Review Article

Agent Orange Exposure and 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) in Human Milk

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Agent Orange was sprayed in parts of southern Vietnam during the U.S.-Vietnam war and was a mixture of two chlorophenoxy herbicides. The mixture was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TCDD and other dioxins and furans are measurable in the milk of Vietnamese women. We explored whether the TCDD in milk from these women was from Agent Orange and whether lactational exposure can be a mode of transgenerational effects of TCDD from Agent Orange. A review of the world's literature on milk concentrations of polychlorinated compounds showed the presence of TCDD and other dioxins and furans in all countries that have been assessed. The congener profile of these chemicals, that is, the proportion of different congeners in the sample, can be used to assess the source of milk contamination. Measurements in most countries, including contemporary measurements in Vietnam, are consistent with non-Agent Orange exposure sources, including industrial activities and incineration of waste. Models and supporting human data suggest that TCDD from breastfeeding does not persist in a child past adolescence and that the adult body burden of TCDD is independent of whether the individual was breast- or bottle-fed as a child. These findings suggest that exposure to Agent Orange in Vietnam did not result in persistent transgenerational exposure through human milk. *Birth Defects Res (Part B)* 104:129–139, 2015. © 2015 Wiley Periodicals, Inc.

Key words: ***Agent Orange; tetrachlorodibenzo-p-dioxin; TCDD; dioxins; milk; lactation; Vietnam***

INTRODUCTION

The U.S. war in Vietnam involved the spraying of herbicides in the south to remove foliage cover for northern and Viet Cong troops and to decrease access of these combatants to food crops. Agent Orange was the herbicide used in the greatest volume and consisted of equal parts of the n-butyl esters of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. The latter was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Given the long half-life of TCDD in human adults and the persistence of TCDD in the environment, there has been concern that TCDD from Agent Orange continues to be present in the milk of Vietnamese women and that milk is a source of transgenerational exposure to TCDD. We here present a general discussion of TCDD in human milk and evaluate the extent to which TCDD in human milk can act as a source of transgenerational exposure to TCDD.

The term, "dioxin" has sometimes been used interchangeably with TCDD. Dioxins, however, are a group of bicyclic compounds with the general structure shown in Figure 1. Dioxins are related to furans, also shown generically in Figure 1, and sometimes the 17 dioxins and furans that are most commonly found in human

Abbreviations: PCB, Polychlorinated biphenyls; PCDD, Polychlorinated dibenzo-dioxins; PCDF, polychlorinated dibenzo-furans; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin

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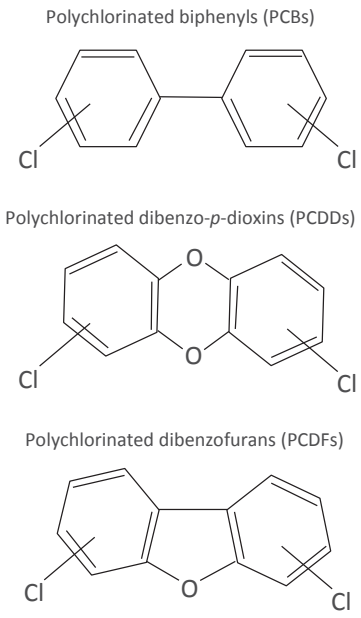

Fig. 1. Generic chemical structures.

matrices are called dioxins. For clarity, we refer here to these compounds as polychlorinated dibenzo-dioxins (PCDDs) and as polychlorinated dibenzo-furans (PCDFs). Polychlorinated biphenyls (PCBs) include compounds with the generic structure shown in Figure 1. Some PCBs are considered dioxin-like, meaning the rings are in the same plane and some biological effects are similar to those of TCDD in experimental systems.

Both analyses of samples of Agent Orange (Rappe, 1978) and investigations of Agent Orange contaminated areas in Vietnam (Schecter et al., 2006; Hatfield Consultants 2007, 2011) showed that the only polycyclic chlorinated compound present in appreciable concentrations in Agent Orange was TCDD. TCDD is not transformed in the body or the environment to higher order chlorinated compounds, and the presence of other PCDDs and PCDFs is not indicative of Agent Orange exposure. PCDDs, PCDFs, and PCBs can be found in communities as a consequence of industrial activities, particularly those involving incineration (U.S. Environmental Protection Agency, 2006). These compounds can also be found in developing countries, especially as a result of burning municipal waste (Kunisue et al., 2004; Tanabe and Kunisue, 2007).

It has been common to consider PCDDs/PCDFs and dioxin-like PCBs together by using toxic equivalency factors (TEFs), which are meant to scale the concentrations of these compounds using fractions of the potency of TCDD. TCDD is considered the most toxic of the dioxins/furans and thus has a TEF of 1. Other dioxin/furan congeners are assigned TEF values that are between 1 and 0.0003 (van den Berg et al., 2006). A mixture of dioxins and furans can be characterized by its toxicity equivalence (TEQ), which is the sum of the concentrations of the various congeners in the mixture weighted by their respective TEFs, to express the toxicity of a mixture in TCDD equivalents. The literature commonly reports mixtures of PCDDs/PCDFs and PCBs using TEQs. The TEQ system has undergone revisions over the years (van den Berg et al., 2006), and it is not always clear in the literature reviewed here which system was being used. However, the central focus of this review is Agent Orange, and TCDD is essentially the only PCDD/PCDF in Agent Orange. Thus, because TCDD has a TEQ of 1 in all historical TEQ systems and the changes in TEF's for other congeners are minor, the issue of changing TEQ systems is not important to this review. When TEQs are listed for various congeners, the proportion represented by TCDD is sometimes used to indicate the contribution of TCDD to the TEQ of the sample. This use does not reflect the TCDD contribution to the total mass of PCDDs/PCDFs in the sample. For example, as discussed below, the most abundant PCDD in environmental samples in the literature we reviewed was the octachloro congener, which has a TEF of 0.0003. Thus, a listing of TEQs of a mixture will represent octachlorodibenzodioxin at 0.03% of its weight proportion in the mixture.

Concentrations of PCCDs/PCDFs in biological samples including human milk and blood can be reported as either picograms (pg) per gram (g) lipid (equivalently parts per trillion, ppt) or as pg/g wet weight. In the first case, the denominator is the grams of the sample represented by lipid, while in the second case the denominator is the entire sample weight. The first measure is the most common and unless specifically noted, all references to concentration are the "lipid-adjusted" version.

QUANTIFICATION OF TCDD AND RELATED COMPOUNDS IN HUMAN MILK

Outside of Vietnam

There has been concern in several communities outside Vietnam about human milk concentrations of chlorinated polycyclic compounds associated with industrial activities and the incineration of waste (reviewed by (Ulaszewska et al., 2011). In terms of concentration, in industrialized countries octachlorodibenzodioxin is present in the highest concentrations, followed by hepta, hexa, and pentachlorodibenzodioxins (Yrjänheikki, 1989). TCDD accounts for a relatively small proportion of milk PCDDs (Fürst et al., 1989), although TEQ weighting results in a larger contribution of TCDD to total milk TEQs. The concentration of PCDDs/PCDFs in human milk decreases with the number of children nursed and with the time spent nursing (Fürst et al., 1989; Schecter et al., 1998; Vartiainen et al., 1998; Kunisue et al., 2004), consistent with the understanding that lactation is an effective route of excretion of a woman's body burden of these compounds. The decline over time of milk concentrations of PCDDs in a single subject is shown in Figure 2. In another report, milk concentrations of TCDD declined with time in three of four women (Abraham et al., 1998; Fig. 3). Milk concentration of PCDDs/PCDFs, expressed as TEQs, increased from morning to evening in eight healthy Dutch women from a mean ± SEM of 29.56 ± 3.18 to 31.60 ± 3.09 pg/g lipid (Pluim et al., 1992; Fig. 4). There was no corresponding change in lipid content from morning to evening. The study authors postulated that increased mobilization of fatty acids from maternal adipose tissue during the day made more stored PCDDs/PCDFs available for transfer to milk.

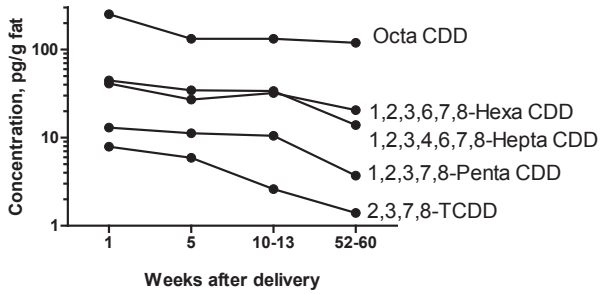

Fig. 2. Concentration of PCDDs in milk from a single subject sampled for more than 1 year after giving birth. Drawn from data presented in Fürst et al. (1989).

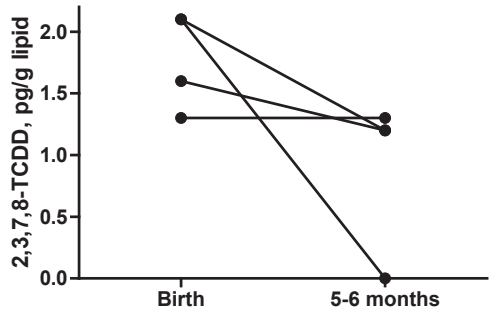

Fig. 3. Milk TCDD concentrations evaluated serially in four women reported by Abraham et al. (1998).

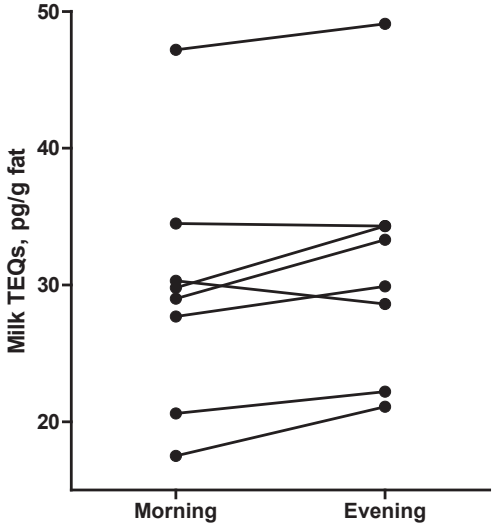

Fig. 4. Milking TEQ concentration by time of day in eight women from the Amsterdam region. Drawn from data in Pluim et al. (1992).

The World Health Organization (WHO) Regional Office for Europe organized a Working Group to assess health risks to infants from exposure to PCBs, PCDDs, and PCDFs in human milk (Yrjänheikki, 1989). As part of this effort, interlaboratory performance using pooled milk samples was evaluated in the late 1980s using PCDD/PCDF results from 11 laboratories and PCB results from 6 laboratories. Methods for PCDDs/PCDFs included cleanup of milk samples by liquid chromatography followed by quantification using gas chromatography/mass spectrometry. Agreement between laboratories was described as good, although statistical analysis had not been applied to the results.

As part of the WHO effort, reports were collected on milk concentrations of PCDDs and PCDFs from 1986 to 1988. Data originated from12 European countries, Canada, India, Japan, New Zealand, Thailand, the United States, and Vietnam. More than half of the 200 samples represented were from the Federal Republic of Germany. The highest TCDD concentrations in milk were identified in some samples from southern Vietnam, but there was large variability between samples from southern Vietnam, and the report noted the small number of Vietnamese samples and questioned whether these samples could be considered representative. The Vietnamese data will be considered in the next section.

The WHO Working Group concluded that the average TEQ concentration in milk was 17 pg/g lipid, resulting in daily consumption by a breastfed infant of 70 pg/kg body weight or 12.6 ng/day during a 6-month nursing period, accounting for less than 5% of an individual's lifetime intake. Breastfeeding was not believed to lead to increased concentration of PCDDs/PCDFs in adipose tissue due to the rapid accretion of PCDD/PCDF-free body fat during infancy. Due to benefits of breastfeeding, the Working Group recommended that nursing be encouraged.

Measurements of TCDD or TEQs from PCDDs/PCDFs in human milk from the WHO and other sources are shown in Supporting Information Table 1 for countries other than Vietnam. Measurements of PCDDs and PCDFs in milk have decreased over time (Fürst, 2006; LaKind, 2007).

Vietnam

Milk concentrations of TCDD and PCDD/PCDFs from Vietnam are presented in Table 1. There is likely to be some duplication of reporting in this table, but we have erred on the side of being overinclusive rather than underinclusive. For example, an extended abstract (Nishijo et al., 2013) and a full paper (Manh et al., 2015) appear to be reporting the same samples, but differences in the collection dates given in these sources prevented us from being certain that the samples were the same.

Milk samples from Vietnamese women collected in the 1970s during the war were frozen and analyzed in 1984 (Schecter et al., 1995; Table 1). In 1970, when Agent Orange was last being sprayed, milk concentrations of TCDD up to 1832 pg/g lipid were measured, although there were also an unspecified number of samples with undetectable TCDD. In 1973, after spraying of Agent Orange in Vietnam had been discontinued, the highest reported TCDD milk concentration was 333 pg/g lipid. More than a decade later, in 1985 to 1988, milk concentrations of TCDD up to 11 pg/g lipid were reported by these authors.

In 1991 to 1992 in the south, the TCDD concentration in 433 pooled blood samples was 12.9 pg/g lipid and the total PCDD concentration was 759 pg/g lipid (TEQ 22.7 pg/g lipid; Schecter et al., 1995). In the north, where Agent Orange was not sprayed, TCDD in blood from 82 pooled specimens was 2.2 pg/g lipid and total PCDDs

Table 1
TCDD Concentrations in Human Milk in VIETNAM

Location, year, number	Concentration, pg/g milk lipid pooled values: TCDD	PCDDs/PCDFs WHO TEQ unless otherwise specified	Reference
The former South Vietnam			
1970, Five positive samples only	333–1832		Schecter et al. (1995)
1973, Three positive samples only	133–266		Schecter et al. (1995)
1985–1988, pools of 2, 2, and 30	5, 11, 2.1		Schecter et al. (1995)
A Lưới Valley, 1999 Southern Vietnam			
A So, $n = 4$	5.5–19.0	6.15–21.9	Dwernychuk et al. (2002)
Hương Lâm, $n = 4$	2.9–12	9.44–14.6	Dwernychuk et al. (2002)
Hồng Thượng, $n = 4$	7.7–11	9.73–18.5	Dwernychuk et al. (2002)
Hồng Vân, $n = 4$	1.4–5.0	2.99–13.2	Dwernychuk et al. (2002)
Biên Hòa, Southern Vietnam, near Biên Hòa air base			
2010, $n = 22$	<1–30.3		Hatfield Consultants (2011)
Para 1, 2012, mean ± SD, $n = 52$	2.47 ± 2.02	9.89 ± 1.57	Nishijo et al. (2013)
Para 1, 2008–2010, $n = 51$	0–27	3–35	Manh et al. (2015)
Cẩm Xuyên Central Vietnam			
Para 1, 2008–2009, geometric mean, $n = 38$	0.63	2.34	Tai et al. (2011)
Para 2, 2008–2009, geometric mean, $n = 37$	0.47	1.62	Tai et al. (2011)
Para 1, 2012, mean ± SD, $n = 19$	0.72 ± 1.41	3.41 ± 1.29	Nishijo et al. (2013)
Cẩm Phúc, 2002–2003; mean ± SD, $n = 59$	0.54 ± 1.66	4.04 ± 1.52	Tawara et al. (2011)
Cần Giờ Southern Vietnam, approximately 1987, $n = 3$	9.0	11.1 EPA; 13.2 Nordic	Yrjänheikki (1989)
Đà Nẵng area Southern Vietnam			
Thanh Khê within 3 km of air base			
Para 1, 2008–2009, geometric mean, $n = 43$	1.97	8.33	Tai et al. (2011)
Para 2+, 2008–2009, geometric mean, $n = 104$	1.47	7.21	Tai et al. (2011)
Para 1, 2012;mean ± SD, $n = 43$	1.97 ± 1.90	14.30 ± 1.57	Nishijo et al. (2013)
Para 1, 2008–2010, $n = 43$	1–10	5–65	Manh et al. (2015)
An Khê, 2011, $n = 7$	3.0–43	14–51	Hue et al. (2014)
Chính Gián, 2011, $n = 7$	1.5–24	8.7–45	Hue et al. (2014)
Khuê Trung 2011, $n = 6$	0.75–2.4	4.3–12	Hue et al. (2014)
Hòa Thuận Tây 2011, $n = 7$	2.4–27	6.8–51	Hue et al. (2014)
Sơn Trà 7–10 km from air base			
Para 1, 2008–2009, geometric mean, $n = 26$	1.39	7.93	Tai et al. (2011)
Para 2+, 2008–2009, geometric mean, $n = 54$	0.98	5.86	Tai et al. (2011)
Para 1, 2012; mean ± SD, $n = 43$	1.39 ± 1.82	13.87 ± 1.47	Nishijo et al. (2013)
Para 1, 2008–2010, $n = 26$	0–7	8–42	Manh et al. (2015)
Thanh Khê and Sơn Trà, 2008–2009, $n = 210$	0.13–9.98	3.73–72.34	Nishijo et al. (2012)
Hanoi, Northern Vietnam, 28	2.2	4.9 EPA; 8.4 Nordic	Yrjänheikki (1989)
Near dump, 2000, $n = 8$	0.48–1.2	2.9–9.3	Kunisue et al. (2004b)
Remote from dump, 2000, $n = 10$	0.56–1.4	3.6–8.1	Kunisue et al. (2004b)
Ho Chi Minh City, Southern Vietnam, approximately 1987, pools of 38, 15, 8	7.1, 9.9, 5.0	12.3, 15.2 18.7, 22.1	Yrjänheikki (1989)
Ho Chi Minh City, 1985–1987, $n = 7$	4.5		Schecter et al. (1989)
Kim Bảng, Northern Vietnam, geometric mean			
Para 1, 2008–2009, $n = 19$	0.50	2.59	Tai et al. (2011)
Para 2+, 2008–2009, $n = 44$	0.31	1.66	Tai et al. (2011)
2008, median and interquartile range, 8		6.03 4.95–6.94	Nhu et al. (2011)
Para 1, 2012, mean ± SD, $n = 19$	0.5 ± 2.35	3.58 ± 1.36	Nishijo et al. (2013)
Para 1, 2008–2010, $n = 19$	0–1.3	2.4–7.1	Manh et al. (2015)
Long Xuyên, Southern Vietnam, approximately 1987, $n = 2$	2.0	4.0 EPA; 6.8 Nordic	Yrjänheikki (1989)

(*Continued*)

Table 1
Continued

Location, year, number	Concentration, pg/g milk lipid pooled values: TCDD	PCDDs/PCDFs WHO TEQ unless otherwise specified	Reference
Phù Cát 3–6 km from airbase; rural			
Para 1, 2008–2009, geometric mean, $n = 23$	1.66	14.05	Tai et al. (2011)
Para 2+, 2008–2009, geometric mean, $n = 36$	1.09	9.87	Tai et al. (2011)
Para 1, 2012, mean ± SD, $n = 23$	1.66 ± 1.51	12.53 ± 1.41	Nishijo et al. (2013)
Para 1, 2008–2010, $n = 23$	1–3	7–24	Manh et al. (2015)
Phù Cát, 2008, median and interquartile range, $n = 8$	15.65 10.99–22.13	Nhu et al. (2011)	
Quảng Trị near 17th parallel			
2004 /2007, Para 1, $n = 3$	2.2	11.7	Shelepchikov et al. (2009)
2004/2007, Para 2, $n = 2$	1.7	8.4	Shelepchikov et al. (2009)
Cam Lộ district			
Para 1, 2008–2009, geometric mean, $n = 27$	1.05	5.78	Tai et al. (2011)
Para 2, 2008–2009, geometric mean, $n = 69$	0.75	3.92	Tai et al. (2011)
Para 1, 2012; mean ± SD, $n = 15$	1.09 ± 2.20	9.32 ± 1.66	Nishijo et al. (2013)
Cam Chính, 2002–2003, mean ± SD, $n = 66$	0.82 ± 2.04	8.96 ± 1.83	Tawara et al. (2011)
Quảng Bình, Central Vietnam, 2007			Shelepchikov et al. (2009)
Para 1, $n = 3$	0.39	7.7	
Para 2, $n = 3$	0.06	5.6	
Sông Bé Province, Southern Vietnam, approximately 1987, 12	17	23.8 EPA; 31.8 Nordic	Yrjänheikki (1989)
Sông Bé Province, 1985–1987, $n = 3$	<2		Schecter et al. (1989)
Tân Thành, Southern Vietnam, 1985–1987, $n = 2$	3.0		Schecter et al. (1989)
Tân Uyên, Southern Vietnam, approximately 1987, three pools of two samples each	2.9–11	9.7, 15.3 EPA; 26.3, 19.5 Nordic	Yrjänheikki (1989)

Single values are pooled samples or central tendency where indicated. Ranges are full ranges except where indicated.

was 185.8 ng/g lipid (TEQ 6.9 pg/g lipid). The fraction of PCDDs represented by TCDD was 0.017 in the south and 0.012 in the north, suggesting that by 1991 to 1992, much of the TCDD in human milk from the south had originated from sources other than Agent Orange exposure.

Measurements of human milk PCDDs and PCDFs in the A Lưới Valley, which was described as a site of repeated Agent Orange spraying, were made in 1999 (Dwernychuk et al., 2002). Among the 16 samples reported, TCDD made up more than 75% of the total PCDD/PCDF TEQs in seven samples, including all four from A So, the site of a U.S. Special Forces base where Agent Orange was stored.

Japanese and Vietnamese researchers reported concentrations of PCDDs and PCDFs in milk from 520 Vietnamese women four decades after the war (Tai et al., 2011). A distinction was made between "hot spots" (areas near former U.S. air bases where Agent Orange was stored and sometimes spilled; Young, 2009) and areas in which Agent Orange was sprayed from airplanes. In this study, hot spots were represented by two communities close to the Đà Nẵng air base, and sprayed areas were represented by a community in Quảng Trị province, close to the 17th parallel. Unsprayed areas were represented by a community 280 km above the 17th parallel and a community in the north. TCDD and PCDD/PCDF TEQ concentrations were characterized as highest in the hot spots, intermediate in the sprayed area, and lowest in the unsprayed areas. Although the authors attributed this hierarchy of concentrations to Agent Orange exposure, TCDD contributed 16 to 23% to the PCDD/PCDF TEQ concentration in the hot spots, 18 to 19% in the sprayed area, and 18 to 29% in the unsprayed areas, none of which are suggestive of an exclusive Agent Orange source. Blood samples from individuals with documented exposure at the Biên Hòa and Đà Nẵng airbases typically showed 80% or more of the TEQ as being from TCDD (Hatfield Consultants 2007, 2011). As is the case for dioxins of combustion origin, the most abundant congener was octachlorodibenzodioxin in the milk samples reported by Tai et al. (2011). These authors noted that the congener distribution they detected was not typical of an Agent Orange source and postulated that in the decades since the spraying of Agent Orange in Vietnam, there might have been transformation of TCDD to other congeners as it passed through living organisms, presumably within the food chain. We have not located evidence that such transformation can occur.

Another study compared PCDDs and PCDFs in human milk from a hot spot (Phù Cát, a U.S. airbase during the war and currently an active Vietnamese Air Force Base) and an unsprayed area (Kim Bảng, a rural agricultural community in the north) and reported statistically higher total TEQs in the hot spot than the unsprayed area (Nhu et al., 2011). Here, contemporary exposures to PCDD/PCDF sources are more likely to be important than remote Agent Orange exposure in influencing human milk concentration of these compounds.

A study comparing human milk PCDD/PCDF concentrations in 2002 to 2003 in Cam Chính, where Agent Orange was sprayed, and Cẩm Phúc, where there were no spraying activities, found that PCDD/PCDF TEQ concentrations were higher in milk from Cam Chính than Cẩm Phúc (mean ± SD = 8.96 ± 1.83 vs. 4.04 ± 1.52 pg/g lipid; Tawara et al., 2011). TCDD comprised 9% of the total TEQ concentration in Cam Chính and 13% in Cẩm Phúc, and hexa-, hepta-, and octachlorinated congeners predominated. The study authors suggested that the congener profile in Cam Chính was more suggestive of pentachlorophenol contamination than of Agent Orange, but could not explain how pentachlorophenol exposure had occurred.

An extended abstract compared human milk concentrations of PCDDs/PCDFs in 2012 in communities in hot spots (Nishijo et al., 2013). The investigators reported that human milk concentrations of TCDD were higher in Biên Hòa than Sơn Trà, which is near the Đà Nẵng air base, although TCDD concentrations were not higher in Biên Hòa than in Tranh Khê, which is located even closer than Sơn Trà to the Đà Nẵng air base. Moreover, the proportion of PCDD/PCDF TEQs represented by TCDD was higher in Biên Hòa than in the Đà Nẵng communities. Although the authors of this abstract concluded that the Biên Hòa milk TCDD was likely to have been from Agent Orange based on the TCDD proportion in Biên Hòa compared to other hot spot communities, the proportion of PCDD/PCDF TEQs represented by TCDD in Biên Hòa milk samples was not higher than that in samples from Cẩm Xuyên, which was not sprayed with Agent Orange during the war. It is not clear how comparisons were made in this study; only means and standard deviations were given for the distributions, which appeared to have been highly skewed.

Risk factors for the appearance of PCDDs/PCDFs in human milk in Tranh Khê were evaluated based on questionnaire responses in 140 women whose milk was collected 1 month after delivery in 2008 to 2009 (Anh et al., 2014). Maternal age, years of residency in the community, and parity were associated with concentration of TCDD in milk as well as with the concentrations of several other congeners and with PCDD/PCDF TEQs. Although there were relationships with some of the other congeners, TCDD milk concentration was not associated with the use of well water or the frequency in the diet of meat, freshwater fish, seafood, or eggs. This article was not supportive of the hypothesis that Agent Orange contamination on the air base was elevating contemporary human milk concentrations of TCDD due to contamination of the local food chain. In response, the study authors proposed that the results could have been affected by food imported from outside the area.

A comparison of the ratios of TCDD to total PCDD/PCDF TEQs is shown in Figure 5 for countries other than Vietnam (from Supporting Information Table 1) and Figure 6 for Vietnam (from Table 1). Ratios were constructed based on means or means of ranges from studies that used a variety of different analytical methods and different methods of displaying data, and these ratios should be considered rough approximations. Except for samples from some of the hot spots in Vietnam, ratios of milk concentrations of TCDD to total TEQs are similar in Vietnam and the rest of the world, suggesting non-Agent Orange sources.

TOXICOKINETICS IN INFANTS AND MODELS OF EXPOSURE

Studies on the handling by infants and young children of PCDDs and PCDFs have been published by non-Vietnamese scientists. In one of the earliest studies, PCDDs and PCDFs were measured in three infants who died of sudden infant death syndrome, one of whom was breastfed for almost 3 months and died at 9.7 months, one of whom was breastfed for a week and died at 3.8 months, and one of whom was not breastfed and died at 4.8 months (Beck et al., 1990). TCDD was present in adipose tissue at 1.0 pg/g in the infant who had been breastfed for 3 months and was not detectable (<0.5 pg/g) in the infant who had not been breastfed. Total adipose tissue TEQs from PCDDs and PCDFs were 3.4 pg/g in the breastfed infant and 2.1 pg/g in the infant who had not been breastfed. Adipose tissue concentrations of PCDDs and PCDFs were higher than concentrations in other tissues including spleen, thymus, liver, and brain. Brain TEQ concentration was 1 to 2% of adipose tissue concentration. Brain TCDD concentration in the infant who had been breastfed was 0.2 pg/g lipid. Brain TCDD concentration in the other two infants was less than the limit of detection (0.5 pg/g).

Based on the findings from four German and four Swedish infants, TCDD was estimated to be nearly completely absorbed from human milk (Jödicke et al., 1992; McLachlan, 1993; Abraham et al., 1994; Dahl et al., 1995). A toxicokinetic model was developed to predict lifetime exposure to TCDD, including exposure during infancy, by Kreuzer et al. (1997). Measurements of adipose tissue and hepatic TCDD concentrations in infants who died of sudden infant death syndrome were in general agreement with the model. The finding of TCDD in tissues from stillborn infants supported the assumption that fetal adipose tissue TCDD concentration was similar to maternal adipose tissue TCDD concentration. The concentration of TCDD in adipose tissue was higher in breast- than formula-fed infants (Fig. 7).

The Kreuzer model predicted transfer of maternal TCDD to the infant in milk resulting in a decrease in maternal lipid concentrations by about 70% over the first 6 months of lactation. The estimated blood half-life of TCDD in infants was 0.42 years (5 months). Over the same time period, infant adipose tissue and blood TCDD concentrations increased in breastfed infants and decreased in bottle-fed infants. Infant lipids increased with growth,

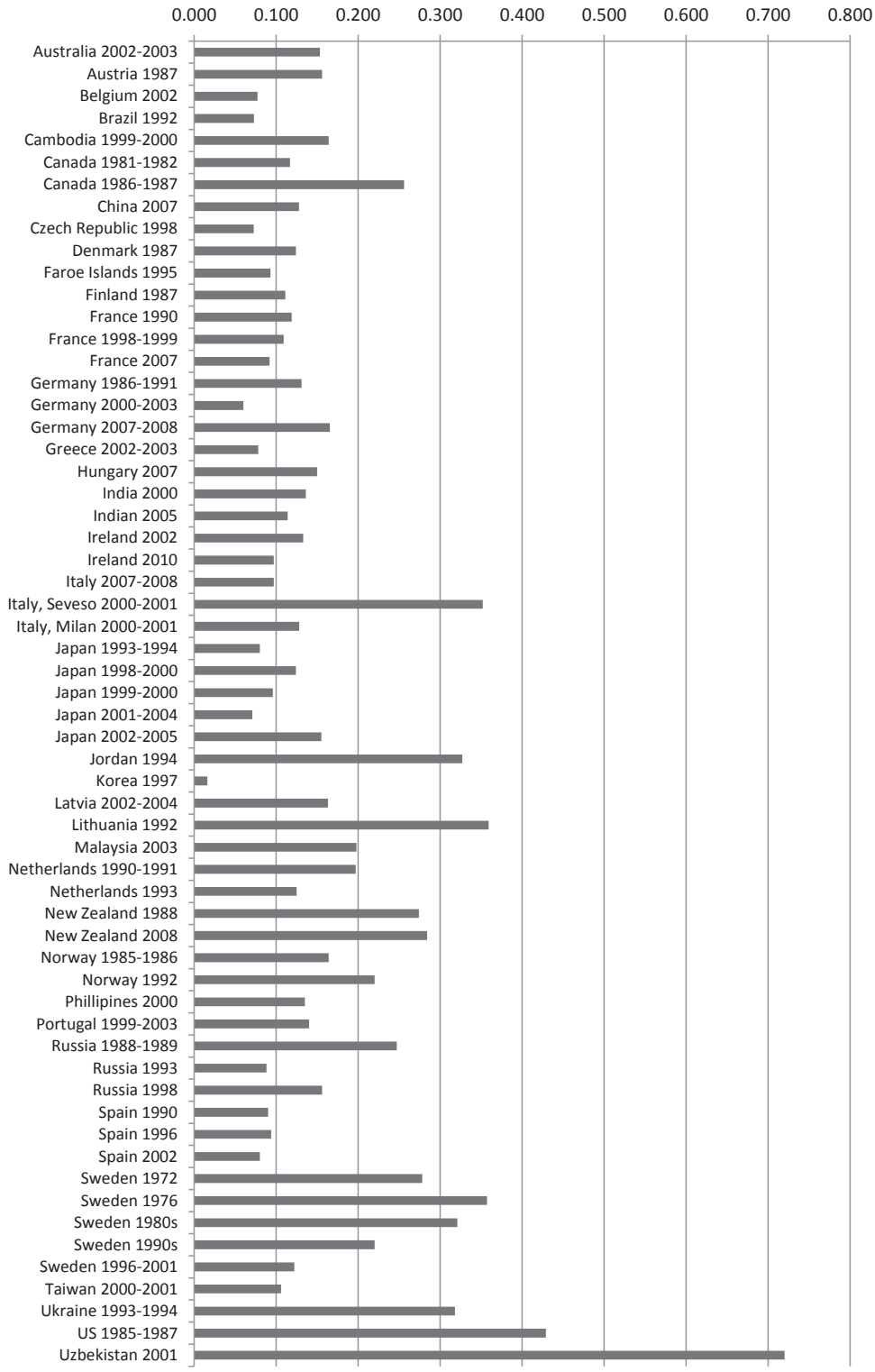

Fig. 5. Ratio of TCDD TEQs to total PCDD/PCDF TEQs in milk samples outside of Vietnam. Calculated from data in Supporting Information Table 1.

diluting the existing TCDD in fat stores. During the first 6 months of lactation, this lipid accretion was not sufficient to offset the accumulation of TCDD from human milk. After 6 months, with the decreasing milk concentrations of TCDD and the introduction of other foods, infant blood TCDD concentrations fell rapidly. By contrast, in three of four German maternal–child pairs, milk TCDD concentrations were higher at 11 to 12 months postpartum than at 5 to 6 months and blood TCDD concentrations were higher in infants than in their mothers at 11 to 12 months

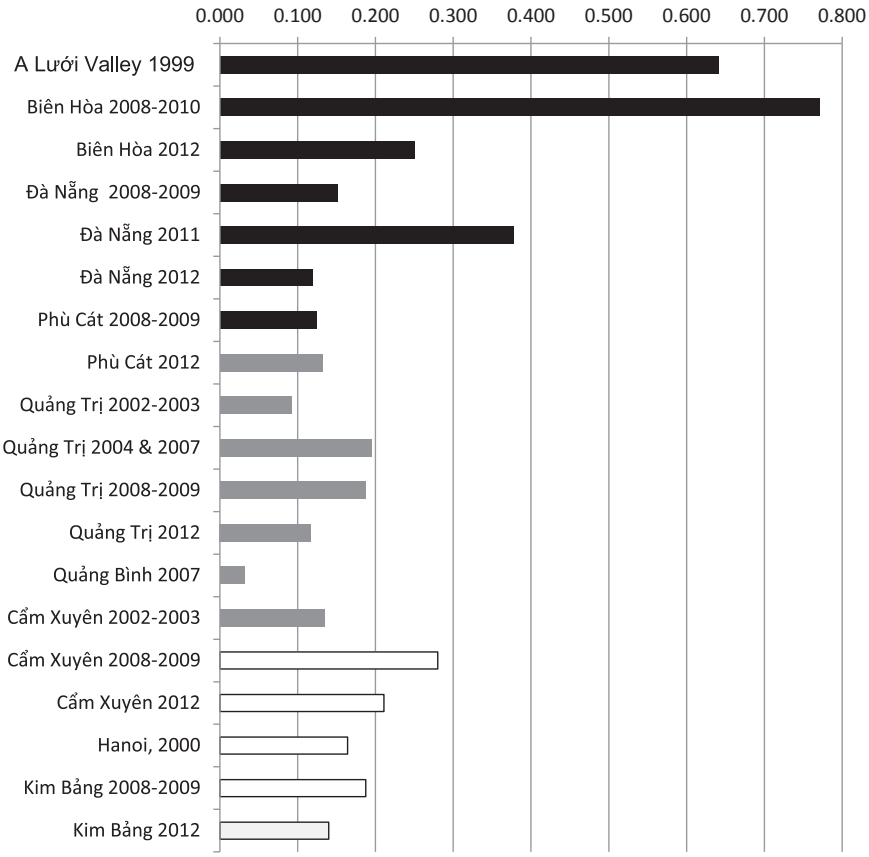

Fig. 6. Ratio of TCDD TEQs to total PCDD/PCDF TEQs in milk samples from Vietnam. Black bars represent "hot spots," gray bars are sprayed areas, and white bars are unsprayed areas. Calculated from data in Table 1.

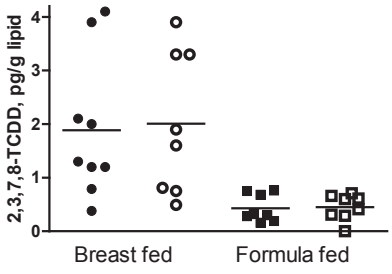

Fig. 7. Infant tissue concentration distribution for TCDD by feeding method. Closed symbols, adipose tissue; open symbols, liver. Horizontal bars are means. Distributions for each tissue are significantly different between feeding method (Mann-Whitney *U*-test performed by current author). Drawn from data presented by Kreuzer et al. (1997).

of age (Abraham et al., 1998). This report suggested that a decrease in infant blood TCDD concentration might not occur as early as 5 to 6 months as predicted by the Kreuzer model. There was little if any decrease in TCDD milk concentration in two Japanese women serially sampled over the first year after giving birth, although total TEQ from PCDD/PCDFs and PCBs decreased in both women (Takekuma et al., 2011). Although these reports did not confirm the decrease in maternal adipose or milk concentrations of TCDD over the first year of nursing, the TCDD blood half-life in infants of 0.4 years was subsequently confirmed using measurements from two breastfed children (Leung et al., 2006). Blood half-life does not necessarily represent total body half-life, because TCDD is present in adipose tissue to a greater extent than in blood; however, toxicokinetic models generally assume that TCDD in adipose tissue is proportional to TCDD in blood and that the compound is exchanged between lipid compartments (Thomaseth and Salvan, 1998; Schuhmacher et al., 2014).

A possible explanation for departures from the model predictions was offered by LaKind et al. (2009), who found that maternal blood and milk concentrations of PCDDs, PCDFs, and PCBs varied over time, with some women showing an increase in concentrations rather than the anticipated decrease with duration of breastfeeding. These authors suggested that variable dietary intakes during lactation might contribute to variations in plasma and milk concentrations of these compounds. TCDD measurements were not reported in this article, which focused on compounds with a higher number of chlorines.

According to the Kreuzer model, within 4 to 6 years, the TCDD blood concentrations in infants who were breastfed and infants who were bottle-fed do not differ (Kreuzer et al., 1997). A more detailed model developed by LaKind et al. (2000) agreed with an infant half-like of 0.42 years for TCDD, based in part on a 40-fold increase in lipid stores in young children. In the LaKind model, infant TCDD body burden based on U.S. statistics on

nursing behavior peaked at 4 to 5 months of age. The 95th percentile body burden was approximately 1.4 ng/kg body weight.

A subsequently developed model adopted some but not all of the assumptions of the Kreuzer and LaKind models (Lorber and Phillips, 2002). This model evaluated TEQs from PCDDs/PCDFs as a single compound with a half-life of 0.4 years at birth increasing to 1 year at 6 months of age, 2 years at 5 years of age, and close to 10 years at 55 years of age. The daily infant TEQ dose level was 800 pg/day decreasing to 200 pg/day by 1 year of age based on a modeled decrease in milk concentration of PCDDs/PCDFs. The model assumed an initial TEQ body burden of 10 pg/g lipid and an initial milk TEQ concentration of 25 pg/g lipid. The model predicted that a child breastfed for 6 months would have a peak TEQ blood concentration of 44.3 pg/g lipid at 9 weeks of age. The timing and height of the peak TEQ concentration would not change with breastfeeding for up to 2 years. Infants nursing for up to 2 years would have TEQ lipid concentrations similar to those of bottle-fed infants by the age of 10 years. Using area under the time–concentration curve (AUC) as a surrogate for lifetime exposure, at 70 years of age, a person who was breastfed for 6 months would have had an exposure 9% higher than a person who was not breastfed, and a person who was breastfed for 2 years would have had an exposure 18% higher than a person who was not breastfed. Doubling the initial infant body burden and milk TEQ concentration doubled the peak TEQ concentration at 9 months of age, but increased lifetime exposure to age 70 years by only 9%.

Other models also have found peak exposure of a breastfed infant to occur at about 6 months of age (Trapp et al., 2008). A probabilistic model based on 2000 to 2006 Swedish human milk measurements demonstrated a decline in probabilistic mean TEQ intake from PCDDs/PCDFs from 24.4 pg/kg body weight/day at 1 month of age to 9.6 pg/kg body weight/day at 6 months of age. The worst-case scenario intake decreased from 60.8 to 24.1 pg/kg body weight/day over the same interval (Bergkvist et al., 2010).

An additional model of internal dose through age 7 came to similar conclusions about the lack of long-term impact of breastfeeding on PCDD/PCDF body burden (Kerger et al., 2007). All the models predicted that lipid concentrations of PCDDs/PCDFs would be similar in children who were and were not breastfed by the time they reached sexual maturity. The stores of PCDDs/PCDFs from an adult woman's lipid that gained access to her milk during lactation, therefore, would not reflect whether or not the breastfeeding woman herself had been exposed to these compounds through breastfeeding when she was an infant.

The conclusion that milk concentrations of TEQs would not be affected by early childhood exposures of a woman to breastfeeding was challenged by a paper using Swedish milk measurements and questionnaire responses to model contributors to milk TEQs (Lignell et al., 2011). A history of the mother having been breastfed was significantly associated with total TEQs in milk (adjusted geometric mean 11.6 ng/g lipid in women who were breastfed and 10.1 ng/g lipid in women who were not breastfed), but the most important contributors to this finding were PCBs and, to a lesser extent, PCDFs. PCDDs apparently did not contribute to this finding. A study in Japan showed that a history of the mother having been breastfed as a child did not contribute to PCDD concentration in her milk as an adult. The concentration of TCDD in milk was 1.65 pg/g lipid in women who had been breastfed and 1.39 pg/g lipid in women who had been formula fed, $p = 0.056$ by analysis of covariance (Takekuma et al., 2004).

A lack of influence of breastfeeding on transgenerational transfer of TCDD was supported by the Yusho oil experience. In 1968, contamination of rice oil with PCBs and PCDDs/PCDFs in Japan led to illness among exposed individuals. A study in 2002 to 2008 of women at 54 to 66 years of age and their offspring at 24 to 40 years of age showed lower blood concentrations of TCDD and other PCDDs/PCDFs in offspring than in mothers (Tsukimori et al., 2011). Offspring blood concentrations were not influenced by a history of breast- or formula-feeding. Among the 14 children sampled, only 3 had detectable blood concentrations of TCDD compared to 7 of 9 exposed mothers.

DISCUSSION

Measurements of TCDD in human milk in Vietnam today do not support the idea that Agent Orange is a substantial source, because the only dioxin present in appreciable concentrations (>0.1 ppm) in Agent Orange was TCDD. Other dioxin sources might contain TCDD, but most of the mixture is dioxin and furan congeners other than TCDD. If most or all of the TEQs in a milk sample were from Agent Orange, most or all of the milk TEQ would be from TCDD. Because other sources contain TCDD, a modest proportion of total TEQs from these other sources would be due to TCDD.

In the Vietnamese milk samples as in samples from the rest of the world, the proportion of PCDD/PCDF TEQ due to TCDD is generally less than 0.2. These findings are in contrast to blood samples taken from clearly Agent Orange exposed populations near airbases, where the total TEQ is clearly elevated and the TEQ proportion attributed to TCDD is more than 80% (Hatfield Consultants, 2007, 2011). The only report of TCDD concentrations more than 100 pg/g lipid in human milk from Vietnamese women is from milk collected during the Vietnam War (Baughman, 1974; Schecter et al., 1987). In the Baughman data, reported concentrations were measured using analyses performed when the analysis of biological samples for dioxins was very early in its development. However, the TCDD concentrations reported by Schecter et al. (1987) are in the same range as the 1973 samples analyzed by Baughman, which suggests that at the time of the war some women had elevated TCDD concentrations in their milk, consistent with Agent Orange exposure as the source.

When human milk contains TCDD, breastfed infants have transiently higher body burdens of PCDDs/PCDFs, but by the time of sexual maturity, body burdens are similar between individuals who were breast- and bottle-fed as children. Therefore, breastfeeding is not a mechanism by which TCDD from Agent Orange can be transmitted from one generation to the next. Because most of the body burden of TCDD is in adipose tissue, the body burden of an individual will depend on the amount of adipose

tissue and the TCDD concentration in the sources of adipose tissue consumed over the lifetime.

Our observations suggest that current TCDD concentrations in human milk in Vietnam are not pervasively elevated by Agent Orange used during the war. These observations plus the pharmacokinetic considerations presented here suggest that human milk is not a significant pathway for Agent Orange-related second generation TCDD exposure.

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