution and (iii) rural and alpine locations. The average concentrations of PCDD/Fs in milk were as follows: 0.59, 0.71 and 0.36 pg TEQ/g fat, for samples of groups (i), (ii) and (iii), respectively. The comparison of these PCDD/F levels with data previously obtained, showed in general terms, decreases in the samples from the neighbourhood of former, remediated point sources, but also in remote locations.

Ireland

Adekunte *et al*. (2010) developed a probabilistic exposure assessment model for PCDD/Fs (and also DL-PCBs) in pasteurised bovine milk. That was the first study carried out on human exposure assessment to PCDD/Fs through the consumption of pasteurised milk. The estimated mean PCDD/F was 0.06 ± 0.07 pg WHO-TEQ/g using Monte Carlo simulation. The simulated model estimated a mean exposure for PCDD/Fs of 0.19 ± 0.29 and 0.14 ± 0.22 pg WHO-TEQ/kg bw/day, for men and women, respectively. At the time of that study, exposure to PCDD/Fs from consumption of pasteurised bovine milk was below the provisional maximum tolerable monthly intake (PTWI) recommended by the JECFA. In turn, Tlustos *et al*. (2014) estimated the dietary exposure of the Irish adult population to PCDD/Fs (and PCBs). For it, results of dioxin monitoring programmes conducted in the country between 2003 and 2010 were used, while data on food consumption were obtained during the period 2008–2010. Among the various food groups included in that survey, for milk and dairy products, only milk samples (39) were analysed. The mean concentrations of

PCDD/Fs (plus DL-PCBs) were 0.30 and 0.32 pg WHO-TEQ/g fat (lower and upper bound, respectively). The total mean intake of total WHO-TEQ (for PCDD/Fs + PCBs) was estimated to be 0.3 pg/kg bw/day, with dairy products contributing 25% to that total intake.

Germany
At the beginning of the current century, Malisch (2000) reported that, in Germany, between 1993 and 1997 the concentrations of PCDD/Fs in foodstuffs decreased slowly, although constantly. Nevertheless, for milk and butter, this trend was gradually reversed, beginning in September 1997. Thus, in different regions of the country, the mean PCDD/F concentration of dairy products increased from a low level of about 0.6 pg I-TEQ/g fat in summer 1997 to 1.41 pg I-TEQ/g fat in February 1998. Since in meat samples the levels of PCDD/Fs also increased, it was concluded that animal feed was contributing considerably to that food contamination. More recently, Schwarz *et al*. (2014) estimated the combined dietary intake of PCDD/Fs (and DL-PCBs) using consumption data from a German food consumption survey. It was found that milk and dairy products, meat, and fish and seafood were the food groups with the highest contributions to the intake of PCDD/Fs + DL-PCBs. The total combined intakes were 2.11 (UB) and 1.53 (LB) pg/kg bw/day for an average consumer.

Spain
According to the scientific literature, in the present century Spain has been the country in which more surveys on the human exposure to PCDD/Fs through the diet have been carried out. Most of these studies have been conducted in Catalonia (NE Spain). These surveys have included milk and dairy products among the analysed foodstuffs. Llobet *et al*. (2003) estimated the dietary intake of PCDD/Fs by the population of Catalonia and compared these first results with those from recent international reports. Among the food samples (composite) collected and analysed between June and August 2000, eight samples of cow milk (whole and semiskimmed) and dairy products (yoghurt and cheese) were included in that survey. The mean PCDD/F concentrations in the group of milk and dairy products were 0.80 pg WHO-TEQ/g fat, an amount highly exceeded only by the group of fish and shellfish (5.57 pg WHO-TEQ/g fat). The percentage of contribution from milk and dairy products to the total dietary intake of PCDD/Fs by the general population of Catalonia (95.4 pg WHO-TEQ) was 27% (25.42 pg WHO-TEQ). In a subsequent study carried out by the same research group (Llobet *et al*. 2008), food samples were again randomly acquired in local markets, big supermarkets and grocery stores from 12 representative cities of Catalonia between March and June 2006. The levels of PCDD/Fs were measured. Samples of cow milk (whole and semiskimmed) and dairy products (yoghurt and cheese) were again analysed. The mean PCDD/F concentrations (pg WHO-TEQ/g fw) were the following: whole milk, 0.015; semiskimmed milk, 0.003; yoghurt, 0.007; and cheese, 0.107. A significant decreasing trend in the human dietary exposure to PCDD/Fs was noted. Thus, the estimated dietary intake of PCDD/Fs by the general population of Catalonia, Spain, (assuming ND = 1/2 LOD) was 25.7 pg WHO-TEQ/day vs 95.4 pg WHO-TEQ/day found in the previous survey (Llobet *et al*. 2003). The percentages of contribution of milk and dairy products to the total intake of PCDD/Fs were 5.7 and 7.1%, respectively. In November–December 2008, food samples for a new survey were again collected (Perelló *et al*. 2012). That study was aimed at establishing the temporal trend in the total dietary intake of PCDD/Fs in Catalonia. For that, food items belonging to the same food groups included in the two previous surveys (2000 and 2006) (Llobet *et al*. 2003, 2008) were collected and composite samples were analysed for the levels of PCDD/Fs. Milk (whole and semiskimmed) and dairy products (yoghurt, cheese I – with low fat, cheese II – medium fat cheese, cheese III – extra fat cheese, and cream-custard-caramel) were among the analysed foodstuffs. The mean concentrations of PCDD/Fs in these samples were the following: 0.005 pg WHO-TEQ/g fw for milk and 0.056 pg WHO-TEQ pg/g fw for dairy products, with the lowest and highest levels corresponding to yoghurt and cheese III (0.010 and 0.136 pg WHO-TEQ/g fw, respectively). The estimated total dietary intake of PCDD/Fs was 15.72 pg WHO-TEQ/day, being 0.70 and 1.95 pg WHO-TEQ/day the contributions to that total intake of milk and dairy products, respectively (5.5 and 15.4%). The results of that study showed again an important decreasing trend in the dietary exposure to PCDD/Fs for the population living in Catalonia.

On the contrary, Bocio and Domingo (2005) determined the concentrations of PCDD/Fs in 36 composite samples corresponding to the most consumed foodstuffs in Tarragona County (South of Catalonia) by a population living near a hazardous waste incinerator (HWI). Analysed food items belonged to various food groups and included various samples of milk (whole and semiskimmed) and dairy products (cheese, yoghurt, petit-Swiss, cream caramel and custard). Foodstuffs were randomly purchased in various food establishments of the area, but independently on the specific origin of the food. The mean concentrations of PCDD/Fs were 0.79 and 0.59 pg WHO-TEQ/g fat for milk and dairy products, respectively. The total dietary intake was estimated to 63.8 pg WHO-TEQ/day, being the contributions of milk and dairy products to that intake 3.9 (6.4%) and 8.3 (13.7%) pg WHO-TEQ/day, respectively. In that survey, the data were within the range of international studies on the same topic conducted at similar times. In 2006, a new survey was performed in the same area (Tarragona County). Martí-Cid *et al*. (2008) measured the levels of PCDD/Fs in 35 composite samples belonging to various food groups, being composite samples of milk (whole and semiskimmed) and dairy products (three different kinds of cheese, yoghurt, ‘petit-Swiss’, cream caramel and custard) again among the analysed food items. The mean PCDD/F concentrations in the composite samples of milk and dairy products were 0.019 and 0.029 pg WHO-TEQ/g fw, respectively. The estimated total daily intake of PCDD/Fs by the general population living near a HWI in Tarragona County was 27.81 pg WHO-TEQ/day, being the contributions of milk and dairy products, 0.06 and 3.02 pg WHO-TEQ/day, respectively. In January–February 2012, food samples were again collected to establish the temporal trend in the dietary intake of PCDD/Fs by the population living in the vicinity of the HWI in Tarragona County. The methodology of that new survey was the same than that already used in the previous studies performed in the same area (Bocio and Domingo 2005; Martí-Cid *et al*. 2008). A total of 45 samples composed by subsamples of 67 food items were analysed. Milk (whole and semiskimmed) and dairy products (soft, semicured and cured cheese, yoghurt, ‘petit-Swiss’, cream caramel and crème brûlée) were again included. The mean levels of PCDD/Fs in the composite samples of milk and dairy products were 0.007 and 0.036 pg WHO-TEQ/g fw, respectively. The estimated total daily intake of PCDD/Fs was 33.1 pg WHO-TEQ/day, being the contributions of milk and dairy products, 1.59 and 3.79 pg WHO-TEQ/day, respectively (4.5 and 11.4%). Based on these results, (Domingo *et al*. 2012), the dietary PCDD/F intakes estimated for various age groups were notably lower (for all age groups) than the reference/safety values established by international organisations. The last survey of that series was conducted in 2018. As in the previous surveys, González *et al*. (2018) estimated the dietary intake of PCDD/Fs by the population living near the HWI in Tarragona County. In January–February 2018, food samples were randomly purchased at various hypermarkets, supermarkets, local markets and grocery stores from eight cities and villages of the zone. The group of milk and dairy products included whole and semiskimmed milk, yoghurts, petit-Swiss, custards and cheeses (tender, semicured and cured). The mean levels of PCDD/Fs were 0.005 and 0.018 pg WHO-TEQ/g fw, for milk and dairy products, respectively. The estimated total dietary intake of PCDD/Fs, 8.54 pg WHO-TEQ/day showed a very relevant decrease (74%) regarding the intake estimated in the previous survey (33.1 pg WHO-TEQ/day) (Domingo *et al*. 2012). The contributions to the intake of milk and dairy products decreased also considerably: 48 and 83% for milk (from 1.50 to 0.78 pg WHO-TEQ/day) and dairy products (from 3.79 to 0.63 pg WHO-TEQ/day), respectively. The considerable differences in the total dietary exposure to PCDD/Fs were explained not only by the reduction in the levels of these contaminants in foodstuffs, but also taking into account that the consumption data used for the 2012 and 2018 showed notable differences. Specifically, the milk consumption decreased from 217 to 141 g/day, while the consumption of dairy products was reduced from 106 to 35 g/day.

Between 2006 and 2008, Marin *et al*. (2011) carried out a monitoring programme on PCDD/Fs (and DL-PCBs) in foods collected in another Spanish region, Valencia. A total of 150 food samples belonging to eight food groups were analysed. Among these, 19 samples of milk and dairy products (cheese and yoghurt) were included, being the mean concentration of PCDD/Fs in this food group, 0.60 pg WHO-TEQ/g fat (range: 0.23–1.2). For an adult living in the region of Valencia, the estimated total intake of PCDD/Fs was 2.86 pg WHO-TEQ/kg bw/day (in the range of the TDI recommended by the WHO), being 11.84% the contribution of milk and dairy products (0.34 pg WHO-TEQ/kg bw/day). In a subsequent survey conducted by the same research group (Quijano *et al*. 2018), the dietary exposure by the population of the Valencia region to PCDD/Fs (and PCBs) was again assessed. For it, in 2010–2011, 770 food samples were collected. Sixty of those samples corresponded to milk and dairy products. In that study, the authors reported the results concurrently for PCDD/Fs plus PCBs. The total estimated dietary intakes of these pollutants were 1.58 and 2.76 pg WHO-TEQ/kg bw/day, for adults and children, respectively, being within the tolerable daily intake of 1–4 pg WHO-TEQ/kg bw/day. In that survey, specific data for PCDD/Fs were not given.

Other European Union countries

Other European surveys aimed at assessing the dietary intake of PCDD/Fs have been also conducted. However, in most studies, the authors included also DL-PCBs and/or NDL-PCBs. Thus, the concentrations of PCDD/Fs in the analysed food groups, including milk and dairy products, were concurrently given with those of PCBs. Similarly, the estimated dietary intakes were also given for both groups of environmental pollutants. These are the countries for which that information is available in the scientific literature: the Netherlands (Baars *et al*. 2004), Belgium (Windal *et al*. 2010), Finland (Karjalainen *et al*. 2012), Austria (Rauscher-Gabernig *et al*. 2013), Greece (Costopoulou *et al*. 2013) and Poland (Rusin *et al*. 2019). Taking into account that the specific data for PCDD/Fs were not shown, we have not included the results of these studies in the current review. On the contrary, a review by Malisch and Kotz (2014) from a European perspective on dioxins and PCBs in feed and food is also available. In that review, it was highlighted that fish, meat and dairy products (in that order) were usually the highest contributing food groups to dietary exposure to PCDD/Fs (and also PCBs).

Other European/Asian countries: Turkey, Egypt and Kuwait

In Turkey, Aslan *et al*. (2010) carried out a survey focussed mainly on determining the concentrations of PCDD/Fs in food samples collected in Kocaeli, one of the highly polluted areas in that country. The results were compared with those corresponding to commercial products. Samples of cow milk were included in the survey. The mean PCDD/F concentrations (lower and upper bound) in local milk samples (n = 7) were 1.66 and 1.83 pg TEQ/g fat, while in commercial samples were 0.85 and 1.04 pg TEQ/g fat. For milk and dairy products, in Turkey the PCDD/F limit for action is 3 pg TEQ/g fat. Karademir *et al*. (2013), also in Kocaeli, estimated the dietary exposure to PCDD/Fs *via* animal products, among which milk (local and commercial) samples were included. The concentrations of PCDD/Fs in milk were in the range of 0.02–0.19 pg WHO-TEQ/g fat and 0.02–0.05 pg WHO-TEQ/g fat, for local and commercial samples, respectively. On average, the PCDD/F intakes through the consumption of animal products in Kocaeli were estimated to be between 0.4 and 1.8 pg WHO-TEQ/kg bw/day, which were within the range of 1–4 pg WHO-TEQ/kg bw/day, proposed by the WHO as TDI. The contribution of milk to that total intake ranged between 22 and 65% of the total when the data were compared according to the age of the consumers and the place of residence (rural, urban and semiurban zones). The maximum contribution (>60%) corresponded to children <10 years old living in rural areas, while the minimum (22%) corresponded to seniors (≥70 years old) living in urban areas. In turn, Uçar *et al*. (2011) reported the results of a survey in which butter samples (all from cow milk) were collected in 2007 from 14 different cities and 18 different rural and industrial zones of Turkey and the concentrations of PCDD/Fs, DL-PCBs and PBDEs were analysed. PCDD/F levels ranged between 0.12 and 1.56 pg TEQ/g fat. In a previous study of the same research group, it was reported that dairy products and fish were the main contributors to the total dietary intake of PCDD/Fs plus DL-PCBs (Kilic *et al*. 2011).

In Egypt, Loutfy *et al*. (2007) performed a survey aimed at determining the levels of various POPs – including PCDD/Fs – in a number of foodstuffs of animal origin from Ismailia. Butter was the only selected dairy product in that survey. The results were compared with recent international studies and the EU standards on this issue. The highest upper bound levels of PCDD/Fs were observed in the butter samples, 4.67 pg TEQ/g fat, which were notably contaminated in relation to the EU national average concentrations (range 0.3–2.1 pg I-TEQ/g fat). Interestingly, in that survey the lowest contribution of the congener OCDD was found in butter samples, which would mean that the source of contamination in this item should not be necessarily an atmospheric deposition. The profiles of PCDD/Fs in butter suggest a possible impact from variable sources of these contaminants. In Kuwait, Husain *et al*. (2014) determined the concentrations of PCDD/Fs (and DL-PCBs) in samples of animal origin, being milk also included. The dietary intake of PCDD/Fs (and DL-PCBs) through the consumption of the analysed foodstuffs by the Kuwaiti population was subsequently estimated. The mean concentration of PCDD/Fs in the 80 samples of milk was 2.10 pg DR CALUX-BEQ/g fat (range: 0.60–5.90). The average intakes of PCDD/Fs plus DL-PCBs (pg DR CALUX-BEQ/kg bw/day) through milk consumption ranged between 0.07 for females ≥50 years old and 0.25 for children 6–9 years old, for a total intake of PCCD/Fs of 1.20 and 3.48, for those same groups, respectively. No specific data for PCDD/Fs were reported.

DISCUSSION AND CONCLUSIONS

This review summarises data on the topic here reviewed: concentrations of PCDD/Fs in cow milk and dairy products, as well as the dietary intake of these environmental pollutants through a regular consumption of this food group. Given their important content in fats, whole milk and dairy products can easily accumulate liposoluble compounds such as PCDD/Fs. It should be noted that the present review is neither a *meta*-analysis, nor a systematic review. It just summarises the available scientific information published on this topic in the current century. It is important to highlight that an important number of the reviewed papers report data on human dietary intakes that correspond to the sum of PCDD/Fs and DL-PCBs (some of them even include certain NDL-PCBs). Although data on DL-PCBs corresponding to studies where PCDD/Fs and PCBs were jointly assessed have not been here specifically discussed, total data (PCDD/Fs + DL-PCBs) are also given, if in the respective papers the authors did not report the results separately. PCBs were not included in the present review because of the important differences between studies regarding the analysed PCBs: none, DL-PCBs and different NDL-PCBs.

It is well known that the primary source of human exposure to PCDD/Fs is the diet (EFSA 2015). In 2001, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the United Kingdom proposed a tolerable daily intake (TDI) of 2 pg WHO-TEQ/kg bw/day, while at the same time, the Scientific Committee on Food (SCF) of the European Commission set a tolerable weekly intake (TWI) of 14 pg WHO-TEQ/kg bw/week. In June 2011, the JECFA-WHO and the FAO recommended for PCDD/Fs, a provisional tolerable monthly intake (PTMI) of 70 pg/kg bw/month. This level is the amount of PCDD/Fs that might be ingested over lifetime without detectable adverse health effects. Until now, these have still been recommendations for the dietary intake of PCDD/Fs (EFSA 2015). These tolerable intakes are lower than the previously TDI of PCDD/Fs + DL-PCBs established in the range of 1–4 pg WHO-TEQ/kg bw/day for the noncarcinogenic effects of these environmental contaminants (van Leeuwen *et al*. 2000). In turn, that TDI had replaced a previous one, which had been estimated in 10 pg I-TEQ/

kg/day (van Leeuwen *et al*. 2000). More recently, the EFSA's expert Panel on Contaminants in the Food Chain (CONTAM) stated that 'The Panel had set a new TWI for dioxins and dioxin-like PCBs in food of 2 pg/kg bw/week' (EFSA 2018).

Recently, we reviewed the available information on the levels of PCDD/Fs in foodstuffs (González and Domingo 2021). We found a continuous reduction of these levels in most industrialised countries. Given this reduction, logically the human intake of PCDD/Fs through the diet has been also decreasing (González and Domingo 2021). Based on the data examined in the current review, for those countries in which periodical studies have been conducted, in general terms the concentrations of PCDD/Fs in milk and dairy products are decreasing. A similar trend is also noted for their contributions to the total dietary intake of PCDD/Fs. This is an important issue taking into account that most surveys have found that after fish and other seafood, and also meat and meat products, milk and dairy products are often a food group with a notable contribution to the total dietary intake of PCDD/Fs. Unfortunately, due to the considerable differences in the methodologies of the surveys carried out over the world, to establish comparisons of the data reported for different regions and countries is – in fact – not possible. Finally, as it was also suggested in the recent review on toxic metals in cow milk (Domingo 2021), to conduct periodical national surveys to determine the concentrations of PCDD/Fs (and other POPs) in milk and dairy products (as well as in other widely consumed foods) is highly recommendable in order to prevent health risks for the consumers.

AUTHOR CONTRIBUTIONS

Jose L Domingo: Conceptualization; formal analysis; methodology; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors state that there is not any conflict of interest.

DATA AVAILABILITY STATEMENT

Data were obtained from papers listed in PUBMED and SCOPUS.

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