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EWG Science Analysis

Dioxin's Risks to Human Health and the Need for Expedited Action

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Environmental Working Group (EWG) is a non-profit public health and environmental research and advocacy organization based in Washington, DC. We focus much of our research on human and environmental health risks from chemical contamination.

The purpose of this document is to provide estimates of the implications of dioxin exposures for the general population, including breast-fed infants, children, and adults who ingest dioxin in a wide range of dioxin-contaminated foods; and to lay out the many reasons for the Environmental Protection Agency (EPA) to expedite the completion of its dioxin assessment begun 25 years ago and still unfinished.

Dioxin (2,3,7,8-Tetrachlorodibenzo-p-dioxin, also known as 2,3,7,8-TCDD, or TCDD) may well be one of the most-studied chemical pollutants. An unprecedented range and depth of human and animal studies have systematically explored various aspects of dioxin toxicity. Indeed, as more research is done, scientists are finding dioxin to be more, not less, toxic than what was determined by earlier studies.

As the Science Advisory Board (SAB) launches its fourth analysis of EPA's dioxin assessment in the past quarter century, EWG urges the board to expedite its review process and help EPA finalize this important document that will serve as a cornerstone for the agency's efforts to protect public health from chemical contaminants.

EWG strongly supports the scientific rationale of the "Draft EPA's Reanalysis of Key Issues Related to Dioxin Toxicity." We urge the SAB and the members of the Dioxin Review Panel to uphold the EPA's risk assessment approach and to help speed the agency's efforts to establish the safety standard for oral exposure to dioxin, as presented in the draft reanalysis.

About dioxin. Chlorinated dioxins are a family of persistent, highly toxic compounds that form as byproducts of waste incineration (Shibamoto 2007) and various industrial processes, such as smelting, chlorine paper bleaching and pesticide manufacturing (Rappe 1990; Weber 2008). The most toxic and most extensively studied member of this family, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) has been associated with a panoply of adverse health effect in people including cardiovascular disease; diabetes; cancer; endometriosis; early menopause; reduced testosterone and thyroid hormones; altered immune responses; and skin, tooth, and nail abnormalities (Birnbaum 2000; Schecter 2006; White 2009).

Similar harmful effects, though of lesser magnitude, are associated with exposure to related compounds, including various polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), which generally co-occur with TCDD (Lorber 2009). For these contaminants, the World Health Organization and health agencies in a number of countries apply Toxic Equivalency Factors that represent the relative potency of PCDDs and PCDFs relative to TCDD toxicity (Van den Berg 2006; WHO 2005). These toxicity-weighted concentrations are then summed to give a single, adjusted PCDD/PCDF concentration expressed as a Toxic Equivalent (TEQ) (U.S. EPA 2007).

EWG strongly supports an expedited SAB review of this document so that EPA can meet its goal of finishing the project in 2010. This timely completion is essential because:

> Infants and young children receive the highest dose of dioxins from food exposures, relative to their body weight, of any other segment of the population, in significant excess of the EPA's estimated reference dose (RfD), safe daily dose, of 0.7 picograms per kilogram of body weight per day (pg/kg-day).
>
> At the current contamination levels of dioxins in food, the cancer risk is orders of magnitude above the EPA's benchmark one-in-one-million risk level that provides a reasonable certainty of no harm. Americans are routinely exposed to dioxins from popular foods at levels close to EPA's proposed reference dose.
>
> EPA's proposed standards indicate a need for rapid action towards restricting dioxin exposures.

Details and rationale for our recommendations are listed below.

1. Infants and young children receive the highest dose of dioxins from food exposures, relative to their body weight, of any other segment of the population, in significant excess of the EPA's estimated reference dose (RfD), safe daily dose, of 0.7 pg/kg-day.

Outside of known dioxin-contaminated industrial and military hazardous waste sites (Casanova 1987; Garabrant 2009) and industrial accidents (Pesatori 2003), the primary source of dioxin contamination in people is from food, starting with breast milk and formula for infants and continuing to dioxin exposure from meat, dairy products, fish and shellfish for children and adults (Schecter 2001; WHO 2010). Infants and children between 1 and 10 years of age have the highest relative dietary exposure, since children consume more food than adults in relation to their body weight (Charnley 2006; Gies 2007).

Breast-fed infants in particular receive a high dose of dioxin during their first months of life, when breast milk is their only, or primary, food source (LaKind 2007). Adverse impacts of dioxins on children's health are of great concern, because developmental and/or early-life dioxin exposure has been linked to neurological alterations, including effects on hearing, psychomotor function, cognition, and gender- specific behaviors; effects on the reproductive organs; and hormonal changes (Baccarelli 2008; Mocarelli 2008; Wormley 2004).

Two recent, key human studies have clarified and expanded our understanding of the heightened susceptibility of the developing fetus and young children to dioxin:

> A study of 51 mother-child pairs in Seveso, Italy exposed to TCDD from an industrial explosion. In the study, infants born to mothers in the highly contaminated Seveso region 18 to 29 years after the explosion showed elevated blood levels of thyroid-stimulating hormone (TSH), an indicator of neonatal primary hypothyroidism. Higher maternal serum TCDD concentration correlated with elevated TSH levels in newborns, confirming the specificity of the association (Baccarelli 2008). The thyroid hormone tests were performed 72 hours after birth, indicating that effects observed by the scientists were due to fetal exposure to TCDD that had crossed the placenta.
>
> A study of 71 men exposed at a young age to TCDD from the Seveso explosion showed a reduction in various sperm parameters, such as sperm concentration and motility, and changes in the levels of two hormones, estradiol and follicle-stimulating hormones. These reproductive changes were particularly noticeable among a group of men exposed before the age of 10 (mean age of exposure 6.2 years), compared to control groups of men exposed after the age of 10 (mean age at exposure, 13.2 years) and men exposed as adults (mean age at exposure, 21.5 years) (Mocarelli 2008). The authors of the study suggested that TCDD exposure during sensitive developmental windows may "permanently alter the programming of the primordial germ cells" (Mocarelli 2008), with adverse reproductive health consequences for the rest of the person's life.

EWG scientists carefully reviewed the EPA's method for estimating a reference dose (RfD) for the oral safety standard, considering both human and animal studies of TCDD toxicity. We support the agency's methods. We agree with the EPA's conclusion that the Baccarelli 2008 and Mocarelli 2008 studies have been conducted with the necessary level of scientific rigor to render them adequate and appropriate for the derivation of an RfD protective for non-cancer health effects. Both studies produced a comparable Point of Departure (POD, defined as the Lowest Observed Adverse Effect level (LOAEL) detected in these studies) for oral exposure from contaminated food at 0.02 nanograms of dioxin per kilogram of body weight per day (ng/kg/day). EPA then applied an uncertainty factor of 30-fold, which included a 10-fold factor for lack of a No Observed Adverse Effect Level (NOAEL) and a 3-fold factor for interindividual variability. The resultant RfD, calculated as POD/30, was determined to be 0.7 picograms (pg) per kg/day (pg/kg-day).

EWG notes that this RfD based on human epidemiological studies is, in fact, in the middle of the candidate RfD array derived by EPA from a wide range of animal toxicity studies (Figure 4-4 in the Draft Reanalysis). An argument can be made that, in view of very high toxicity of TCDD, the most conservative and health-protective RfD should be adopted. The RfD recommended by the EPA is based on sound science, is consistent with the full range of available data and would constitute an important step forward for protecting public health and decreasing dioxin exposures from contaminated foods. Of note, our analysis of the amount of TCDD and related compounds (polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF)) that infants and children ingest daily indicates these vulnerable groups of kids would be significantly overexposed for the first several, critical years of their lives (Tables I and II).

Table I. Dioxin contamination in human breast milk – US data [a]

Reference	Dioxin toxic equivalent (TEQ) [b] levels in breast milk (on a lipid basis)	Dioxin TEQ levels (whole- milk basis) and total TEQ exposure from breast milk for 6 months-old infant [c]	Dioxin TEQ dose for 6 month-old breast-fed infant [d]	Infant exposures relative to "safe" daily dose (RfD of 0.7 pg/kg-day [e])
(Malisch 2003), cited in (LaKind 2007)	7.18 ppt (pg/g) PCDD+PCDF TEQs (as reported)	0.14-0.35 parts per trillion (ppt) PCDD+PCDF TEQs for 2-5% milk lipid contentf, corresponding to 109-273 pg dioxin TEQ from breast milk/day	15-37 pg/kg- day	21-52 times higher than RfD
(Schecter 2001)	not reported	0.35 ppt PCDD+PCDF TEQ (3.7% milk lipid content), corresponding to 273 pg dioxin TEQ from breast milk/day	37 pg/kg-day	52 times higher than RfD
(Charnley 2006)	not reported	Daily intake of 80-400 ppt PCDD+PCDF TEQs from breast milk/day	11-54 pg/kg- day	15-77 times higher than RfD

Source: EWG analysis of dioxin exposures considering breast milk tests and infant exposure factors from EPA and the peer-reviewed scientific literature.

For comparison, similar range of PCDD/PCDF concentrations in breast milk was reported by several other studies conducted in North America (all numbers are on the lipid basis): 2.6 pg/g (ppt) for a selected group of 8 PCDD/F TEQs (did not include TCDD) (LaKind 2009); 12 ng/kg (ppt) PCDD/F and PCBs TEQs (Wang 2003), cited in (Charnley 2006); and 15 ppt (ng/kg) PCDD/PCDF TEQs, based on Canadian data for 1986-87 (Ryan 1993).

Overall toxic equivalency (TEQ) for body burden of TCDD and related compounds, PCDDs and PCDFs as reported in the individual studies. For a PCDD/PCDF mixture, total TEQ is the sum of the product of the concentration of an individual dioxin- like compound and the corresponding TCDD TEF for that compound. TCDD commonly comprises ~10% of total dioxin TEQs in different matrices such as food, body burden, etc. (Lorber 2009; Van den Berg 1998).

According to EPA's Exposure Factors Handbook (U.S. EPA 2009), mean breast milk intake for infants 1-6 months of age is in the range of 673-896 ml/day. For this analysis, we used the volume of 780 ml/day

located in the middle of the range and typical for 3-6 months-old infants, as identified in other studies (LaKind 2000; Neville 1988). Human breast milk density is 1.03 g/ml (LaKind 2000).

For infants from 3 to less than 6 months of age, EPA recommends assuming a mean body weight of 7.4 kg (U.S. EPA 2009).

Proposed in the EPA's 2010 Draft Reanalysis (U.S. EPA 2010).

The total fat content of 24-hour human breast milk sample is typically in the range of 20-50 g/L. National Academy of Sciences (NAS). 1991. Nutrition during lactation.

http://www.iom.edu/Reports/1991/Nutrition-During-Lactation.aspx

Table II. Estimates of dietary exposure to PCDD/F TEQs for U.S. children up to 10 years of age [a]

Age	Average intake, pg/kg-day	Children's average exposures relative to "safe" daily dose (RfD of 0.7 pg/kg-day)	High intake (95%), pg/kg-day [b]	Children's high exposures relative to "safe" daily dose (RfD of 0.7 pg/kg- day)
2 years (Charnley 2006)	0.7-1.2 [c]	1-1.7 times higher than RfD	1.5-2.2	2.1-3.1 times higher than RfD
2 years (FDA 2006)	0.78	1.1 times higher than RfD	not reported	
6 years (Charnley 2006)	0.6-0.9	0.9-1.3 times higher than RfD	1.3-1.8	1.8-2.5 times higher than RfD
6 years (FDA 2006)	0.62	0.9 of the RfD	not reported	
10 years (FDA 2006)	0.44	0.6 of the RfD	not reported	

General US population (Charnley 2006)	0.2-0.4	0.3-0.6 of the RfD	0.8-1.2	1.1-1.7 times higher than RfD

Source: EWG compilation of dioxin exposure estimates for the U.S. population from the FDA data and the peer-reviewed scientific literature.

FDA Total Diet Study (TDS) did not include breast milk. Thus we could not estimate exposures for infants 6-11 months of age, a group that ingests breast milk in addition to other foods.

As reported by Charnley 2006 study.

Charnley 2006 reported two estimates for each category of PCDD/F exposure, one estimate assuming that non-detect samples included the tested compound at 1/2 of the limit of detection, corresponding to the higher estimate listed; and a second estimate assuming that non-detect samples did not contain the analyte in question (assigned zero value), corresponding to the lower estimate listed.

As demonstrated by the data in Table I, all breast-fed infants and children up to 2 years of age are currently ingesting amounts of PCDD/F TEQs significantly greater than the proposed RfD (U.S. EPA 2010). Higher dietary intakes persist for children 2-10 years of age and, in the highest exposure group (95% or top 5% of exposure), remain above RfD, as shown in Table II. These elevated exposures for children compared to adults are of serious concern, since younger humans or laboratory animals appear to be more sensitive to dioxin's effects on hormones (Mocarelli 2008; Su 2010). The full range of health effects that would be triggered by the early, high-dose exposure to dioxin in infants is still incompletely understood. However, as new research on dioxin toxicity in humans is conducted, scientists are finding evidence of adverse changes at progressively lower doses of dioxin, as evidenced by the long-term follow up studies from the Seveso cohort (Alaluusua 2004; Baccarelli 2008; Mocarelli 2008).

Children eliminate TCDD from their bodies faster than adults and have a shorter TCDD half-life, possibly due to differences in the relative contribution of toxicant clearance pathways (Kerger 2006). However, the rate of dioxin clearance from the body is inversely related to the proportion of adipose tissue in the body, the Body-Mass Index (BMI). In people of all ages, greater BMI is associated with longer residence times of TCDD and related compounds in the body (Collins 2007; Kerger 2006; Landi 1998). For example, the half-life of TCDD is longer in females compared to males, due to higher BMI (Landi 1998). Due to the rising numbers of overweight and obese American children and adolescents (Balistreri 2010), children's cumulative exposure to TCDD and related contaminants would also increase, with negative effects on their reproductive and hormonal systems and general metabolism.

Appropriate, balanced nutrition is important for human health from the moment of birth. Numerous studies have found that, despite the presence of industrial chemical contaminants in breast milk, breast- feeding remains an essential foundation for growth; resistance to infections; neurological development; and many other parameters of wellbeing (Massart 2008; Mead 2008). While scientific evidence indicates that the advantages of breast-feeding generally outweigh the health risks from contaminants, it is essential to work towards decreasing life-time exposures to these pollutants and thereby lessen infant ingestion of pollutants from breast milk (Gies 2007; WHO 2009).

2. At the current contamination levels of dioxins in food, the cancer risk is orders of magnitude above the EPA's benchmark one-in-one-million risk level that provides a reasonable certainty of no harm. Americans are routinely exposed to dioxins from popular foods at levels close to EPA's proposed reference dose.

Dioxin carcinogenicity to humans has been demonstrated by several large-scale occupational studies (Becher 1998; Cheng 2006; Ott 1996; Steenland 2001); cancer findings in the Seveso cohort (Pesatori 2009) and supporting animal data (La Merrill 2010; McGregor 1998; Steenland 2004). EWG agrees with EPA's scientific rationale for characterizing

TCDD as “carcinogenic to humans.” We find this description to be well supported by the multiple lines of evidence outlined in the EPA draft. The definition “carcinogenic to humans” would apply equally to intense exposures for people contaminated in workplace settings or industrial explosions, as well as for lower exposures from contaminated food typical for general population, as determined by the U.S. National Toxicology Program and the International Agency for Research on Cancer (IARC 1997; NTP 2005).

In the draft reanalysis, EPA determined an oral cancer slope factor of 1 x 106 per (mg/kg-day). After reviewing the EPA’s cancer risk assessment method, EWG agrees with the appropriateness of this slope factor and finds it consistent with carcinogenicity data from both human and animal studies.

In its earlier assessment, EPA estimated that dioxin exposures for the general population would be above the risk level that assures a reasonable certainty of no harm (one-in-a-million risk level) (U.S. EPA 1994). Same findings have been made by government agencies in other countries (Gies 2007). As reported by a study published in 1990s, based on the cancer slope factors from EPA’s 1994 assessment, 7,800-78,000 excess cancers over a lifetime could be attributed to dioxin exposure from food (Schecter 1997).

Studies of dioxin carcinogenicity published over the past decade only deepen concerns about dioxin’s toxicity and carcinogenicity. The table below presents some estimates for the excess number of cancer cases that would arise from the levels of dioxin exposure found in the general population.

Table III. Excess cancer risk associated with ingestion of dioxins (PCDD/F) from food for the U.S. population.

Exposed group	Daily ingestion dose for PCDD/F TEQ, pg/kg bw-day	Excess cancer risk, method 1 [a]	Number of cancer cases per million [b]	Excess cancer risk, method 2 [c]	Number of Americans developing cancer from dioxin exposure, per million people [b]
General population (FDA 2006)	0.32	2.1×10^{-4}	210	3.2×10^{-4}	320
General population, 95% exposure (Charnley 2006)	0.8-1.2 [d]	4.1×10^{-4} to 5.5×10^{-4}	410-550	8×10^{-4} to 12×10^{-4}	800-1200
At the draft RfD (EPA 2010)	0.7	3.7×10^{-4}	370	7×10^{-4}	700

Source: EWG analysis of cancer risk considering typical daily dioxin intakes and exposure factors from EPA, FDA and the peer-reviewed scientific literature.

Excess cancer risk (ER) calculated according to the formula ER = [exp(AUC*6.04E-6)*0.112-0.112]/0.888, as described in the EPA Draft Reanalysis Table 5-3.

This number of excess cancer cases corresponds to lifetime (70 years) exposure to dioxins.

Excess cancer risk (ER) according to the formula that utilizes Oral Slope Factor (OSF) of 1 x 106 per (mg/kg-day). OSF = 1E6*ER/daily ingestion dose (D), as described in the EPA Draft Reanalysis Table 5-3. Based on this formula, we calculated ER=OSF*D/1E6

Range of values for the PCDD/F TEQ ingestion described in footnote 2 in Table II above.

The excess cancer risk due to dioxin exposure represents a significant public health concern. As demonstrated by the data in Table III, excess lifetime cancer risk ranges from 320 to 1,200 per million people exposed. People within the highest 5% of dietary exposure to dioxin would face 2-4 fold greater cancer risk compared to the general population with average exposures. Across the population, the estimated cancer risk is 2 to 3 orders of magnitude above one-in-a-million cancer risk that regulatory agencies associate with a virtually safe dose for carcinogens in food (Edler 2005; Gaylor 1997; Wardlaw 1985). These findings clearly point to the urgent need for restricting dioxin exposures and decreasing the human health burden from dioxin contamination in food (WHO 2010).

EWG analysis of data from the peer-reviewed literature finds that a 130-pound adult eating a single hamburger or drinking two glasses of milk per day can be exposed to dioxin and dioxin-like compounds (PCDDs and PCDFs, excluding PCBs) at levels very close to EPA's proposed reference dose. For example:

One quarter-pound hamburger (90% lean ground beef) = 15% of the RfD for dioxin

Two 8-ounce glasses of whole milk = 17% of the RfD

One 4-ounce block of cheese = 39% of the RfD

One cheeseburger (1 ounce of cheese) and an 8-ounce glass of whole milk = 33% of the RfD

For this analysis, typical amounts of fat in the representative foods were identified from USDA and EPA reports as well as published literature (U.S. EPA 2003; USDA 2010a, b). Mean concentration of PCDD/PCDF TEQs in beef at 0.55 pg/gram lipid was reported in the 2007-2008 USDA survey of dioxins and furans in U.S. meat and poultry (Huwe 2009). Mean concentration of dioxins and furans in milk at 14.3 pg PCDD/F TEQs per liter was reported in the EPA's national survey of persistent, bioaccumulative, and toxic (PBT) pollutants in the United States milk supply (Schaum 2003).

According to EPA's estimates of TCDD carcinogenicity, these routine, daily exposures correspond to a cancer risk between 0.5x10-4 and 2.7x10-4, up to 270 times greater than the one-in-a-million cancer risk considered acceptable for the general population. Thus, these common foods that contain PCDD/F at levels close to, but below, the RfD would be associated with an incremental cancer risk well above the levels expected to provide a reasonable certainty of no harm.
3. EPA's proposed standards indicate a need for rapid action towards restricting dioxin exposures.

EWG commends EPA for preparing a thorough, rigorous, and scientifically justified risk assessment for TCDD and for developing an RfD and cancer slope factor based on the key studies published over the past five years. We also note that this year's external peer review of EPA's Draft Reanalysis is the fourth time that the Science Advisory Board has reviewed EPA's dioxin assessment, with the first one in 1988, followed by reviews in 1995, 2001, and the current, 2010 review.

Dioxins and related synthetic chemical pollutants accumulate in the bodies of people from daily ingestion of dioxin-contaminated fatty foods, such as beef, pork, poultry and other meats; milk and dairy products; fish; and eggs (FDA 2006; Lorber 2009; Schecter 2001; USDA 2009). Based on the National Health and Nutrition Examination Survey (NHANES) 2001-2002 data, EPA and USDA researchers determined that the blood levels of PCDD/F in the general population are in the range of 12.9-17.5 pg/g (on a lipid basis) and the background intake is ~ 0.5 pg TEQ/kg-day at the 50th percentile (Lorber 2009). Several research groups have reported that background human exposures from dioxins and other chemical pollutants in food have declined in the U.S. population over the past two decades (LaKind 2009; Patterson 2008). These findings are encouraging; yet, dioxins remain as persistent, highly toxic pollutants that threaten the health of all Americans and especially the health of infants and children.

TCDD may well be one of the most-studied chemical pollutants with an unprecedented range and depth of human and animal studies that have systematically explored various aspects of dioxin toxicity. As more research is done, scientists are finding dioxin to be more, not less toxic than what was determined by earlier studies. Thus, EWG urges the SAB to expedite its review process and help EPA finalize this important document that will serve as a cornerstone for the Agency's efforts to protect public health from chemical contaminants.

References for the attachment

Alaluusua S, Calderara P, Gerthoux PM, Lukinmaa PL, Kovero O, Needham L, et al. 2004. Developmental dental aberrations after the dioxin accident in Seveso. Environ Health Perspect 112(13): 1313-8.

Baccarelli A, Giacomini SM, Corbetta C, Landi MT, Bonzini M, Consonni D, et al. 2008. Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. PLoS Med 5(7): e161.

Balistreri KS, Van Hook J. 2010. Trajectories of Overweight Among US School Children: A Focus on Social and Economic Characteristics. Matern Child Health J: in press.

Becher H, Steindorf K, Flesch-Janys D. 1998. Quantitative cancer risk assessment for dioxins using an occupational cohort. Environ Health Perspect 106 Suppl 2: 663-70.

Birnbaum LS, Tuomisto J. 2000. Non-carcinogenic effects of TCDD in animals. Food Addit Contam 17(4): 275-88. Casanova JN, Olfenbuttel RF. 1987. Military Sites Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin: Permitting Remedial Action Research. In: Solving Hazardous Waste Problems: Learning from Dioxins (Exner JH, ed): American Chemical Society, 229-43.

Charnley G, Kimbrough RD. 2006. Overview of exposure, toxicity, and risks to children from current levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in the USA. Food Chem Toxicol 44(5): 601-15. Cheng H, Aylward L, Beall C, Starr TB, Brunet RC, Carrier G, et al. 2006. TCDD exposure-response analysis and risk assessment. Risk Anal 26(4): 1059-71.

Collins JJ, Bodner K, Burns CJ, Budinsky RA, Lamparski LL, Wilken M, et al. 2007. Body mass index and serum chlorinated dibenzo-p-dioxin and dibenzofuran levels. Chemosphere 66(6): 1079-85.

Edler L, Kitsos CP, eds. 2005. Recent Advances in Quantitative Methods in Cancer and Human Health Risk Assessment: John Wiley & Sons.

FDA. 2006. PCDD/PCDF Exposure Estimates from TDS Samples Collected in 2001-2004. Available: http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/ChemicalContaminants/DioxinsPCBs/ ucm077498.htm [accessed June 23, 2010].

Garabrant DH, Franzblau A, Lepkowski J, Gillespie BW, Adriaens P, Demond A, et al. 2009. The University of Michigan Dioxin Exposure Study: predictors of human serum dioxin concentrations in Midland and Saginaw, Michigan. Environ Health Perspect 117(5): 818-24.

Gaylor DW, Axelrad JA, Brown RP, Cavagnaro JA, Cyr WH, Hulebak KL, et al. 1997. Health risk assessment practices in the U.S. Food and Drug Administration. Regul Toxicol Pharmacol 26(3): 307-21.

Gies A, Neumeier G, Rappolder M, Konietzka R. 2007. Risk assessment of dioxins and dioxin-like PCBs in food-- comments by the German Federal Environmental Agency. Chemosphere 67(9): S344-9.

Huwe J, Pagan-Rodriguez D, Abdelmajid N, Clinch N, Gordon D, Holterman J, et al. 2009. Survey of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and non-ortho-polychlorinated biphenyls in U.S. meat and poultry, 2007-2008: effect of new toxic equivalency factors on toxic equivalency levels, patterns, and temporal trends. J Agric Food Chem 57(23): 11194-200.

IARC. 1997. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 69. Polychlorinated Dibenzo-para-Dioxins and Polychlorinated Dibenzofurans. Available: http://monographs.iarc.fr/ENG/Monographs/vol69/volume69.pdf [accessed July 6, 2010].

Kerger BD, Leung HW, Scott P, Paustenbach DJ, Needham LL, Patterson DG, Jr., et al. 2006. Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. Environ Health Perspect 114(10): 1596-602.

La Merrill M, Harper R, Birnbaum LS, Cardiff RD, Threadgill DW. 2010. Maternal dioxin exposure combined with a diet high in fat increases mammary cancer incidence in mice. Environ Health Perspect 118(5): 596-601.

LaKind JS. 2007. Recent global trends and physiologic origins of dioxins and furans in human milk. J Expo Sci Environ Epidemiol 17(6): 510-24.

LaKind JS, Berlin C, Sjodin A, Turner WE, Wang RY, Needham L, et al. 2009. Do Human Milk Concentrations of Persistent Organic Chemicals Really Decline During Lactation? Chemical Concentrations During Lactation and Milk/Serum Partitioning Environ Health Perspec 117(10): 1625-31.

LaKind JS, Berlin CM, Park CN, Naiman DQ, Gudka NJ. 2000. Methodology for characterizing distributions of incremental body burdens of 2,3,7,8-TCDD and DDE from breast milk in North American nursing infants. J Toxicol Environ Health A 59(8): 605-39.

LaKind JS, Hays SM, Aylward LL, Naiman DQ. 2009. Perspective on serum dioxin levels in the United States: an evaluation of the NHANES data. J Expo Sci Environ Epidemiol 19(4): 435-41.

Landi MT, Consonni D, Patterson DG, Jr., Needham LL, Lucier G, Brambilla P, et al. 1998. 2,3,7,8- Tetrachlorodibenzo-p-dioxin plasma levels in Seveso 20 years after the accident. Environ Health Perspect 106(5): 273-7.

Lorber M, Patterson D, Huwe J, Kahn H. 2009. Evaluation of background exposures of Americans to dioxin-like compounds in the 1990s and the 2000s. Chemosphere 77(5): 640-51.

Malisch R, van Leeuwen FXR. 2003. Results of the WHO-coordinated exposure study on the levels of PCBs, PCDDs and PCDFs in human milk. Organohalogen Compd 64: 136-40.

Massart F, Gherarducci G, Marchi B, Saggese G. 2008. Chemical Biomarkers of Human Breast Milk Pollution. Biomark Insights 3: 159-69.

McGregor DB, Partensky C, Wilbourn J, Rice JM. 1998. An IARC evaluation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis. Environ Health Perspect 106 Suppl 2: 755-60.

Mead MN. 2008. Contaminants in Human Milk: Weighing the Risks against the Benefits of Breastfeeding. Environ Health Perspec 116(10): A427-A34.

Mocarelli P, Gerthoux PM, Patterson DG, Jr., Milani S, Limonta G, Bertona M, et al. 2008. Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. Environ Health Perspect 116(1): 70-7.

Neville MC, Keller R, Seacat J, Lutes V, Neifert M, Casey C, et al. 1988. Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. Am J Clin Nutr 48(6): 1375-86.

NTP. 2005. National Toxicology Program 11th Report on Carcinogens. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD); "Dioxin". Available: http://ntp.niehs.nih.gov/index.cfm?objectid=32BA9724-F1F6-975E-7FCE50709CB4C932 [accessed July 7 2010].

Ott MG, Zober A. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med 53(9): 606-12.

Patterson DG, Jr., Turner WE, Caudill SP, Needham LL. 2008. Total TEQ reference range (PCDDs, PCDFs, cPCBs, mono-PCBs) for the US population 2001-2002. Chemosphere 73(1 Suppl): S261-77.

Pesatori AC, Consonni D, Bachetti S, Zocchetti C, Bonzini M, Baccarelli A, et al. 2003. Short- and long-term morbidity and mortality in the population exposed to dioxin after the "Seveso accident". Ind Health 41(3): 127-38.

Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. 2009. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ Health 8: 39.

Rappe C. 1990. Environmentally stable chlorinated contaminants from the pulp and paper industry. IARC Sci Publ(104): 341-53.

Ryan JJ, Lizotte R, Panopio LG, Shewchuk C, Lewis DA, Sun WF. 1993. Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) in human milk samples collected across Canada in 1986-87. Food Addit Contam 10(4): 419-28.

Schaum J, Schuda L, Wu C, Sears R, Ferrario J, Andrews K. 2003. A national survey of persistent, bioaccumulative, and toxic (PBT) pollutants in the United States milk supply. J Expo Anal Environ Epidemiol 13(3): 177-86.

Schecter A, Birnbaum L, Ryan JJ, Constable JD. 2006. Dioxins: an overview. Environ Res 101(3): 419-28.

Schecter A, Cramer P, Boggess K, Stanley J, Papke O, Olson J, et al. 2001. Intake of dioxins and related compounds from food in the U.S. population. J Toxicol Environ Health A 63(1): 1-18.

Schecter A, Olson JR. 1997. Cancer risk assessment using blood dioxin levels and daily dietary TEQ intake in general populations of industrial and non-industrial countries. Chemosphere 34(5-7): 1569-77.

Shibamoto T, Yasuhara A, Katami T. 2007. Dioxin formation from waste incineration. Rev Environ Contam Toxicol 190: 1-41.

Steenland K, Bertazzi P, Baccarelli A, Kogevinas M. 2004. Dioxin revisited: developments since the 1997 IARC classification of dioxin as a human carcinogen. Environ Health Perspect 112(13): 1265-8.

Steenland K, Deddens J, Piacitelli L. 2001. Risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on an epidemiologic study. Am J Epidemiol 154(5): 451-8.

Su PH, Chen JY, Chen JW, Wang SL. 2010. Growth and thyroid function in children with in utero exposure to dioxin: a 5-year follow-up study. Pediatr Res 67(2): 205-10.

U.S. EPA. 1994. Health assessment document for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds EPA/600/BP-92/001c. Available: http://cfpub.epa.gov/ncea/CFM/nceaQFind.cfm?keyword=Dioxin [accessed June 24, 2010].

U.S. EPA. 2003. Continuing Survey of Food Intakes by Individuals (CSFII) Analysis of Food Intake Distributrions EPA/600/R-03/029. Available: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=132295 [accessed July 2, 2010].

U.S. EPA. 2007. TRI Dioxin and Dioxin-like Compounds Toxic Equivalency (TEQ) Information Rule. Available: http://www.epa.gov/tri/lawsandregs/teq/teqprule.html [accessed July 7 2010].

U.S. EPA. 2009. Exposure Factors Handbook: 2009 Update EPA/600/R-09/052a. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=209866 [accessed June 23, 2010].

U.S. EPA. 2010. EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments (External Review Draft). Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=222203 [accessed July 7, 2010].

USDA. 2009. Dioxins and Dioxin-Like Compounds In the U.S. Domestic Meat and Poultry Supply. Available: http://www.fsis.usda.gov/factsheets/Dioxin_Resources/index.asp [accessed July 1, 2010].

USDA. 2010a. Ground Beef Calculator - User selects fat/lean percentage. Available: http://www.nal.usda.gov/fnic/foodcomp/cgi-bin/measure.pl?MSRE_NO=23999 [accessed July 6 2010].

USDA. 2010b. USDA National Nutrient Database for Standard Reference. Available: http://www.nal.usda.gov/fnic/foodcomp/search/ [accessed July 2 2010].

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, et al. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 106(12): 775-92.

Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, et al. 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93(2): 223-41.

Wang RY, Needham LL. 2003. Levels of polychlorinated dibenzo- p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) in human milk at two US locations [Abstract]. Journal of Toxicology—Clinical Toxicology 41(730).

Wardlaw GM. 1985. Assessing the cancer risk from foods. J Am Diet Assoc 85(9): 1122-7.

Weber R, Gaus C, Tysklind M, Johnston P, Forter M, Hollert H, et al. 2008. Dioxin- and POP-contaminated sites-- contemporary and future relevance and challenges: overview on background, aims and scope of the series. Environ Sci Pollut Res Int 15(5): 363-93.

White SS, Birnbaum LS. 2009. An overview of the effects of dioxins and dioxin-like compounds on vertebrates, as documented in human and ecological epidemiology. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 27(4): 197-211.

WHO. 2005. Project for the re-evaluation of human and mammalian toxic equivalency factors (TEFs) of dioxins and dioxin-like compounds. Available: http://www.who.int/ipcs/assessment/tef_update/en/ [accessed July 1 2010].

WHO. 2009. Biomonitoring of Human Milk for Persistent Organic Pollutants (POPs). Available: http://www.who.int/foodsafety/chem/pops/en/index.html [accessed July 1, 2010].

WHO. 2010. Dioxins and their effects on human health. Available: http://www.who.int/mediacentre/factsheets/fs225/en/ [accessed June 18 2010].

Wormley DD, Ramesh A, Hood DB. 2004. Environmental contaminant-mixture effects on CNS development, plasticity, and behavior. Toxicol Appl Pharmacol 197(1): 49-65.