Risk–Benefit Analysis for the Breastfed Infant Based on the WHO- and UNEP Human Milk Surveys for Dioxin-like Compounds

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Abstract

Dioxin-like compounds (DLC) are still present in human milk and this chapter describes a risk–benefit analysis based on decades of WHO global human milk surveys. At present there is no health-based guidance value (HBGV) available for the breastfed infant. Although formally these HBGVs have been set to protect human health for a lifetime exposure period, much of the underlying experimental data focus on the perinatal and/or childhood period. Therefore, it is justifiable to use these HBGVs for early life and shorter than lifetime exposures, e.g. breastfeeding. With this approach the present HBGVs for DLC were generally exceeded one order of magnitude or more in industrialized countries over the period 2000 to 2019. If HBGVs of 1 or 0.1 pg TEQ/kg/day are used to calculate toxicological acceptable levels for DLC in human milk, it can be estimated that such levels will not be reached before, respectively, 2030 or 2050. When the subtle adverse health effects of DLC in the breastfed infant reported in the 1990s

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were compared with benefits of breastfeeding for the infant and mother, it is concluded that benefits grossly outweigh the potential adverse health. Therefore, it is concluded that the WHO has rightfully encouraged breastfeeding for the last decades.

Keywords

Human milk · Dioxin-like compounds · PCDD/PCDF ("dioxins") · PCB · Breastfeeding · Risk-benefit

1 Introduction

In the mid-1980s and early 1990s, the World Health Organization (WHO) coordinated two exposure studies on concentrations of polychlorinated biphenyls (PCB), polychlorinated dibenzo-p-dioxins (PCDD), and polychlorinated dibenzofurans (PCDF) in human milk (WHO 1989; WHO 1996). After adoption of the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2001, the WHO and the United Nations Environment Programme (UNEP) agreed to collaborate in joint studies starting in 2004 to support the implementation of this convention by assessing its effectiveness as required under its Article 16. Between 2000 and 2019, WHO and UNEP performed five global voluntary surveys to determine concentrations of POPs in human milk with participation of 82 countries (Malisch et al. 2023a).

As a result of these regular surveys, the present data provide significant and valuable information regarding regional aspects and time trends for a broad range of POPs, including dioxin-like compounds (DLC). Findings between 2000 and 2019 have been described in detail in various publications of compendium, including PCB and PCDD/PCDF in Part III (Malisch et al. 2023b). As such, this information can be used to estimate the possible health risks of some POPs that may be associated with breastfeeding but can also be used to estimate a possible reduction in future health risks. PCDD and PCDF were the first group of POPs that were monitored in these human milk surveys (WHO 1989; 1996). Temporal trends of PCB and PCDD/PCDF derived from repeated participation of countries between 1987 and 2019 have also been assessed in Part IV (Malisch et al. 2023c). Consequently, possible time trends and associated risks of these compounds for the neonate can already be determined as early as the 1980s and 1990s.

With increasing knowledge about the mechanism of action and toxicity of these PCDD and PCDF, there was a growing awareness within the scientific community that some PCB were structural analogs of DLC. These so-called dioxin-like PCB (DL-PCB) were found to have similar toxic symptoms as the more classic DLC, like 2,3,7,8-TCDD (Safe 1990; 1994). Based on these scientific insights, most leading toxicologists in the field agreed that for human risk assessment the group of DLC needed to be expanded with DL-PCB. A broad range of experimental studies has also established that most, if not all, toxicological effects of DLC were mediated by one receptor, the aryl hydrocarbon receptor (AhR). This knowledge led to the

concept of additivity for DLC. Although not perfect, it is still considered the most realistic way to describe mixture toxicity of these compounds (Birnbaum 1994).

Subsequently, it was globally accepted by regulatory authorities that human risk assessment for mixtures of these DLC should follow an additive approach. To support and globally harmonize the human risk assessment of DLC, the WHO initiated several expert meetings during the last decades. During these meetings (interim) toxic equivalency factors (TEF) were proposed to standardize the assessment for these compounds (Ahlborg et al. 1994; Van den Berg et al. 1998; Van den Berg et al. 2006). These WHO-TEF have now worldwide acceptance by regulatory authorities and are commonly used to determine toxic equivalency values (TEQ) of chlorinated DLC in, e.g., feed and food, environmental samples, or human matrices. Moreover, it has been brought forward that this TEF concept should also be expanded to POPs with a similar mechanism of action, e.g. brominated analogs of DLC. As a result, the brominated dioxins and dibenzofurans have more recently also been included in the WHO TEF model (Van den Berg et al. 2013).

2 Global Measurements and Time Trends

Although not all countries consistently participated in the WHO/UNEP-coordinated human milk surveys since the start of this program, the present database provides a unique opportunity to study the decrease in human exposure over time. In countries with a repeated participation in these surveys, the PCDD/PCDF concentrations in human milk decreased from a median level of 17 pg WHO_{2005}-PCDD/PCDF-TEQ/g lipid in the mid-1980s to 3 pg WHO_{2005}-PCDD/PCDF-TEQ/g lipid in the 2016–2019 period (WHO 1989; Malisch et al. 2023c). Undoubtedly, this significant and worldwide reduction of more than 80% during a 30-year period was caused by rigorous regulatory actions that started in the 1990s. These measures significantly reduced the emissions of PCDD and PCDF from combustion processes, e.g. from municipal incinerators, as well as their reduction in a variety of chemical products. As could be expected, this reduction was also reflected in human milk contamination with these compounds and should no doubt be considered as a success story for global regulatory actions.

With growing awareness of the dioxin-like properties of some PCB, the WHO human milk surveys also offer unique insights into the decrease of levels over time as the DL-PCB were included in the analyses from the beginning of the 1990s. Overall, the decreasing time trend of DL-PCB in human milk followed the same declining trend as PCDD and PCDF (Malisch et al. 2023c). Unlike unintentionally formed PCDD and PCDF, PCB were produced commercially for open applications, e.g. in paints and sealants, and in closed applications like transformers and capacitors as cooling fluids. In the case of PCB, it is important to realize that this observed reduction of PCB in human milk was caused by severe restrictions on commercial production of these compounds that already started in the 1970s and 1980s.

Due to the similar mechanism of action of DL-PCB compared with PCDD and PCDF, the WHO assigned TEF values for these congeners since the 1990s (Ahlborg

et al. 1994; Van den Berg et al. 1998). However, with growing scientific insights into the dioxin-like properties of these PCB, some WHO-TEF values changed over time (Van den Berg et al. 2006). To provide a consistent insight into time trends, human milk levels of PCDD, PCDF, *and* DL-PCB in this assessment have all been expressed as total TEQ (WHO-PCDD/PCDF-PCB-TEQ) using the TEF as agreed upon in the 2005 WHO expert meeting (Van den Berg et al. 2006). It was observed in 52 countries during the 2000–2010 period of WHO surveys that DL-PCB represented approximately 30 to 50% of the total WHO_{2005}-TEQ in human milk, albeit with some noticeable regional differences (Van den Berg et al. 2017). In 82 countries participating between 2000 and 2019, DL-PCB contributed between 8% and 62% (median: 33%) to the total WHO_{2005}-TEQ (Malisch et al. 2023b). In most industrialized countries, a decline of 80% or more in total WHO_{2005}-TEQ can be observed over the last 25 years. The highest levels of total WHO_{2005}-TEQ were observed in Western Europe with a median level of nearly 30 pg WHO_{2005}-TEQ/g lipid in the 1990s (countries with repeated participation; range about 20 WHO_{2005}-TEQpg/g lipid to 35 pg WHO_{2005}-TEQ/g lipid) decreasing to approximately 5 pg WO_{2005}-TEQ/g lipid in the period 2016–2019.

In view of the presence of these dioxin-like compounds in human milk and their decreasing time trend, the major issue addressed in this chapter is the possible health risk to the breastfed infant via breastfeeding. Such possible health risk has been assessed earlier with the WHO human milk surveys performed in the period 2000 to 2010 (Van den Berg et al. 2017). In that study, it was concluded that global TEQ levels in human milk were still above the levels that would be toxicologically acceptable for the breastfed infant. Nevertheless, it was also concluded in the previous assessment that the benefits of breastfeeding by far outweighed the possible health risks of these DLC for the breastfed infant. In this chapter, this earlier risk–benefit analysis is revisited against the decreasing time trend of DLC over the last 25 years.

3 Most Sensitive Endpoint for the Breastfed Infant

When determining possible or potential health risks of DLC for the breastfed infant, a major uncertainty is the contribution of prenatal versus postnatal exposure. These different exposure routes cannot easily be separated under normal perinatal conditions. In addition, it has been established that prenatal exposure is also highly relevant for the developmental toxicity of these compounds (Peterson et al. 1993). Moreover, at present there is no health-based guidance value (HBGV) available for the infant in relation to lactational exposure that would distinguish an effect between pre- and postnatal exposure. However, many regulatory agencies have set HBGVs for lifetime exposure situations and DLC, and a number of these are presented in Table 1 (ATSDR 1998; WHO 2000; US-EPA 2010; EFSA 2018).

Irrespective of whether a HBGV for DLC is applied based on 2,3,7,8-TCDD or on total TEQ, it is clear that global levels in human milk almost always exceed existing guidance values of exposure (see Table 1). These exceedances of HBGVs

Table 1 Health-Based Guidance Values (HBGVs) determined by various regulatory authorities with their underlying health effects in animals and humans with an estimated acceptable HBGV in WHO_{2005}-TEQ in human milk

Organization	Health-based guidance value (HBGV)		Exceedance HBGV[a,b] (2015–2020)	Associated HBGV milk level in pg TEQ/g lipid[c]	Health endpoints used in offspring
WHO (2000)	TDI	1–4 pg TEQ/kg bw/day	4–14 x	0.2–0.9	Offspring monkey, mouse, rat: Decreased sperm count, genital malformations, immune suppression, neurobehavioral effects after perinatal exposure
JECFA (2002)	TMI	70 pg TEQ/kg bw/month	6 x	0.5	Male rat: Reproductive tract deficits after prenatal exposure
US-EPA (2010)	RfD[d]	0.7 pg TEQ/kg bw/day	19 x	0.2	Human: Decrease sperm count and motility after childhood exposure
ATSDR (1998)	$MRL_{subchronic}$	20 pg TCDD/ kg bw/day	0.7 x	4.6	Weanling Guinea pig: Immunosuppression after 3 months exposure
ATSDR (1998)	$MRL_{chronic}$	1 pg TCDD/kg bw/day	14 x	0.2	Offspring rhesus monkey: Neurobehavioral effects after perinatal exposure
EFSA (2018)	TWI	2 pg TEQ/kg bw/week	47 x	0.07	Human: Decreased sperm concentration after childhood and perinatal exposure

[a]Based on recent median exposure levels of 3 pg TEQ/g lipid
[b]Based on 3.5% lipid weight in human milk and infant consumption of 125 g milk/kg bw/day, set a 4.5 g lipid/kg bw/d
[c]HBGV derived level pg TEQ/g lipid (HBGV in pg TEQ/kg bw/day)/4.375 g lipid/kg bw/day
[d]Reference dose

are generally a factor 10 or more, based on the medians of samples from more heavily industrialized countries, e.g., in Western Europe, from the period 2000 to 2019. The only exception is found for the ATSDR assigned semi-chronic MRL that was established before 2000 (ATSDR 1998). In this respect, it should be noted that significant additional insights into health effects of dioxin-like compounds were obtained from 2000 onward (US-EPA 2010; EFSA 2018).

Formally, these HBGVs have usually been defined and set to assure a lifetime daily exposure without human health risk. Therefore, it has frequently been argued that these HBGVs should not be applied for the breastfed infant situation, as lactational exposure is usually limited to a period of approximately three months to two years. Though, if the underlying experimental studies that serve as a point of departure for these HBGVs are given a more detailed look, it can be observed that their exposure time-period was significantly shorter than a full lifespan of the animals. Moreover, several regulatory agencies derived their HBGVs from developmental effects in animal and epidemiological studies. These originated from either prenatal, perinatal, or childhood exposure to DLC, thereby often including the lactational period, as illustrated below.

In the total daily intake (TDI) determination of 1 to 4 pg TEQ/kg bw day, the WHO used experimental studies with offspring of monkeys, rats, and mice that were perinatally exposed, as can be seen in Table 4 from their publication (WHO 2000). Subsequently, the 57th joint FAO/JECFA meeting also considered developmental effects on the male reproductive tract in rats after prenatal exposure as the most sensitive endpoint to derive a tolerable monthly intake (TMI) value (JECFA 2002). Moreover, the ATSDR established MRL for both semi-chronic and chronic exposure scenarios. For the semi-chronic exposure scenario, immunosuppression in weanling guinea pigs was used after a period of three months exposure, while for chronic exposure the perinatal exposure situation in Rhesus monkeys was used (ATSDR 1998). Most recently, EFSA derived a human based HBGV from one epidemiological study with exposure during childhood, which resulted in decreased sperm concentrations at adult age as the most sensitive human endpoint. Based on the observed NOAEL in that particular study EFSA also calculated that an amount of 5.9 pg TEQ/g lipid in human milk was associated with this NOAEL later in life (EFSA 2018). The above information is summarized in Table 1.

Considering the endpoints that were used to derive HBGVs, it can be concluded that generally toxicological and epidemiological studies were used with perinatal animal or childhood exposure to DLC, thus including the lactational period. It is well-established that developmental effects of DLC originating from early lifetime exposure are by far the most sensitive endpoints in all vertebrates (Peterson et al. 1993; WHO 2000; US-EPA 2010). Therefore, it can be concluded that risks from lactational exposure is covered by established HBGVs and that HBGVs for lifetime exposure may provide the highest protection, including vulnerable populations, such as the neonate and developing child. Noteworthy, these HBGVs were then "upgraded" by regulatory authorities to be used for the lifetime exposure situation either for TCDD or TEQ. In our opinion, it is justifiable to use established HBGVs for early life and shorter than lifetime exposure, e.g. breastfeeding.

Taken together, the results from these experimental studies used to derive HBGVs already suggest a further decrease of DLC in human milk since the 1990s. Moreover, epidemiological studies in the 1990s with breastfed infants from The Netherlands already showed an association between thyroid hormone level changes, immunological and (neuro)developmental effects with increasing levels of DLC (Pluim et al. 1993; Koopman-Esseboom et al. 1994; 1996; Weisglas-Kuperus et al. 1995, 2000, 2004). Many of these studies were performed at the end of the previous century when TEQ levels in human milk were at least one order of magnitude higher than in the most recent decade. The question arises whether such associations could still be found with current levels of DLC in human milk and maternal blood. With this in mind, it remains unclear if the effects found in the Dutch studies at that time were (in part) caused by prenatal exposure or postnatal human milk exposure. For DLC, animal studies clearly support a significant role for prenatal exposure for a range of sensitive toxicological effects of DLC (Peterson et al. 1993). The importance of prenatal exposure is also supported by more recent human studies. For example, a mother–child cohort study with children from Greece and Spain suggests a decrease in anogenital distance (AGD) in young boys with increasing maternal blood levels of DLC (Vafeiadi et al. 2013). In this study, median TEQ levels in blood declined after birth (52.3 ± 20.7 and 49.7 ± 26.7 pg TEQ/g lipid in newborns and young children, respectively). Moreover, the duration of breastfeeding was short (median 2 months) and was not associated with AGD, possibly suggesting a prevailing prenatal effect of DLC on AGD.

When considering all underlying toxicological and epidemiological information, there are good arguments to use established HBGVs (see Table 1) also for the breastfed infant and not only for lifetime exposure. Here, the strongest supporting argument would be the fact that many, if not all, underlying studies for these HBGVs are addressing a relatively short early lifetime exposure situation, including the lactational period, instead of a full lifespan. In Table 1, the calculated "acceptable" human milk levels of DLC associated with different HBGVs are presented. With the current state of knowledge, these toxicological "acceptable" levels are estimated to be in the range of 0.1 to 1 pg WHO_{2005}-TEQ/g lipid in human milk. This estimated "acceptable" range of TEQ in human milk is slightly lower than that calculated by EFSA (2018), which is 5.9 pg TEQ/g lipid. When reviewing this modest difference between EFSA's calculated safe human milk level and our "acceptable" TEQ range it should be recognized that the EFSA calculation is based only on one human study, while our estimated "acceptable" range contains a multiplicity of experimental studies.

When these projected "acceptable" levels are evaluated with the average decreases in some European countries with the highest concentrations of DLC in human milk, it can be estimated when "acceptable" levels will be reached in the foreseeable future. For a decline extrapolated with a HBGV of 1 pg WHO_{2005}-TEQ/g lipid, a toxicologically acceptable level may be reached around 2030, while for 0.1 WHO_{2005}-TEQ/g lipid such a level would not be reached before 2050. These situations are illustrated in Fig. 1. In either case it will still take decades from now to attain toxicologically "acceptable" levels of DLC in human milk. This estimation

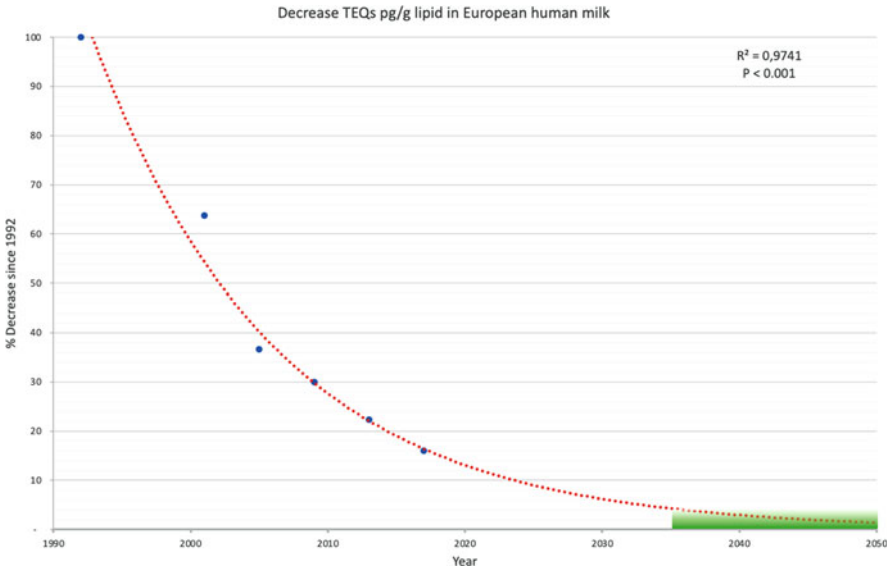

Fig. 1 Average percent decline in human milk WHO_{2005}-TEQ levels* in European countries** since 1992 and expected levels based on health-based guidance levels of 0.1 to 1 pg TEQ/g lipid (see Table 1). * Average for these countries in 1992 set at 25 pg WHO_{2005}-TEQ/g lipid and 100% with the green bar indicating an HBGV based projected decline of 0.4 to 4% of the 1992 level. ** Including The Netherlands, Lithuania, Belgium, Germany, Norway, Slovak Rep., Finland, Czech Rep., Croatia

clearly points out that (further) remedial actions are still needed, especially if the goal is to reach these "acceptable" levels for the breastfed infant sooner.

When considering the potential adverse health effects of DLC in human milk for the infant, it is of utmost importance to evaluate these in conjunction with the benefits of breastfeeding. There is no doubt, that a wide array of epidemiological studies convincingly showed the important health benefits of breastfeeding for both the infant and mother (Horta et al. 2007; Ip et al. 2007; James et al. 2009; Victora et al. 2016; Del Ciampo and Del Ciampo 2018). It is beyond the scope of this chapter to review and discuss all of these, but results of these studies are summarized in Table 2. As an indication, a recent study using meta-analyses of benefits from breastfeeding calculated that it may annually prevent 823,000 deaths in children younger than 5 years and 20,000 maternal deaths from, e.g., breast cancer (Victora et al. 2016). In contrast, the adverse health effects observed at concentrations of DLC in human milk that were present in the 1990s were considered limited from a clinical point of view and often transient (Lapillonne et al. 2021), e.g. thyroid hormone changes and liver functions (Ten Tusscher and Koppe 2004). Nevertheless, it should also be recognized that some of these subtle effects on, e.g., cognitive functions and the immune system were persistent beyond the prenatal and childhood period (Ten Tusscher et al. 2003, 2014). At present, the impact of these sustained effects later in life is unclear but should not be neglected due to lack of knowledge.

Table 2 General overview for the observed benefits* of breastfeeding for the infant and mother (Van den Berg et al. 2017)

Benefits for the infant:	**Benefits for the mother**:
• Optimal nutrition • Strong bonding with mother • Safe milk • Enhanced immune system • Reduced risk of acute otitis media, gastroenteritis, lower respiratory tract infections, and asthma • Protection against allergies • Correct development of jaw and teeth • Association with higher IQ/school performance • Reduced risk of chronic diseases, e.g. obesity, diabetes, heart disease, hypertension, hypercholesterolemia, childhood leukemia • Reduced risk of sudden infant death syndrome • Reduced risk of overall morbidity and mortality	• Strong bonding with infant • Increased energy expenditure, faster return to prepregnancy weight • Faster shrinking of the uterus • Reduced postpartum bleeding and delay menstrual cycle • Decreased risk of chronic diseases, e.g. breast, and ovarian cancer, diabetes • Improved bone density, decreased risk hip fracture • Decreased risk of postpartum depression • Enhanced self-esteem in the maternal role Time and money saved from preparing and not buying formula, less medical expenses

Thus, when comparing the significant beneficiary health effects of breastfeeding with these effects associated with DLC in human milk and maternal blood in the 1990s, the health benefits for infant and mother still grossly outweighed these potential adverse subtle health effects of these compounds. In addition, the question can be raised if reported adverse health effects of DLC in the 1990s were (partly) attributable to prenatal exposure. Furthermore, it is unknown whether these adverse effects would still be found with the present DLC levels in human milk, as levels of DLCs in breast milk are now at least one order of magnitude lower. Based on the above arguments and evaluation it can be concluded that the WHO has rightfully encouraged breastfeeding globally for the last decades and should continue to do so (WHO 2009).

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