

Environmental Chemicals in Breast Milk and Formula: Exposure and Risk Assessment Implications

Geniece M. Lehmann,¹ Judy S. LaKind,^{2,3} Matthew H. Davis,⁴ Erin P. Hines,¹ Satori A. Marchitti,⁵ Cecilia Alcala,⁶ and Matthew Lorber^{7†}

¹Office of Research and Development (ORD), U.S. Environmental Protection Agency (EPA), Research Triangle Park, North Carolina, USA

²LaKind Associates, LLC, Catonsville, Maryland, USA

³Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland, USA

⁴Office of Children's Health Protection, U.S. EPA, Washington, District of Columbia, USA

⁵Oak Ridge Institute for Science and Education (ORISE), ORD, U.S. EPA, Athens, Georgia, USA

⁶Association of Schools and Programs of Public Health (ASPPH), ORD, U.S. EPA, Washington, District of Columbia, USA

⁷ORD, U.S. EPA, Washington, District of Columbia, USA

BACKGROUND: Human health risk assessment methods have advanced in recent years to more accurately estimate risks associated with exposure during childhood. However, predicting risks related to infant exposures to environmental chemicals in breast milk and formula remains challenging.

OBJECTIVES: Our goal was to compile available information on infant exposures to environmental chemicals in breast milk and formula, describe methods to characterize infant exposure and potential for health risk in the context of a risk assessment, and identify research needed to improve risk analyses based on this type of exposure and health risk information.

METHODS: We reviewed recent literature on levels of environmental chemicals in breast milk and formula, with a focus on data from the United States. We then selected three example publications that quantified infant exposure using breast milk or formula chemical concentrations and estimated breast milk or formula intake. The potential for health risk from these dietary exposures was then characterized by comparison with available health risk benchmarks. We identified areas of this approach in need of improvement to better characterize the potential for infant health risk from this critical exposure pathway.

DISCUSSION: Measurements of chemicals in breast milk and formula are integral to the evaluation of risk from early life dietary exposures to environmental chemicals. Risk assessments may also be informed by research investigating the impact of chemical exposure on developmental processes known to be active, and subject to disruption, during infancy, and by analysis of exposure–response data specific to the infant life stage. Critical data gaps exist in all of these areas.

CONCLUSIONS: Better-designed studies are needed to characterize infant exposures to environmental chemicals in breast milk and infant formula as well as to improve risk assessments of chemicals found in both foods. <https://doi.org/10.1289/EHP1953>

Introduction

Because of the numerous established health benefits of breastfeeding for both children and their mothers (Section on Breastfeeding 2012; Ip et al. 2007; Victora et al. 2016), various programs of the United States government support and promote breastfeeding, as do many state and local government programs [U.S. Department of Labor 2015; U.S. Department of Health and Human Services (DHHS) 2010a, 2010b, 2014, 2015]. The promotion of breastfeeding is but one part of multifaceted efforts of the U.S. government to prioritize the improvement of maternal, infant, and child health (DHHS 2000, 2010b, 2011). In 1997, Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks tasked all federal agencies to make it a “high priority to identify and assess environmental health risks and safety risks

that may disproportionately affect children; and . . . ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks . . . (U.S. EPA 2017e).”

Achievement of these goals requires accurate determination of levels and types of environmental chemical exposures during infancy and childhood and assessment of potential health outcomes (Lehmann et al. 2014). A major environmental chemical exposure pathway for infants is via diet, either from breastfeeding or formula feeding. Breast milk is a complex and constantly changing mixture of endogenous substances including fats, water, proteins, carbohydrates, vitamins, minerals, and antibodies. In addition, chemicals from foods, pharmaceuticals, illicit drugs and alcohol, tobacco products, personal care products, and the environment in general are present in breast milk (Berlin et al. 2002). Formula is also complex and contains formula constituents in addition to those present in the water used to prepare the formula.

Assessing the potential for health risk to exist as a result of infant exposures to environmental chemicals in breast milk and/or infant formulas requires data on exposure (e.g., measurements of environmental chemicals in breast milk and infant formula and quantities of milk consumed) and exposure–response (e.g., identification and quantification of associations between exposure and health outcomes in humans and/or laboratory animals) as well as an understanding of the strengths and weaknesses of those data. In this paper, we describe available published information on the types and levels of environmental chemicals in breast milk and infant formula in the United States and discuss the use of models to study the potential for adverse health effects in infants from chemicals in breast milk. We then discuss the appropriate use of established benchmarks such as the reference dose (RfD) to understand the potential for health risk from infant dietary exposures. We evaluate three examples of published assessments that

Address correspondence to G.M. Lehmann, U.S. Environmental Protection Agency, MD B243-01, Research Triangle Park, NC 27711, USA. Telephone: (919) 541-2289. Email: Lehmann.Geniece@epa.gov

†Retired.

LaKind Associates (J.S.L.) is a private consulting firm specializing in strategic risk management, assessment of human exposures and health risks, biomonitoring, state-of-the-science reviews, and environmental regulatory review; LaKind Associates consults to governmental and private sectors. J.S.L.'s research for this manuscript was partially supported by the U.S. EPA. All other authors declare that they have no actual or potential competing financial interests.

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Table 1. Environmental chemical concentrations in breast milk samples collected from women in the U.S. in 2000–2014.

Chemical	Lowest reported median	Highest reported median	Years of sample collection	Number of women sampled (range of studies' <i>n</i>)	U.S. locations	References
Dioxin/furans and dioxin-like PCBs (ng/g lipid)			2004–2005	10	Pennsylvania	LaKind et al. 2009
1,2,3,6,7,8-HxCDD	0.011	NA				
1,2,3,4,6,7,8-HpCDD	0.011	NA				
OCDD	0.07	NA				
2,3,4,7,8-PnCdf	0.004	NA				
1,2,3,4,7,8-HxCDF	0.0019	NA				
1,2,3,6,7,8-HxCDF	0.0016	NA				
1,2,3,4,6,7,8-HpCDF	0.002	NA				
OCDF	0.00017	NA				
PCB-126	0.012	NA				
PCB-169	0.0074	NA				
PCBs (ng/g lipid) [ng/g milk in brackets]			2002–2007	10–304	California, Montana, North Carolina, Oregon, Pennsylvania, Washington	LaKind et al. 2008, 2009; She et al. 2007; Park et al. 2011; Pan et al. 2009, 2010; Weldon et al. 2011
PCB-28	2.12	2.78				
PCB-66	0.95	3.68				
PCB-74	2.08	6.4				
PCB-99	3.54	5.47				
PCB-105	1.65	1.90				
PCB-110	<LOD	3.48				
PCB-118	6.10 [0.0170]	7.97 [0.0928]				
PCB-138	[0.0382]	[0.183]				
PCB-138–158	11.2	20.47				
PCB-146	2.01	2.4				
PCB-153	17 [0.0436]	22.85 [0.242]				
PCB-156	2.04	5.39				
PCB-170	3.32	4.78				
PCB-177	0.58	0.86				
PCB-178	0.66	0.97				
PCB-180	7.78 [0.239]	10.6 [0.683]				
PCB-183	1.19	1.55				
PCB-187	2.79	3.66				
PCB-194	0.94	1.46				
PCB-196–203	1.07	1.63				
PCB-201	1.49	NA				
PCB-206	0.32	0.5				
Organochlorine pesticides (ng/g lipid) (μg/L in parentheses) [ng/g milk in brackets]			2002–2011	10–304	California, Georgia, Massachusetts, North Carolina, Pennsylvania	LaKind et al. 2008, 2009; Johnson-Restrepo et al. 2007; Chen et al. 2014; Pan et al. 2009, 2010; Weldon et al. 2011
Dacthal	[0.00279]	[0.00343]				
<i>p,p'</i> -DDD	2.7	NA				
<i>o,p'</i> -DDE	<0.6 (0.03) [0.00517]	NA [0.00565]				
<i>p,p'</i> -DDE	35.3 (1.37) [3.17]	142 [3.49]				
<i>o,p'</i> -DDT	0.5 (0.03) [0.0366]	NA [0.0624]				
<i>p,p'</i> -DDT	<0.6 [0.102]	5.46 [0.107]				
<i>p,p'</i> -dicofol	(0.11)	NA				
Endosulfan-α	<LOD	NA				
Endosulfan-β	<LOD	NA				
HCB	1.6 (0.66) [0.191]	9.0 [0.223]				
α-HCH	1.4	NA				
β-HCH	3.7 [0.220]	4.4 [0.443]				
γ-HCH (lindane)	<LOD	5.1				

Note: AHTN, 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene; BDE, brominated diphenyl ether; BPA, bisphenol A; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; Et-PFOA-AcOH, 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; HBDD, hexabromocyclododecane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HHCB, 1,3,4,6,7,8-hexahydro-4,6,6,7,8-hexamethylcyclopenta[*g*]-2-benzopyran; HpCDD, heptachlorodibenzo-*p*-dioxin; HpCDF, heptachlorodibenzofuran; HxCDD, hexachlorodibenzo-*p*-dioxin; HxCDF, hexachlorodibenzofuran; LOD, limit of detection; LOQ, limit of quantification; MCP, mono (3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; Me-PFOA-AcOH, 2-(N-methyl-perfluorooctane sulfonamido) acetic acid; NA, not available; OCDD, octachlorodibenzo-*p*-dioxin; OCDF, octachlorodibenzofuran; PCB, polychlorinated biphenyl; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluoro-*n*-nonanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFOA, perfluorooctane sulfonamide; PnCDF, pentachlorodibenzofuran; TBCD, tetrabromocyclododecane.

^aGeometric mean is reported.

^bAlthough breast milk levels of metals such as cadmium and mercury are available for other countries, no such published data for U.S. breast milk were found.

Table 1. (Continued.)

Chemical	Lowest reported median	Highest reported median	Years of sample collection	Number of women sampled (range of studies' n)	U.S. locations	References
δ-HCH	<1.6	NA				
Heptachlor epoxide	(0.97)	NA				
Mirex	0.5	0.84				
<i>trans</i> -Nonachlor	4.2	14.6				
<i>cis</i> -Nonachlor	2.6	NA				
Oxychlorane	3.8	13.65				
Brominated flame retardants (ng/g lipid)			2001–2007	10–304	California, Massachusetts, Montana, New Hampshire, North Carolina, Oregon, Pennsylvania, Texas, Washington	Marchitti et al. 2017 ; Daniels et al. 2010 ; Dunn et al. 2010 ; Wu et al. 2007 ; Johnson-Restrepo et al. 2007 ; LaKind et al. 2008, 2009 ; Schecter et al. 2003, 2005, 2006a, 2010a, 2010b ; Park et al. 2011 ; She et al. 2007 ; Adgent et al. 2014 ; Hoffman et al. 2012 ; Carignan et al. 2012
BDE-17	0.02	NA				
BDE-28	1.3	2.0				
BDE-47	7.7	31.5				
BDE-66	0.14	0.2				
BDE-77	<LOD	NA				
BDE-85	0.3	0.5				
BDE-99	1.5	6.4				
BDE-100	0.5	5.7				
BDE-138	0.19	NA				
BDE-153	1.1	8.0				
BDE-154	0.2	0.3				
BDE-183	0.06	0.2				
BDE-209	<LOD	1.41				
α-HBCD ^a	0.710	NA				
β-HBCD ^a	0.080	NA				
γ-HBCD ^a	0.200	NA				
TBCDs ^a	0.050	NA				
Phthalates (μg/L)			2002–2005	3–34	North Carolina, California	Hines et al. 2009 ; Calafat et al. 2004
MCPP	<LOD	NA				
MECPP	<LOD	NA				
MEHHP	<LOD	NA				
MEOHP	<LOD	NA				
Per- and polyfluoroalkyl substances (μg/L)			2004–2005	34–45	North Carolina, Massachusetts	von Ehrenstein et al. 2009 ; Tao et al. 2008a
PFHxS	<LOQ	0.01				
PFOA	<LOQ	0.04				
PFOS	<LOQ	0.11				
PFOSA	<LOQ	NA				
Et-PFOSA-AcOH	<LOQ	NA				
Me-PFOSA-AcOH	<LOQ	NA				
PFNA	<LOQ	0.007				
Phenols (μg/L)			2004–2010	4–34	North Carolina, Massachusetts, Georgia	Hines et al. 2015 ; Mendonca et al. 2014 ; Ye et al. 2006, 2008 ; Zimmers et al. 2014 ; Duty et al. 2013
Benzophenone-3	<LOD	0.7				
BPA	0.49	1.3				
2,4-Dichlorophenol	<LOD	NA				
2,5-Dichlorophenol	<LOD	NA				
4- <i>tert</i> -Octylphenol	<LOD	NA				
<i>ortho</i> -Phenylphenol	<LOD	2.2				
Triclosan	<LOD	2.05				
Parabens (μg/L)			2004–2007	4–8	North Carolina, Georgia	Hines et al. 2015 ; Ye et al. 2008
Benzyl paraben	<LOD	NA				
Butyl paraben	<LOD	NA				
Ethyl paraben	<LOD	NA				
Methyl paraben	0.72	1.1				
Propyl paraben	<LOD	0.3				
Perchlorate (μg/L)	3.3	14.2	2002–2011	10–457	California, Colorado, Connecticut, Florida,	Borjan et al. 2011 ; Pearce et al. 2007 ; Kirk et al. 2005, 2007, 2012 ;

Table 1. (Continued.)

Chemical	Lowest reported median	Highest reported median	Years of sample collection	Number of women sampled (range of studies' <i>n</i>)	U.S. locations	References
					Georgia, Hawaii, Maine, Maryland, Massachusetts, Michigan, Missouri, Nebraska, New Jersey, New Mexico, New York, North Carolina, Texas, Virginia, Washington, West Virginia	Dasgupta et al. 2008 ; Leung et al. 2012 ; Shelor et al. 2012
Thiocyanate (µg/L)	5.6	46.5	2008–2011	10–64	Colorado, Florida, Massachusetts, Missouri, New Mexico, North Carolina, Texas	Leung et al. 2012 ; Kirk et al. 2007
Metals ^b (µg/L)			2012–2013	9	New Hampshire	Carignan et al. 2015
Arsenic	0.31	NA				
Volatile organic compounds (µg/L)			2005	8	Maryland	Kim et al. 2007
Benzene	0.12	NA				
Chloroform	0.55	NA				
Methyl <i>tert</i> -butyl ether	0.09	NA				
Toluene	0.46	NA				
Organophosphates (µg/L) [ng/g milk in brackets]			2002–2011	10–34	California, Georgia	Chen et al. 2014 ; Weldon et al. 2011
Azinphos-methyl	0.39	NA				
Chlorpyrifos	0.06 [0.0245]	NA [0.0280]				
Chlorpyrifos-methyl	<LOD	NA				
Diazinon	0.04	NA				
Fonofos	<LOD	NA				
Pyrethroids (µg/L) [ng/g milk in brackets]			2002–2011	10–34	California, Georgia	Chen et al. 2014 ; Weldon et al. 2011
Cyfluthrin	<LOD	NA				
Cypermethrin	<LOD	NA				
Fenvalerate	<LOD	NA				
Permethrin	<LOD	NA				
<i>cis</i> -Permethrin	[0.0819]	[0.103]				
<i>trans</i> -Permethrin	[0.0931]	[0.176]				
Trichloroethylene (µg/L)	<LOD	NA	2010	20	Arizona	Beamer et al. 2012
Polycyclic aromatic hydrocarbons (ng/g lipid)			2005	12	Maryland	Kim et al. 2008
Anthracene	<LOD	NA				
Benzo[<i>a</i>]anthracene	<LOD	NA				
Dibenzo[<i>a,h</i>]anthracene	<LOD	NA				
Chrysene	<LOD	NA				
Fluoranthene	1.6	NA				
Benzo[<i>b</i>]fluoranthene	<LOD	NA				
Benzo[<i>k</i>]fluoranthene	<LOD	NA				
Fluorene	3.0	NA				
Benzo[<i>g,h,i</i>]perylene	<LOD	NA				
Phenanthrene	11.8	NA				
Pyrene	1.1	NA				
Benzo[<i>a</i>]pyrene	<LOD	NA				
Indeno[1,2,3- <i>cd</i>]pyrene	<LOD	NA				
Synthetic musk compounds (ng/g lipid)			2004	7–31	Massachusetts	Reiner et al. 2007
AHTN	18.6	53.0				
HHCB	121	136				
HHCB-lactone	<LOQ	58.3				
Musk ketone	22.2	58.2				
Musk xylene	17.0	39.7				

characterized infant exposure by combining breast milk or formula chemical concentrations with information on ingestion rate and duration to yield an estimate of a chemical-specific dose. In these examples, exposure estimates were compared with health risk

benchmarks in a simple risk assessment framework. Comparisons such as these can be useful for supporting risk management decisions to protect human health. For example, the results of risk assessments that include information on infant lactational exposures

may be used to set health-protective clean-up goals at hazardous waste sites, to track the effectiveness of environmental remediation efforts for reducing infant exposures and health risks, or to compare the potential health risks of emerging chemicals with those already found in the environment. We conclude the paper by offering suggestions for research that would improve future risk assessments for infant dietary exposures to environmental chemicals.

Methods

Throughout the paper, we define environmental chemicals as those found in exposure sources such as air, soil, water, personal care products, food and drinks, clothes, and furniture. Pharmaceuticals, illicit drugs, alcohol, and tobacco are not considered here; information on these substances has been published previously (Jansson 2009; Sachs and Committee on Drugs 2013). Also not considered were studies of essential nutrients, mycotoxins, substances related to spoilage, and chemicals intentionally added to foods. Our principal purpose is to describe breast milk and formula sources of infant exposure to environmental chemicals at levels of maternal exposure typically found in the present-day United States; therefore, we focus on recent (post-2000) sampling data [for more detailed information on international levels of environmental chemicals in breast milk, the reader is referred to LaKind et al. (2004, 2011) and Marchitti et al. (2013a)].

Peer-reviewed data on environmental chemicals in breast milk and formula were identified by searching PubMed and Web of Science (WoS) for publications appearing between 1 January 2000 and 31 December 2014. The following search strings were used to identify studies that measured environmental chemicals in breast milk:

- PubMed: (“human milk” [All Fields] OR “breast milk” [All Fields]) AND (“chemicals” [All Fields] OR “metals” [All Fields] OR “pesticides” [All Fields] OR “phytoestrogens” [All Fields] OR “volatile organic compounds” [All Fields] OR “BPA” [All Fields] OR “brominated flame retardant” [All Fields] OR “chlorpyrifos” [All Fields] OR “DDE” [All Fields] OR “DDT” [All Fields] OR “dieldrin” [All Fields] OR “dioxin” [All Fields] OR “furan” [All Fields] OR “organophosphate” [All Fields] OR “parabens” [All Fields] OR “PCB” [All Fields] OR “perchlorate” [All Fields] OR “perfluorinated chemicals” [All Fields] OR “phthalates” [All Fields] OR “phenol” [All Fields] OR “polybrominated diphenyl ether” [All Fields] OR “triclosan” [All Fields] OR “contaminants” [All Fields] OR “pollutants” [All Fields] OR “toxicants” [All Fields] OR “xenobiotics” [All Fields]) AND (“2000/01/01” [PDAT]: “2014/12/31” [PDAT]).
- WoS: TOPIC: [(“human milk” OR “breast milk”) AND (“chemicals” OR “metals” OR “pesticides” OR “phytoestrogens” OR “volatile organic compounds” OR “BPA” OR “brominated flame retardant” OR “chlorpyrifos” OR “DDE” OR “DDT” OR “dieldrin” OR “dioxin” OR “furan” OR “organophosphate” OR “parabens” OR “PCB” OR “perchlorate” OR “perfluorinated chemicals” OR “phthalates” OR “phenol” OR “polybrominated diphenyl ether” OR “triclosan” OR “contaminants” OR “pollutants” OR “toxicants” OR “xenobiotics”)], Time span: 2000–2014. Indexes: SCI-EXPANDED, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC.

Search strings used to identify studies measuring environmental chemicals in infant formula were as follows:

- PubMed: (“infant formula” [All Fields]) AND (“chemicals” [All Fields] OR “metals” [All Fields] OR “pesticides” [All Fields] OR “phytoestrogens” [All Fields] OR “volatile organic compounds” [All Fields] OR “BPA” [All Fields] OR “brominated flame retardant” [All Fields] OR “chlorpyrifos” [All Fields] OR “DDE” [All Fields] OR “DDT” [All Fields] OR

“dieldrin” [All Fields] OR “dioxin” [All Fields] OR “furan” [All Fields] OR “organophosphate” [All Fields] OR “parabens” [All Fields] OR “PCB” [All Fields] OR “perchlorate” [All Fields] OR “perfluorinated chemicals” [All Fields] OR “phthalates” [All Fields] OR “phenol” [All Fields] OR “polybrominated diphenyl ether” [All Fields] OR “triclosan” [All Fields] OR “contaminants” [All Fields] OR “pollutants” [All Fields] OR “toxicants” [All Fields] OR “xenobiotics” [All Fields]) AND (“2000/01/01” [PDAT]: “2014/12/31” [PDAT]).

- WoS: TOPIC: (“infant formula” AND (“chemicals” OR “metals” OR “pesticides” OR “phytoestrogens” OR “volatile organic compounds” OR “BPA” OR “brominated flame retardant” OR “chlorpyrifos” OR “DDE” OR “DDT” OR “dieldrin” OR “dioxin” OR “furan” OR “organophosphate” OR “parabens” OR “PCB” OR “perchlorate” OR “perfluorinated chemicals” OR “phthalates” OR “phenol” OR “polybrominated diphenyl ether” OR “triclosan” OR “contaminants” OR “pollutants” OR “toxicants” OR “xenobiotics”)), Time span: 2000–2014. Indexes: SCI-EXPANDED, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC.

Titles and abstracts of literature search results were then manually screened by two study authors (J.S.L. and G.M.L.) to include only those studies reporting data on measured levels of environmental chemicals in infant formula or milk from breastfeeding women in the United States. Studies were excluded if *a*) they did not measure and/or report levels of environmental chemicals in breast milk or infant formula; *b*) samples were collected outside the United States; *c*) the study’s primary purpose was analytical method development and it did not measure and/or report environmental chemical levels in unadulterated milk or formula samples; *d*) samples were collected before 1 January 2000; *e*) the study was a conference abstract or was not published in a peer-reviewed journal; *f*) milk was collected as part of a controlled-exposure study in which mothers were intentionally exposed to chemicals that were then measured in their breast milk; or *g*) samples were taken from a milk bank. Data from milk bank samples were not included because the provenance of the samples is generally not known.

Results

The PubMed and WoS searches for studies of breast milk yielded 1,145 and 1,931 citations, respectively, and the corresponding searches for studies of infant formula yielded 192 and 293 citations. Additional details (e.g., citations for each of the excluded studies) can be accessed via the online interactive figures: (https://public.tableau.com/views/EHP1953_HumanMilk/Dashboard1?:embed=y&:display_count=yes&publish=yes) and (https://public.tableau.com/shared/TZKYNH32Z?:display_count=yes). Citation titles and/or abstracts were reviewed to determine whether the articles met the inclusion criteria as described in the “Methods” section. After removal of duplicates (820 from the breast milk search, 91 from the formula search) as well as articles that did not meet inclusion criteria based on titles/abstracts (2,217 from the breast milk search, 386 from the formula search), 39 articles remained from the search for studies of breast milk and 8 remained from the search for studies of formula. These publications were initially identified as potentially containing relevant information based on the criteria given in the “Methods” section, and full articles were retrieved and reviewed. Review of publication bibliographies yielded an additional 6 citations on breast milk and 16 citations on formula, and those papers were retrieved. Of these 45 breast milk papers and 24 formula papers, studies were excluded when, upon review, it was determined that they did not contain relevant information or did not meet the inclusion criteria as described above (1 study from the breast milk search, 11 from the formula search). Forty-four publications on breast milk and 13 on formula were ultimately included. In the

Table 2. Environmental chemicals measured in infant formulas from the United States in 2000–2014.

Chemicals	U.S. locations	Formula type and number of samples (<i>n</i>)	Concentrations	Notes	References
PBDEs					
BDE-17, 28, 47, 66, 77, 85, 99, 100, 138, 153, 154, 183, 209	Texas	Constituted formula, <i>n</i> = 2	Sum PBDEs = 32 and 25 pg/g wet weight (ww)	BDEs detected in both samples	Schecter et al. 2006b
BDE-17, 29, 47, 49, 99, 100, 153, 183, 209		Widely used formula products, <i>n</i> = 12	Individual BDEs means: 1–84 pg/g; sum PBDEs mean: 127 pg/g Mean 21 pg/g	BDEs detected in: 1 of 12 (BDE-17) to 11 of 12 (BDE-209) samples Detected in 7 of 12 samples	Liu et al. 2014
Total DP			Mean 1 pg/g	Detected in 1 of 12 samples	
PBBZ			Mean 6 pg/g	Detected in 2 of 12 samples	
HBB			Mean 19 pg/g	Detected in 4 of 12 samples	
DBDPE					
Per- and polyfluoroalkyl substances					
PFOS, PFOA, PFHxS, PFNA, PFBS, PFHpA, PFDA, PFUnDA, and PFDoDA	Massachusetts and District of Columbia	Ready-to-use liquid formula, <i>n</i> = 10; powdered formula constituted, <i>n</i> = 9; concentrated liquid, constituted, <i>n</i> = 2	PFOS: 11.3 ng/L; PFHxS: 1.36 and 3.59 ng/L	PFOS detected in 1 sample and PFHxS detected in 2 samples. PFOA, PFNA, PFBS, PFHpA, PFDA, PFUnDA, and PFDoDA were not found above the LOQs	Tao et al. 2008b
BPA					
	District of Columbia, southern California, Arizona	Ready-to-feed, <i>n</i> = 40 (23 milk-based, 17 soy-based); liquid concentrate, <i>n</i> = 38 (25 milk-based, 13 soy-based)	Range: 0.48 to 11 ng/g		Ackerman et al. 2010
	New York	Unspecified type of formula, <i>n</i> = 7	High end of range: 20.8 ng/g	Highest BPA concentration found in a soy-based formula	Liao and Kannan 2013
	Texas	Three cans each of ready-to-use liquid formulas, two milk-based and one soy-based, <i>n</i> = 9	Mean of positive samples: 1.10 ng/g ww	BPA detected in 3 of 9 samples, 1 of 3 formulas; LOD = 0.2 ng/g ww	Schecter et al. 2010b
Parabens					
MeP, PrP, BuP, EtP, and BzP	New York	Formula type not specified, <i>n</i> = 5	MeP: range: 0.02 to 18.5 ng/g (median = 0.02 ng/g); PrP: similar results; BuP: 0.2 ng/g; EtP: 0.1 ng/g	Detected MeP in all 5 samples, PrP in 4 of 5 samples, BuP detected in 1 of 5 samples, EtP detected in 1 of 5 samples, BzP not detected; LOD = 0.005 ng/g	Liao et al. 2013
Perchlorate/thiocyanate					
		Powdered formula, 3 samples each of 5 brands, <i>n</i> = 15	Geometric mean, range, median µg/L milk-based: 1.72, 0.68–5.05, 1.37; soy-based: 0.21, 0.1–0.44, 0.24; milk-based, lactose-free: 0.27, 0.1–0.44, 0.24; elemental: 0.18, 0.08–0.4, 0.18		Schier et al. 2010
		Liquid formula, milk-based, <i>n</i> = 14; soy-based, <i>n</i> = 3	Range µg/L milk-based: 0.2–2.5; milk-based thickened with rice: 4.1 (<i>n</i> = 1); milk-based lactose-free: 0.4–1.5; soy-based: 0.3–0.6		Pearce et al. 2007
		Powdered formula, milk-based, <i>n</i> = 7; soy-based, <i>n</i> = 3	Range mg/kg: milk-based: 2.0–5.1 (detected and confirmed in 5 of 7 products); soy-based: ND		Niemann and Anderson 2008
Metals					
Arsenic, cadmium, lead, mercury, nickel		Variable sample numbers (<i>n</i>): arsenic (milk-based), 52; arsenic (soy), 32; cadmium (milk-based), 42; cadmium (soy), 32; lead (milk-based), 42; lead (soy), 32; mercury (milk-based), 24; mercury	Mean, mg/kg (LOD): arsenic (milk-based): 0 (0.01); arsenic (soy): 0.0003 (0.008); cadmium (milk-based): 0.0003–0.0004 (0.001); cadmium (soy): 0.001 (0.001); lead (milk-based): 0 (0.005);		FDA 2014

Note: BDE, brominated diphenyl ether; BPA, bisphenol A; BuP, butyl paraben; BzP, benzyl paraben; DBDPE, decabromodiphenyl ethane; DP, dechlorane plus; EtP, ethyl paraben; HBB, hexabromobenzene; LOD, limit of detection; LOQ, limit of quantification; MeP, methyl paraben; ND, not detected; PBBZ, polybromobenzene; PBDE, polybrominated diphenyl ether; PFBS, perfluorobutanesulfonic acid; PFDA, perfluorodecanoic acid; PFDoDA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluoro-*n*-nonanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFUnDA, perfluoroundecanoic acid; PrP, propyl paraben; SD, standard deviation; ww, wet weight.

Table 2. (Continued.)

Chemicals	U.S. locations	Formula type and number of samples (<i>n</i>)	Concentrations	Notes	References
		(soy), 16; nickel (milk-based), 42; nickel (soy), 32	lead (soy): 0.001 (0.004); mercury (milk-based): 0 (0.01); mercury (soy): 0 (0.01); nickel (milk-based): 0.002–0.004 (0.01); nickel (soy): 0.027 (0.009)		
Arsenic	New Hampshire	Milk-based, <i>n</i> = 9; nondairy-based, <i>n</i> = 6	2.2–12.6 ng/g total arsenic	Arsenic detected in all samples. For samples above 6 ng/g (9 of 15), speciation showed 100% inorganic arsenic	Jackson et al. 2012
Aluminum, antimony, arsenic, barium, beryllium, cadmium, lead, mercury, nickel, silver, strontium, thallium, tin, titanium, uranium, vanadium	Alabama	Powdered (2 milk-based, 2 soy-based)	μg/mL (mean ± SD): aluminum (milk-based): 0.15 ± 0.12; aluminum (soy-based): 0.46 ± 0.16; barium (milk-based): 0.02 ± 0.01; barium (soy-based): 0.05 ± 0.01; beryllium (milk-based): 0.0001 ± 0.0002; beryllium (soy-based): 0.0007 ± 0.00011; nickel (milk-based): 0.00002 ± 0.00007; nickel (soy-based): 0.002 ± 0.004; antimony (milk-based): 0.012 ± 0.019; antimony (soy-based): 0.014 ± 0.016; tin (milk-based): 0.085 ± 0.045; tin (soy-based): 0.085 ± 0.051; strontium (milk-based): 0.24 ± 0.06; strontium (soy-based): 0.17 ± 0.10; titanium (milk-based): 0.021 ± 0.007; titanium (soy-based): 0.034 ± 0.012; thallium (milk-based): 0.04 ± 0.02; thallium (soy-based): 0.026 ± 0.013; vanadium (milk-based): 0.0002 ± 0.0003; vanadium (soy-based): 0.003 ± 0.003; silver, arsenic, cadmium, mercury, lead, and uranium were not detected in any sample type		Ikem et al. 2002

following subsections, we describe the identified literature on measured concentrations of environmental chemicals first in breast milk and then in infant formula. [Tables 1](#) and [2](#) provide synopses of the information and details from studies identified in the literature searches, including chemical concentrations, number of samples, and formula type for infant formula studies.

Review of Infant Dietary Exposure Data

Both breast milk and infant formula may be sources of chemical exposure of infants. As described in this section, these forms of infant nutrition differ in the levels of chemicals present and in the origins of those chemicals. For example, certain persistent chemicals such as polychlorinated biphenyls (PCBs) and dioxins have been found at higher concentrations in breast milk as compared with formula ([Hsu et al. 2007](#); [Koopman-Esseboom et al. 1996](#); [Rogan et al. 1987](#)). In contrast, based on the minimal data available, bisphenol A (BPA) may be present at comparable concentrations (i.e., within an order of magnitude) in infant formula ([Ackerman et al. 2010](#); [Liao and Kannan 2013](#); [Schecter et al.](#)

[2010b](#)) and breast milk ([Hines et al. 2015](#); [Mendonca et al. 2014](#); [Ye et al. 2006, 2008](#); [Zimmers et al. 2014](#)) ([Tables 1](#) and [2](#)). Although it is the mother's exposure [mostly via diet ([von Goetz et al. 2017](#))] that leads to the presence of BPA in breast milk, BPA may enter formula by leaching from polycarbonate baby bottles or product packaging. This highlights the important point that formula-fed infants may be exposed to environmental chemicals derived from the constituted formula itself, from chemicals in water used to reconstitute powdered or liquid concentrate, or from chemicals that may have leached from the formula storage container or from the baby's bottle. To capture exposures for infants fed powdered and concentrated formulas, consideration must be given to chemical levels in the water used to reconstitute the formula ([Baier-Anderson et al. 2006](#)). For studies that address reconstituted formulas, it is generally not known whether the main source of the environmental chemical(s) is the formula itself or the water; one study described below found that arsenic concentrations were primarily from the water ([Carignan et al. 2015](#)).

Below, and in [Tables 1](#) and [2](#), we describe the available data on environmental chemicals in breast milk and formula. Lipophilic,

persistent environmental chemicals and, specifically, organohalogen [e.g., chlorinated dioxins and furans, PCBs, organochlorine pesticides, and polybrominated diphenyl ethers (PBDEs)] are the most commonly measured chemicals in breast milk; we describe information on these first. We then provide information on other classes of chemicals. Although our primary interest is in exposures in infants in the United States, little data are available for some chemicals in breast milk and/or formula, and study sample sizes are often small. Therefore, in the summaries below, we described information from other countries when it was valuable for completeness to provide some sense of the potential for chemicals to be found in breast milk or infant formula. We recognize that the data may not be representative of typical chemical types or levels found in the United States; therefore, these studies have not been included in [Tables 1 and 2](#).

Note that measurements of chemicals in infant formula are generally reported on a dry-weight basis when measured in powdered form, or on a whole-weight basis when reported as constituted or as a concentrate. For the summaries below, the basis of reporting was generally provided in the original study. For the few instances when this information was not given (e.g., the data are part of a larger food sampling program), it was assumed that the measurements were on a whole-weight basis, as constituted.

Environmental chemicals in breast milk and infant formula.

Dioxins/furans/PCBs. Bans and strict limitations on the use and release of dioxins, furans, and PCBs starting in the 1970s and continuing into the 2000s have resulted in decreased exposures ([LaKind 2007](#); [LaKind et al. 2001, 2004](#)). As a result, an international decline in concentrations in breast milk has been observed for these chemicals ([LaKind 2007](#); [LaKind et al. 2001](#)). Certain countries, such as Germany ([Fürst 2006](#); [Wilhelm et al. 2007](#)), Canada ([Ryan and Rawn 2014](#)), and Sweden ([Fång et al. 2013](#)), have been monitoring breast milk for a sufficiently long period of time to allow observations of country-specific declines in levels of dioxins and furans. For PCBs, Sweden ([Norén et al. 1996](#)) and Serbia ([Vukavić et al. 2013](#)) have reported declines in breast milk concentrations. The WHO has conducted international studies of persistent organic chemicals in breast milk since the late 1980s ([UNEP 2012](#)), and these studies have demonstrated a downward trend in levels of dioxins and furans ([van den Berg et al. 2017](#)). However, no similarly standardized and coordinated surveys of breast milk chemical concentrations are available for the United States with which to examine temporal trends. Data for dioxins, furans, and PCBs from U.S. breast milk samples collected since 1 January 2000 are shown in [Table 1](#). It is important to note that the data shown in [Table 1](#) are from small studies in limited geographic locales; thus, they are not representative of the U.S. population of breastfeeding women.

Although no U.S. studies of dioxins, furans, and PCBs in infant formula were identified post-2000, [Schechter et al. \(1989\)](#) measured dioxins and furans in three brands of soy-based infant formula and reported concentration data both in picograms per gram lipid and in toxic equivalents (TEQs). In the TEQ approach, a toxic equivalency factor (TEF) is used to express the relative potency of each chemical compared with that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The concentration of each dioxin-like chemical in a sample of interest, in this case infant formula, is multiplied by its TEF, and these values are summed to arrive at a TEQ for the sample. [Schechter et al. \(1989\)](#) reported the following levels for the three samples (although samples may have been contaminated by a bottle cap liner): 0.08, 0.05, 0.127 pg TEQ/g. More recent data are available from outside the United States. [Hsu et al. \(2007\)](#) measured dioxins and furans in both infant formula and breast milk samples in Taiwan in the early 2000s. They reported a mean concentration of 0.7 pg TEQ/g lipid in formula samples compared

with a mean of 14.7 pg TEQ/g lipid in breast milk. [Pandelova et al. \(2010\)](#) obtained and composited samples representing milk-based, soy-based, and hypoallergenic formulas from six countries in Europe. They reported levels of dioxins, furans, and dioxin-like PCBs as dry weights: 1.01–0.11 pg TEQ/g as dry-weight powder dioxins and furans, 0.0003–0.001 pg TEQ/g dry as dioxin-like PCBs. In the UK, the FSA ([2004](#)) reported a decline in measured upper-bound dioxin TEQs in milk and soy-based formula between 1998 and 2003. They reported the following concentration ranges for 1998 and 2003, respectively: 0.5–3.1 pg TEQ/g lipid and 0.2–0.4 pg TEQ/g lipid.

Organochlorine pesticides. Organochlorine pesticides that have been measured in breast milk include dichlorodiphenyltrichloroethane (DDT) and its metabolites, aldrin and its metabolite dieldrin, chlordanes (oxychlordane, heptachlor, γ -chlordane, *trans*-nonachlor), endosulfan, hexachlorocyclohexanes (HCHs), and mirex ([Jensen and Slorach 1991](#); [Marchitti et al. 2013a](#)). The use of these pesticides has been discontinued in many countries; thus, exposure is decreasing ([LaKind 2007](#); [LaKind et al. 2004](#)). However, although its use has been banned in the United States, in certain countries, DDT is still used for malaria control, and levels in breast milk may reflect current use ([Rodas-Ortiz et al. 2008](#)). As shown in [Table 1](#), only a few recent studies with a small number of women have reported data on organochlorine pesticides in the United States.

No U.S. data on this group of chemicals in infant formula was identified. In New Zealand, the organochlorine pesticides *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE), *p,p'*-DDT, and dieldrin were measured in a survey of 25 commercially available formula samples obtained in 1998 ([Cressey and Vannoort 2003](#)); the formula types included cow's milk-based, soy protein, protein hydrolysate, low-birth-weight, and follow-on formulas. Positive occurrences were infrequent (the highest detection frequency was 7 of 25 samples for *p,p'*-DDE), with all concentrations <0.7 $\mu\text{g}/\text{kg}$. In a multi-residue screen (which included organochlorine and organophosphorous pesticides, fungicides, and others) of five soy-based formulas, there was a single finding of 22 $\mu\text{g}/\text{kg}$ of azinphos-methyl.

Flame retardants. PBDEs, a class of brominated flame retardants, have been measured in breast milk. In contrast with dioxin-like compounds, data from Sweden indicate that breast milk PBDE levels increased between the 1970s and late 1990s as determined from pooled samples from the Mothers' Milk Center in Stockholm ([Meironyté et al. 1999](#)), and only declining post-1998 as determined from a study in Uppsala County, Sweden ([Lind et al. 2003](#)). Similar trends were observed in Germany ([Fürst 2006](#)). The reported increase brought a high degree of attention to this group of compounds; subsequently, data on PBDEs in breast milk samples in the United States were published. Breast milk samples from the United States, specifically from women in select cities in Texas ([Schechter et al. 2003](#)), had PBDE concentrations that were substantially higher than those from women in Europe ([Meironyté et al. 1999](#)) or Asia ([Inoue et al. 2006](#)). This difference in exposure is likely due to the higher use of PBDEs in U.S. products in compliance with California's TB 117 flame retardant standards. Although TB 117 is California state legislation, U.S. manufacturers typically applied these standards for furniture production nationwide so that they would not have to create multiple product lines. Historically, pentabromodiphenyl ether (pentaBDE) was primarily used in polyurethane foam for furniture and carpeting, whereas octaBDE was primarily used in electronic products; production of both mixtures was phased out from the European Union and U.S. markets in 2004, with alternative flame retardants used in their place. More recently, California's amendment TB 117-2013 smolder standard ([State of California 2013](#)) went into effect, requiring flame

resistance for furniture covering material but not the interior materials of a product like the foam of a chair, as was previously required. This could lead to the decreased use of PBDEs and flame retardants because the amendment can be met without the use of chemicals by selecting smolder-resistant fabrics. As shown in Table 1, several studies have measured PBDEs in breast milk in the United States, although, as with other breast milk studies, sample sizes are generally small and include limited geographic areas.

Only one U.S. study reported breast milk levels of brominated flame retardants other than PBDEs: tetrabromobisphenol-A (TBBP-A) and hexabromocyclododecanes (HBCDs) (Carignan et al. 2012). Forty-three samples were collected in 2004–2005 from women residing in and around Boston, Massachusetts. HBCDs were detected in all samples; detection frequencies for TBBP-A and HBCD degradation products ranged from 35% to 56% [limit of quantification (LOQ) = 30 pg/g lipid]. The authors did not calculate average concentrations for TBBP-A or pentabromocyclododecanes (PBCDs) because their detection frequencies were <50% (35% and 42%, respectively). Milk concentrations of TBBP-A ranged from <LOQ to 550 pg/g lipid; concentrations of PBCDs ranged from <LOQ to 320 pg/g lipid.

Two U.S. studies on PBDEs and alternative flame retardants in infant formula were identified: Liu et al. (2014) and Schecter et al. (2006b). Schecter et al. (2006b) reported on two constituted formula samples as part of a larger market basket survey, with the sum of measured PBDEs equal to 32 and 25 pg/g wet weight. Liu et al. (2014) reported results from 12 formula samples from the United States. They measured the suite of PBDE congeners as well as flame retardant alternatives such as Dechlorane Plus[®] [DP; Occidental Petroleum (Oxychem[®])], hexabromobenzene (HBB), pentabromobenzene (PBBZ), and decabromodiphenylethane (DBDPE). BDE 209 was above the limit of detection (LOD) in 11 of 12 samples; detection frequencies and concentrations were lower for other PBDE congeners. Substitutes were found at low frequencies (8–50%) and at concentrations <30 pg/g.

Phthalates and phthalate metabolites. Phthalates are manufactured and applied in the diester formulation; these along with the monoesters formed by metabolism can be measured in breast milk (Högberg et al. 2008). We did not include studies reporting diester phthalates in breast milk in Table 1 because the presence of diesters is the result of contamination of the milk sample from dust or other sources during collection or shipping (Hines et al. 2009). Monoester phthalates have been detected in <10% of breast milk samples in U.S. studies (Calafat et al. 2004; Hines et al. 2009). Other countries, such as Sweden (Högberg et al. 2008), Korea (Kim et al. 2015), and Canada (Zhu et al. 2006), have also reported measurable concentrations of phthalate monoesters in breast milk.

No data were found for phthalates in U.S. formulas, but studies were identified for surveys conducted in the UK in the 1990s (MAFF 1996, 1998) and in Italy (Cirillo et al. 2015) and Germany (Fromme et al. 2011) in the 2000s. In the UK, the Ministry of Agriculture, Fisheries, and Food (MAFF 1996, 1998) reported that only three of seven phthalates were detected in 27 of 39 formula samples (purchased as powdered or constituted), with diethylhexyl phthalate (DEHP) concentrations ranging from 0.05 to 0.44 µg/g. The mean concentration of DEHP in four samples of formula from Germany obtained in the early 2000s was 0.019 µg/g (Fromme et al. 2011). In Italy, DEHP was detected in 40 of 50 formula samples (obtained in 2013), with a median concentration of 1.14 µg/g (Cirillo et al. 2015).

Per- and polyfluoroalkyl substances. Per- and polyfluoroalkyl substances (PFASs) are synthetic organofluorine protein-bound surfactants that are not typically found in appreciable concentrations in human lipids but are ubiquitous in the serum of U.S.

individuals; the most commonly measured PFASs in breast milk are perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) (Kärman et al. 2007). In a study of 34 women in the United States, von Ehrenstein et al. (2009) reported that PFASs were below the LOD in most milk samples. Tao et al. (2008a) reported PFASs—including PFOS, PFOA, perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA)—in a majority of U.S. milk samples ($n = 45$) at levels greater than the LOD. Results from outside the United States confirm the potential for PFASs to be found in breast milk. PFOS and PFHxS were measured above the LOD in breast milk samples from 10 donors in Spain (Kärman et al. 2010), PFOS and PFOA were detected in 100% and 16% of 70 milk samples from Germany and Hungary (Völkel et al. 2008). So et al. (2006) reported detectable levels of various PFASs in all samples from China [PFOS, PFOA, PFHxS, PFNA, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), $n = 19$]. In addition, in Swedish milk samples, PFOS, PFHxS, perfluorooctane sulfonamide (PFOSA), PFNA, and PFOA were above the LOD in 100, 100, 67, 16, and 8% of samples, respectively ($n = 12$) (Kärman et al. 2007).

Only one study was identified on levels of PFASs in formula in the United States (Tao et al. 2008b). Nine PFASs were measured in 21 samples obtained from Massachusetts. According to the authors, most of the formulas were milk- or soy-based, and were packaged as a powdered form or ready-to-use or concentrated liquids. PFOS was detected in one sample (11.3 ng/L), whereas PFHxS was detected in two samples (1.36 and 3.59 ng/L).

Phenols. BPA has been reported in breast milk samples in the United States (Table 1). Total BPA (free plus conjugated) was detected at a frequency of 75% ($n = 27$) to 100% ($n = 4–30$) (Duty et al. 2013; Mendonca et al. 2014; Ye et al. 2008), and free BPA was detected in 20% ($n = 27$) to 100% ($n = 4$) (Mendonca et al. 2014; Ye et al. 2008) of samples. In terms of assessing infant exposures via breastfeeding, it is important to note that measurements from the same mothers at two time points revealed considerable variation in BPA concentration (Hines et al. 2015). Other phenolic compounds, including the ultraviolet-blocking compound benzophenone-3, the antibacterial triclosan, 2,4-dichlorophenol, *ortho*-phenylphenol, and 4-*tert*-octylphenol have also been reported in measurable concentrations in human milk samples from the United States (Table 1). Detection frequencies ranged from 25% ($n = 4$) to 60% ($n = 20$) for benzophenone-3 (Ye et al. 2006, 2008), from 38% ($n = 10$) to 50% ($n = 4$) for triclosan (Hines et al. 2015; Ye et al. 2008), and from 25% ($n = 4$) to 85% ($n = 20$) for *ortho*-phenylphenol (Ye et al. 2006, 2008). In a study of 9 women, 11% of breast milk samples had detectable concentrations of 2,4-dichlorophenol (Hines et al. 2015), and 4-*tert*-octylphenol was found in 25% of samples from 20 women (Ye et al. 2006).

Three U.S. studies on BPA in infant formula were identified (Ackerman et al. 2010; Liao and Kannan 2013; Schecter et al. 2010b). Schecter et al. (2010b) sampled three different canned constituted brands of formula (two milk, one soy; $n = 3$ for each brand). BPA was above the LOD (0.20 ng/g wet weight) in 3 samples corresponding to one of the milk-based products (mean of approximately 1 ng/g wet weight) and below the LOD in all other samples. Liao and Kannan (2013) analyzed 7 samples of infant formulas and reported the highest concentration in a soy-based infant formula (20.8 ng/g). Ackerman et al. (2010) reported BPA concentrations in formula samples from five manufacturers, including both milk- and soy-based ready-to-feed, liquid concentrates, and powdered formulations packaged in containers of different sizes and materials and sold in southern California and Arizona or in the District of Columbia. Only 1 of 26 samples of reconstituted powdered formula contained BPA above the LOD (0.15 ng/g). BPA concentrations in ready-

to-feed and liquid concentrate formulas varied by manufacturer and by the surface area-to-formula mass ratio of the container.

Parabens. Parabens have been measured in breast milk in two U.S. studies (Hines et al. 2015; Ye et al. 2008). In both studies, butyl paraben (BuP) was below the detection limit in all samples; ethyl (EtP), methyl (MeP), and propyl (PrP) parabens were above the LOD of 0.1 µg/L in samples in the study by Hines et al. (2015) (50, 100, and 100% of the eight samples, respectively).

One U.S.-based study on parabens in infant formulas was identified. Liao et al. (2013) included 5 infant formula samples in a study of 267 food samples from Albany, New York, for paraben compounds, including MeP, EtP, PrP, BuP, and benzyl paraben (BzP). One sample had higher levels of parabens compared with the other 4 samples (BuP: 0.2, EtP: 0.1, MeP: 18.5, PrP: 18.6 ng/g whole weight). For the remaining 4 samples, MeP was above the LOD (0.03 to 2.2 ng/g), and PrP was above the LOD in 3 of those samples (0.01 to 1.6 ng/g).

Perchlorate/thiocyanate. Perchlorate—which occurs naturally in the environment, especially in arid regions, and is also manufactured for use in the defense and aerospace industries (Kirk et al. 2012; Leung et al. 2012; Pearce et al. 2007)—has been found to be ubiquitous in U.S. breast milk (Table 1). Perchlorate and chemicals with similar properties, such as thiocyanate, are believed to inhibit iodide transport to the thyroid gland (which may lead to a reduction in thyroid hormone production) and to breast milk (which may reduce the availability of iodine for breastfed infants) (Dasgupta et al. 2008). Of the U.S. studies that measured perchlorate in breast milk, three also measured breast milk iodine levels and found them to be insufficient to meet infants' requirements in 46–92% of the women studied (Dasgupta et al. 2008; Kirk et al. 2007; Pearce et al. 2007). Kirk et al. (2005) found an inverse association between breast milk perchlorate and iodide levels in women with breast milk perchlorate levels >10 µg/L ($n = 6$). However, in a larger study, Pearce et al. (2007) did not find a correlation between breast milk iodine and perchlorate concentrations either in their full study population of 49 women or in 23 women with breast milk perchlorate levels >10 µg/L.

Two U.S. studies included data on perchlorate concentrations in powdered infant formula, while one included data on thiocyanate. A U.S. study from the CDC measured perchlorate concentrations in various infant formulas bought in 2006 (cow's milk-based with lactose, soy-based, cow's milk-based but lactose-free, and elemental formulas) (Schier et al. 2010). All of the powdered infant formulas contained perchlorate; the cow's milk formula with lactose had significantly higher concentrations of perchlorate [geometric mean (GM): 1.72 µg/L, range: 0.69–5.05] than the other types of formula (GMs: soy: 0.21, lactose-free: 0.27, elemental: 0.18 µg/L). A separate study from Boston in 2002–2006 found perchlorate in all of the 17 liquid infant formulas measured, with concentrations ranging from 0.2 to 4.1 µg/L (Pearce et al. 2007). A U.S. Food and Drug Administration (FDA) study measured thiocyanate concentrations in 7 milk- and 3 soy-based powdered formulas (Niemann and Anderson 2008). Thiocyanate was detected and confirmed in 5 of the milk-based formulas but not in any of the soy-based formulas (LOQ = 0.2 mg/kg powder).

Metals. Although various metals [e.g., lead, cadmium, and mercury] have been measured in breast milk samples from several countries (García-Esquinas et al. 2011; Ursinyova and Masanova 2005), almost no data were found for breast milk in the United States post-2000 (Table 1). Although drawn from a very small sample, the low levels of arsenic in breast milk reported by Carignan et al. (2015) comport with other international studies indicating low levels of arsenic in breast milk even among women with high drinking-water exposures to arsenic. The Camden Study of Calcium Metabolism in Pregnancy and

Lactation (1997–2000) reported mean concentrations of lead in breast milk samples from 15 breastfeeding New Jersey mothers of 0.61, 0.56, 0.59, and 0.43 µg/dL at 1.5-, 3-, 6-, and 12-month postpartum collection periods, with corresponding mean maternal blood lead concentrations of 1.4, 1.6, 1.7, and 1.4 µg/dL, respectively (Sowers et al. 2002). For mercury in breast milk, a mean level of 1.19 µg/L (range, 0.012–6.44) was reported in a study from Saudi Arabia (Al-Saleh et al. 2013), similar to the mean and range in an earlier study in Austria (Gundacker et al. 2002).

Concentrations of total arsenic ranged from 2.2 to 12.6 ng/g in 15 samples of powdered formula in the United States (Jackson et al. 2012). Milk-based formula contained significantly less arsenic than nondairy formulas (Jackson et al. 2012). Ikem et al. (2002) measured levels of arsenic as well as 15 other nonessential elements in two brands of milk-based and two brands of soy-based powdered infant formulas purchased in Auburn, Alabama. Arsenic was not detected in any of the samples (LOD not reported), nor were silver, cadmium, mercury, lead, or uranium. However, as with the findings for arsenic reported by Jackson et al. (2012), some of the other elements measured (aluminum, barium, nickel, and vanadium) were found at higher concentrations in the soy-based formulas compared with the milk-based formulas. Additional information on metals in infant formula in the United States is available from the FDA's Total Diet Study (FDA 2014). The Total Diet Study monitors levels of about 800 chemicals (including nutrients) in about 280 foods and beverages in the average U.S. diet. Infant formula (milk- and soy-based ready-to-feed) has been part of the study in recent years. From 2006 to 2013, analysis of chemicals in infant formula (number of samples from <10 to 24 total per chemical) was limited to elements and metals, including arsenic, mercury, cadmium, lead, and nickel. Measurements were mostly below the LOD (Table 2).

Volatile organic compounds. One U.S. study measured volatile organic compounds (VOCs) [methyl *tert*-butyl ether (MTBE), chloroform, benzene, and toluene] in breast milk collected from three women living in Baltimore, Maryland ($n = 8$ samples) (Kim et al. 2007). The authors also measured indoor air concentrations of these four chemicals during the milk sample collection period and estimated infant exposures from both breastfeeding and inhalation. Inhalation exposure was estimated to exceed breastfeeding exposure by 25- to 135-fold.

Although the FDA's Total Diet Study did not measure organic chemicals in formula after the 2003–2004 sampling year, in a summary of data between the 1991–1993 and 2003–2004 samplings, benzene, chloroform, styrene, and toluene were quantified above trace levels in milk-based formula (FDA 2014); of the 44 milk-based samples measured in that time frame and analyzed for these organics, <10% contained levels above the LOD (detection limit of 5 ppb), with a maximum of 25 ppb for chloroform (FDA 2014). Similar results were found for soy-based formula (FDA 2014).

Other chemicals. Other chemicals measured in breast milk in the United States include organophosphates (Chen et al. 2014; Weldon et al. 2011), pyrethroids (Chen et al. 2014; Weldon et al. 2011), trichloroethylene (Beamer et al. 2012), polycyclic aromatic hydrocarbons (Kim et al. 2008), and synthetic musk compounds (Reiner et al. 2007) (Table 1). These databases are small, and corresponding U.S. studies of these chemicals in infant formula are not available.

Phytoestrogens (found in soy formulas). Soy protein-based formulas are often used either as a milk substitute for infants unable to tolerate a cow's milk protein-based formula or simply by preference, accounting for as much as 25% of the formula market (Bhatia et al. 2008). These formulas are rich in naturally occurring phytoestrogens, particularly isoflavones, which are found in legumes such as soybeans. Infant exposures to some isoflavones (e.g., daidzein,

genistein, and equol) have been assessed (Cao et al. 2009), but the published literature on this subject is limited.

Discussion

Concentration data for environmental chemicals in breast milk and infant formula can be used to assess infant exposures (both as intake or dose and levels that may accumulate in the bodies of infants) as well as potential for adverse health outcomes (i.e., risk assessment). Approaches to utilizing concentration data for these public health purposes are described here as well as the strengths and limitations of the available data.

Exposure assessment using breast milk/formula chemical concentrations

Infant dietary exposure can be assessed using chemical concentrations in breast milk or formula in combination with estimates of breast milk or formula consumption rates. A potential average daily dose (ADD) from ingestion of human milk may be estimated according to guidance provided in the U.S. Environmental Protection Agency's (EPA) *Child-Specific Exposure Scenarios Examples* (U.S. EPA 2014), using estimates of chemical concentration in milk (e.g., Table 1) and human exposure factors (U.S. EPA 2011). Limited infant formula intake rate data have also been presented by the U.S. EPA (2011). Use of this guidance is generally appropriate, but some considerations may be important when assessing exposures to certain chemicals.

When estimating infant exposures based on chemical concentrations in breast milk, it is common to assume that the chemical concentration is constant in human milk throughout the breastfeeding period. However, chemicals in breast milk have varying pharmacokinetic properties: Some are persistent (with physiologic half-lives of up to years), whereas others are transient (with half-lives in humans of hours, days, or weeks). Even for persistent chemicals, it can be challenging to predict trends in breast milk levels during lactation (Hooper et al. 2007; LaKind 2007; LaKind et al. 2004, 2009). In addition, when exposure estimates are calculated on a lipid-adjusted basis (e.g., for lipophilic chemicals), uncertainty is introduced by the lipid content correction because the lipid content of human milk changes across the duration of breastfeeding, and even over the course of a single feeding (ICF 2013; LaKind et al. 2004).

Modeling to estimate chemical levels in breast milk

Our ability to assess infant exposure via breastfeeding is limited when breast milk chemical concentration data are lacking, and alternative methods for estimating exposures are needed. One approach involves developing models that extrapolate chemical concentration data in a surrogate or alternative matrix such as maternal serum to predict levels in breast milk using chemical-specific serum:milk partitioning ratios.

Data on chemicals in serum are plentiful because of the proliferation of worldwide efforts to characterize human exposure to chemicals by the measurement of these chemicals in blood and serum. These data can be developed in the context of characterizing exposure for specific groups of people as reported, for example, in epidemiological studies, but more germane to this manuscript are efforts to characterize background, general-population exposure to chemicals. The United States has several years of nationally representative data on many persistent chemicals in serum from its National Health and Nutrition Examination Surveys (NHANES), and these surveys are continuing to produce such data (CDC 2018). Risk assessors have historically assumed that, at steady state, lipophilic and persistent chemicals partition to lipid stores in the body equally, such that the lipid-based concentration in one

matrix, such as serum, can be assumed to be equal to the lipid-based concentration in a different matrix, such as breast milk (LaKind et al. 2009). However, the science has since advanced and recent studies suggest that this approach, although a reasonable starting point for drawing conclusions when no other data are available, is too simplistic and does not accurately take into account what is now understood about the complexities of chemical partitioning (LaKind et al. 2009; Manneje et al. 2012; Marchitti et al. 2013a, 2013b). A recent review of available chemical partitioning data from 13 studies of persistent lipophilic organic chemicals, including polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzo-*p*-furans (PCDFs), PCBs, PBDEs, and organochlorine pesticides, reported that mean serum:milk ratios ranged from 0.7 to 25 among a comprehensive list of specific congeners, with ratios <1 indicating greater chemical distribution into milk as compared with serum (Manneje et al. 2012). The majority of congeners appear to have mean serum:milk ratios that range more narrowly (e.g., between 0.7 and 2). Only two congeners had reported ratios above 3.0: octachlorodibenzo-*p*-dioxin (OCDD) at 5.5, and BDE 209 at 25.0, representing the highest halogenated compounds within the class. Indeed, lower halogenated congeners (i.e., tri- through hexa-substituted) appear to more readily distribute into breast milk, than do congeners with greater halogenation, such as OCDD and BDE 209. This is evident from recent studies of PBDEs where tri- through hexa-substituted congeners (e.g., BDE-28, BDE-47, and BDE-100) generally partition into milk at higher concentrations than in serum, whereas octa- through deca-substituted congeners partition into serum at higher concentrations than milk (Inoue et al. 2006; Marchitti et al. 2013b; Schecter et al. 2010b), with deca-PBDE (BDE-209) demonstrating a mean serum:milk ratio of 25 across 13 studies (Manneje et al. 2012).

In addition to halogenation, other physicochemical properties have been shown to influence partitioning between maternal serum and breast milk, including molecular weight, molecular size, steric hindrance, and lipophilicity (Needham et al. 2011). Congeners that display a greater propensity to distribute into breast milk over serum should be carefully evaluated when determining infant exposure from breastfeeding. To measure the most accurate serum:milk partitioning ratios, careful consideration should be given to study design—milk and serum samples should be taken sufficiently postpartum (after the milk supply has been adequately established), and as close in time as possible from the same woman (i.e., within 1–2 h)—due to differences in day-to-day exposure patterns and physiological changes during pregnancy and lactation that may affect chemical concentrations (Aylward et al. 2003; Marchitti et al. 2013b). Prior to 2006, few data were available for persistent chemicals that fit these criteria. However, recent high-quality data available for PBDEs (LaKind et al. 2009; Schecter et al. 2006a, 2010b) were used to develop congener-specific models for estimating nationally representative breast milk PBDE concentrations in the U.S. population from the NHANES serum concentrations for women of childbearing age (Marchitti et al. 2013b). Additional partitioning data for other environmental chemical classes (e.g., phenols, phthalates) from these and other studies have recently become available and are currently being used to better understand factors that drive the extent of chemical partitioning (Hines et al. 2009, 2015; LaKind et al. 2009; von Ehrenstein et al. 2009).

Levels of persistent environmental chemicals in infants

Infant exposure to persistent environmental chemicals is studied not only by measuring chemical concentrations in milk and formula but also by measuring and modeling levels in infants. The results from both biomonitoring and modeling studies have observed that infants exposed to lipophilic, persistent environmental chemicals during breastfeeding have higher levels in their bodies compared with

infants who are formula fed; this comports with reported concentrations of some lipophilic, persistent environmental chemicals being higher in breast milk compared with infant formula (Koopman-Esseboom et al. 1996; Rogan et al. 1987).

Biomonitoring. Some examples of studies using biomonitoring of infant serum to compare infant exposures to persistent lipophilic chemicals from breastfeeding versus formula feeding follow. Abraham et al. (1994) compared uptake by a formula-fed infant and a breastfed infant; the relative amount of dioxins absorbed by the infant from formula was comparable to that from breast milk (i.e., both infants absorbed over 90% of the dioxin in the formula and breast milk). Although absorption was similar for the two exposure sources, there was a substantially higher total exposure through breast milk due to the higher concentrations in breast milk (Abraham et al. 1994). Carrizo et al. (2007) observed that despite a relatively short lactation period (about 4.5 months on average), PBDE levels in the serum of 4-y-old children were higher among breastfed infants compared with formula-fed infants. Toms et al. (2009) used pooled serum samples to characterize the levels of PBDEs in the Australian general population, including infants. They compared PBDE concentrations for the age ranges of 0–2, 2–6, 7–12, 13–30, and >31 years and reported that the highest concentration of PBDEs was in the 2- to 6-y age range, well above the age when breastfeeding ceases. Toms et al. (2009) suggested that in addition to the exposures from breastfeeding, young children may have higher exposures compared with infants or adults and/or reduced elimination capacities.

Modeling. Models that have been developed to explore infants' levels of lipophilic persistent chemicals (e.g., dioxins, PCBs, PBDEs, organochlorine pesticides) for both breast milk and formula sources of exposure (LaKind et al. 2000; Lorber and Phillips 2002; Toms et al. 2008) predict a decline in infant levels after cessation of breastfeeding with convergence over time with levels found in formula-fed infants. The models referenced here used a simple one-compartment, first-order pharmacokinetic (PK) model in which the single compartment is body lipids (treated as a single reservoir) and the mass of chemical in this reservoir is assumed to decline following first-order kinetics. Lorber and Phillips (2002) conducted model evaluations using specific mother–infant paired data on dioxins and also studied the difference in the increase of infant and toddler dioxin levels in a breastfeeding scenario compared with a formula-only scenario. They found concurrence in their mother–child pair modeling.

Risk Assessment Methods Applied to Infant Dietary Exposures

Human health risk assessment integrates exposure and exposure–response data to predict the potential for health hazard from chemical exposures (NRC 1983). Accordingly, exposure information, such as that provided above, is critical for understanding the potential for health risks associated with chemicals in breast milk or infant formula. Also critical is information on health outcomes that may occur with a given level of exposure. Without such exposure–response information, it is difficult to interpret the significance of the breast milk and formula chemical measurements presented in Tables 1 and 2. A risk assessment conducted for a specific population or community might consider information on exposures at all life stages and from all exposure sources (e.g., ingestion of food, soil, and dust, inhalation of air and dust, and dermal contact with contaminated surfaces) (U.S. EPA 1989). However, the focus of this paper is on the assessment of risk during the infant life stage from dietary exposures to chemicals (i.e., chemicals in breast milk and formula). Our intent is to provide information that will support the improvement of this one specific piece of a larger risk assessment effort. To that end, we will tailor our discussion specifically

to address issues associated with assessing dietary exposure and exposure–response during infancy and childhood.

Human health risk assessment methods, policies, and tools have advanced over time to more accurately estimate risks to infants, including the U.S. EPA's development of a framework to address risks from early life stage exposures, such as those that may occur through breastfeeding or formula feeding (Cohen Hubal et al. 2008; Makris et al. 2008; U.S. EPA 2006). However, many challenges remain, such as default assumptions or values that do not aptly model infants, and gaps in understanding about developmental windows of susceptibility, chemicals' effects on developmental processes, childhood origin of adult disease, and infant exposures via breast milk or formula (LaKind et al. 2005; Landrigan 1999; Landrigan et al. 2002; Lehmann et al. 2014). It has been our experience that current human health risk assessment approaches are not designed to explicitly address the interests of breastfed or formula-fed infants, who may be vulnerable to increased health risk as a result of elevated exposure and/or increased sensitivity to environmental chemical exposures. Also, human health risk assessment approaches usually do not incorporate the health benefits associated with breastfeeding (Section on Breastfeeding 2012; Ip et al. 2007) that may counteract potential negative aspects of environmental chemical exposures.

Here, we describe risk assessment practices that have been used to predict the potential for health outcomes to occur as a result of infant exposures to chemicals in breast milk or formula (Coakley et al. 2013; Llorca et al. 2010). Our goal is to highlight important data gaps and uncertainties that may preclude an adequate characterization of risk in this context. Exposure and exposure–response information may be integrated by comparing an ADD with a health risk benchmark, such as an RfD or a tolerable daily intake (TDI) (NRC 2009). These benchmarks, or reference values, are derived from studies demonstrating a noncancer hazard from chemical exposure. They are often based on the assumption that there is a threshold dose below which no significant health effects occur (NRC 2009). As exposure–response assessment methods continue to advance, reliance on the threshold assumption may diminish as it becomes more common for noncancer health risk to be quantified in terms of a probability of risk associated with a given level of exposure; this would provide more information to support risk management decisions and may better reflect the observation that some associations between exposure and noncancer health effects are linear at low doses (NRC 2009). As new data become available, reference values may also incorporate increasingly precise estimates of the impacts of human variability and uncertainty on risk (NRC 2009). In any case, when using a reference value to support a human health risk assessment, especially for a specific population or life stage with unique sensitivity or susceptibility to the potential effects of exposure, we consider it important to understand the data underpinning the value, the overall database of information on the chemical(s) that was considered during reference value derivation, and the methods used to derive the value.

For example, the U.S. EPA RfD for TCDD (U.S. EPA 2012) is based on decreased sperm count and motility in adult human males who were between 1 and 9 y of age at the time of exposure (Mocarelli et al. 2008). Although it is not clear whether any of the men in this study had been exposed via lactation, the first year of life is known to be a sensitive period of development for the human male reproductive system (Sharpe et al. 2003). Reduction in Sertoli cell numbers, which may result from chemical exposure during this sensitive period, leads to reduced sperm counts in adulthood (Quigley 2002). Further, Mocarelli et al. (2011) observed reductions in sperm concentrations for men who were exposed to TCDD *in utero* and by lactation. Because the TCDD RfD is based on exposure–response

data for a developmental effect sensitive during infancy and observed in humans exposed during early life, it is well suited for use in a life stage-specific human health risk assessment for infant dietary exposure.

The U.S. EPA RfDs for BDE-47, BDE-99, BDE-153, and BDE-209 (U.S. EPA 2017a, 2017b, 2017c, 2017d) were derived from exposure–response data for behavioral impairments observed in adult mice following a single oral dose of the relevant PBDE congener administered within 10 d after birth, which represents a period of maximum vulnerability for mouse brain development (Eriksson et al. 2001; Viberg et al. 2003a, 2003b, 2004). Because the RfDs are based on exposure–response data for neurodevelopmental effects observed in animals exposed during the neonatal period, these may also be relevant for assessing risk from infant dietary exposures.

However, the TDIs for PFOS and PFOA derived by the European Food Safety Authority (EFSA 2008) are not based on life stage-specific toxicity data, but on changes in health end points observed in adult animals following subchronic exposures to these chemicals. For both chemicals, studies have also reported indications of developmental abnormalities in rodents following prenatal and postnatal exposure (Butenhoff et al. 2004; Lau et al. 2006; Luebker et al. 2005) and persistent behavioral impairments in mice following exposure during a critical period of brain development (Johansson et al. 2008). These developmental end points were affected at higher doses compared with the health end points observed in adult animals that were selected as the basis for the TDIs. However, because of important PK differences, humans may be more sensitive than rodents to the developmental effects of PFOS and PFOA exposure. Thus, it would be important to exercise caution when using the PFOS and PFOA TDIs to draw conclusions about the potential for health risk resulting from infant dietary exposures.

In 2016, the U.S. EPA published RfDs for PFOS and PFOA (U.S. EPA 2016a, 2016b); these RfDs were derived based on developmental effect data from animal studies: decreased pup body weight in a two-generation study of PFOS in rats (Luebker et al. 2005), and decreased ossification of the proximal phalanges and accelerated puberty in male pups in a study of PFOA in mice (Lau et al. 2006). These data were used together with PK modeling to predict oral exposure levels in humans that would produce serum PFOS or PFOA concentrations equivalent to those observed at effect levels in animals. Still, the relevance of these values for a life stage-specific human health risk assessment for infant dietary exposures is unclear because the PK modeling used to derive the RfDs for PFOS and PFOA focused on predicting exposures in adult animals and humans corresponding with effects in offspring exposed through gestation and lactation. These RfDs were developed to be compared with measures of maternal PFOS and PFOA exposure to assess risk of adverse effects in children resulting from exposure during pregnancy or through breastfeeding (U.S. EPA 2016a, 2016b). They are not directly applicable to infant exposures estimated using chemical concentrations in breast milk or formula because neither serum chemical concentrations in affected animal offspring nor corresponding oral doses in human infants were modeled when the RfDs were developed. Therefore, even though these reference values incorporated information on developmental end points, additional analysis may be necessary when they are applied and interpreted in the context of infant exposure.

To illustrate the practical utility of the concepts described here, we selected three examples of published assessments that looked at infant dietary exposure to environmental chemicals. Our purpose in presenting these examples, presented below, is to highlight the importance of appropriate interpretation of the results of comparisons between estimates of infant dietary exposure and reference values and the limitations of such comparisons, which may relate

to uncertainty in the reference value and the relevance of that value to responses resulting from early life exposure.

Example 1: PBDEs and breastfed infants. Based on data from breast milk samples provided by 33 mothers in New Zealand, Coakley et al. (2013) reported estimated daily intakes of BDE-47, BDE-99, BDE-153, and BDE-209 for infants <3 months of age: 13.1, 2.8, 3.3, and 1.7 ng/kg per day, respectively. The U.S. EPA RfDs for these PBDE congeners are 100 (U.S. EPA 2017b), 100 (U.S. EPA 2017c), 200 (U.S. EPA 2017d), and 7,000 (U.S. EPA 2017a) ng/kg-day, respectively. As described above, the RfDs are based on neurodevelopmental effects observed in mice exposed soon after birth and may be relevant to a life stage-specific risk assessment for breastfed infant exposures. As described by Coakley et al. (2013), their estimated breastfed infant ADDs of BDE-47, BDE-99, BDE-153, and BDE-209 are all below the respective RfDs for those chemicals, suggesting that infants whose mothers participated in this study would not be expected to experience adverse health effects related to their exposure to each of these PBDE congeners in breast milk. Because all of the PBDEs evaluated in this study are associated with the same health outcome, a cumulative risk assessment approach could also be applied to account for potential dose additivity across all four congeners (NRC 2008; U.S. EPA 2003). To use this approach, the ADD of each PBDE congener is divided by its RfD, and the resulting quotients are summed. Using the data presented by Coakley et al. (2013), the result of this analysis is less than 1 and is interpreted to mean that no effect is expected from the combined exposure to BDE-47, BDE-99, BDE-153, and BDE-209.

Example 2: Dioxins and breastfed infants. Lorber and Phillips (2002) estimated intakes of dioxin-like compounds for infants via breastfeeding ranging from 242 pg TEQ/kg per day at birth to 18 pg TEQ/kg per day at 1 y of age. The TEQ concentration in breast milk at birth was assumed to be 25 ppt TEQ on a lipid basis, based on general population levels in the 1990s. The decline in estimated intakes over the first year of life was due to a modeled decline in breast milk concentration in combination with increases in infant body weight. The RfD for TCDD is 0.7 pg/kg per day (U.S. EPA 2012), and this value can also be applied to dioxin TEQs (U.S. EPA 2010). As described above, this RfD is based on decreased sperm count and motility in adult human males who were exposed to TCDD during childhood, is supported by evidence of potential susceptibility during infancy, and is relevant for use in risk assessments of early life exposures. Although the TCDD RfD was not available when the paper by Lorber and Phillips (2002) was published, and those authors did not compare their calculated infant doses with any benchmark, their estimates indicate that infant ADDs of dioxins from breast milk may be greater than the RfD for TCDD under the assumed exposure conditions. However, based on the 2001–2002 NHANES survey, the U.S. general population serum TEQ level was 21.7 ppt TEQ lipid [i.e., lower than the level assumed by Lorber and Phillips (2002)] (Lorber et al. 2009). Scaling linearly from the data of Lorber and Phillips (2002), this would correspond to infant doses ranging from 210 pg TEQ/kg per day at birth to 16 pg TEQ/kg per day at 1 y of age. Using NHANES 2003–2004 survey data, Chen et al. (2013) estimated median and 75th and 95th percentile TEQ levels to be 14.1, 22.4, and 39.0 ppt lipid, respectively. These values correspond to infant doses of 136, 216, and 376 pg TEQ/kg per day at birth and 10, 16, and 28 pg TEQ/kg per day at 1 y of age. These findings suggest further declines in average TEQ levels in the U.S. population but also illustrate that the range of exposure levels is wide. A recent analysis of the results of global breast milk surveys of PCDDs, PCDFs, and PCBs conducted from 2000 to 2010 (van den Berg et al. 2017) indicated that levels of dioxin-like chemicals in human milk worldwide, while declining, continue to result in infant doses exceeding the TCDD RfD.

Example 3: PFOS/PFOA and formula-fed infants. In the paper by Llorca et al. (2010), risk indices for PFOS and PFOA were calculated by dividing estimates of daily infant intakes of these chemicals from formula by the EFSA TDIs for PFOS (150 ng/kg per day) and PFOA (1,500 ng/kg per day) (EFSA 2008). The estimated daily intakes were calculated using PFOS and PFOA measurements from three brands of powdered milk-based infant formulas from retail stores in Spain. Risk indices calculated by the study authors for both chemicals in all three brands of infant formula were well below 1 for infants ages 40 d to 6 months, suggesting that infants consuming the formulas tested in this study would not be expected to experience adverse effects during infancy or at later life stages as a result of their exposure to PFOS and PFOA in formula. However, as is the case for many reference values widely used in human health risk assessment, the TDIs for PFOS and PFOA are based on health effects observed following exposures during adulthood rather than early life. Depending on the evidence available to support those values, there may be some uncertainty as to whether and how well they reflect potential outcomes of exposure in the developing infant. As described above for PFOS and PFOA, understanding the scientific basis for a reference value may shed light on its utility as a benchmark for evaluating risk from early life exposures.

It is important to note that reference values are used to assess the potential for a human population to experience an increased prevalence of a particular health effect as a result of chemical exposure, not to determine an individual's risk of experiencing an exposure-related effect. Although exceedance of a reference value may suggest the potential for increased risk across a population, it does not, by itself, mean that an adverse health effect will occur. When a reference value is exceeded, this may trigger additional evaluations to determine whether there is a need for stronger public health standards. Indeed, elevated infant exposures via breast milk may prompt consideration of measures to reduce exposures to environmental chemicals. Because persistent chemicals accumulate within women's bodies over extended periods of time, reducing maternal exposures during pregnancy and lactation may not result in significant reductions in breast milk levels of those chemicals, and efforts may be aimed at reducing exposures in women and girls throughout childhood and adolescence as well as during the childbearing years (Lehmann et al. 2014). Such an approach has been implemented in the state of Oregon, where human health risk assessment guidance has been adopted to recognize the impact of long-term maternal exposure to lipophilic and persistent environmental chemicals on subsequent breastfed infant exposure (Oregon DEQ 2010).

As mentioned above, reference values are developed to assess the potential for noncancer health outcomes to occur as a result of exposure. Many environmental chemicals commonly found in breast milk are also known carcinogens, and increased cancer risk is an additional reason to consider approaches for reducing infant exposures to these chemicals. However, the presence of these chemicals in breast milk at current U.S. background concentrations does not necessarily indicate that breastfeeding should be avoided. Using environmental chemical concentration data from breast milk of women in the United States in the 1970s and 1980s, Rogan et al. (1991) used a risk assessment approach to compare cancer risk attributable to six chemicals commonly found in human milk (DDE, dieldrin, heptachlor epoxide, oxy-chlordane, PCBs, and TCDD) with risk of post-neonatal mortality resulting from a failure to breastfeed. They found that the estimated increase in cancer risk associated with excess lifetime exposure to these chemicals in breast milk was 12–80 excess cancers per 100,000 infants. In contrast, they estimated that the risk of post-neonatal mortality associated with not breastfeeding was 256 per 100,000 infants. Of course, parallel assessments for

environmental chemicals in infant formulas would need to be conducted in order to fully understand the potential for cancer risks associated with infant dietary exposures.

Research Needs and Data Gaps

Additional research on risks to infants associated with exposures to environmental chemicals from breastfeeding and formula feeding would strengthen our ability to use risk assessment to provide the underpinnings for decision-making regarding when and how to limit exposures in women who are breastfeeding or who may breastfeed in the future as well as to lessen exposures associated with formula feeding.

Infant dietary exposures to environmental chemicals. Breast milk and environmental chemicals. The lack of nationally representative breast milk data severely limits our understanding of concentrations of chemicals in U.S. breast milk and the potential for infant exposures. Although measurements of chemicals in breast milk are preferred, given the associated costs and the availability of nationally representative data on hundreds of chemicals in serum, methods for estimating breast milk concentrations from serum concentrations will be useful. Although simple assumptions about milk-to-serum relationships have been used as a starting point for some chemicals, it will be important for future studies to continue to investigate the molecular complexities and physicochemical properties that drive serum:milk partitioning, particularly for new classes of chemicals, and to develop models that estimate concentrations of these chemicals in breast milk from serum concentrations, such as the models developed by Marchitti et al. (2013b). In addition, as new chemicals are introduced into the marketplace, resources and tools are needed to analyze breast milk for their presence or to predict the potential for these chemicals to partition into breast milk.

In addition to measuring environmental chemicals in breast milk or using serum concentrations to estimate breast milk concentrations, it would be valuable to be able to use concentrations of chemicals in environmental media (e.g., air, soil, water, food and drinks, consumer products) to model concentrations in breast milk and, in turn, to estimate infant intakes (i.e., linking external maternal exposures to maternal breast milk concentrations and then to infant exposures). Furthermore, data are needed to inform our understanding of the relationships among chemical concentrations in maternal serum, cord serum, breast milk, and infant serum. These data are necessary for the development of PK models for estimating prenatal and lactational exposures.

Infant formula and environmental chemicals. There is a dearth of U.S.-specific data on concentrations of environmental chemicals in infant formula (powdered, ready-to-use, or reconstituted formula). Based on the limited data available, it is inappropriate to assume that infant formulas do not contain measurable concentrations of environmental chemicals of interest. Because dietary options for infants are limited, it is critical for assessments of environmental exposures and health outcomes associated with breastfeeding—as well as dietary recommendations—to consider the comparative exposures associated with formula feeding. Thus, research is needed to obtain data for this aspect of infant exposure.

Changes in chemical concentrations during lactation. In order to estimate infant exposures to environmental chemicals during breastfeeding, information on variations in chemical concentrations over the duration of lactation is needed. Variability introduces uncertainty in exposure assessments for both persistent and short-lived chemicals, and various factors that may be associated with concentration changes have been explored (Harris et al. 2001; LaKind 2007; LaKind et al. 2004, 2011). However, this remains an area that is poorly understood (LaKind et al. in press).

Toxicity assessment. Timing of exposure. Infancy is a time when organ systems are developing (Adams et al. 2000; Dietert et al. 2000; Lemasters et al. 2000; Pryor et al. 2000; Rice and Barone 2000), and the timing of exposure is important in determining the vulnerability of developmental end points (Selevan et al. 2000). Therefore, data based on exposures occurring during the postnatal period in humans, or its developmental equivalent for a study conducted in animals, are preferred for identifying the potential health hazards and exposure–response relationships associated with environmental chemicals in human milk and formula. When these data do not exist for a chemical, this limitation introduces uncertainty into analyses of risk from exposures during infancy. It may also be important to gather information on study subjects for an extended period of time to assess the potential for health outcomes to be persistent or delayed (Brown et al. 2008; Makris et al. 2008; Selevan et al. 2000; WHO 2006). Studies that provide toxicity information on windows of exposure relevant to breastfeeding and formula feeding are needed for a wide array of chemicals.

Chemical mixtures. As described above, breast milk is a complex and dynamic mixture of endogenous and exogenous chemicals. Infant formulas are mixtures of similar complexity. Although issues associated with assessing risks from mixtures are applicable to many exposure scenarios and are not unique to the assessment of risk from exposure to chemicals in breast milk and formula, it is worth mentioning that assessments of individual chemicals may not fully account for potential health risks when populations of interest are also exposed to other chemicals with overlapping toxicities that are not included in the assessment. Cumulative risk assessment approaches are available to account for the potential combined toxicity of exposure to multiple chemicals that cause the same types of health outcomes (NRC 2008; U.S. EPA 2003).

Conclusions

This paper provides detailed information on risk assessment for early life exposures to environmental chemicals in breast milk and formula and describes research needed to improve the risk assessment process. We compiled data on environmental chemicals in breast milk in the United States and environmental chemicals in infant formula from U.S. and international data sources, highlighting data gaps for exposure assessments for both breast milk and infant formula. Data are available for persistent, lipophilic chemicals in breast milk; less information is available on other chemicals in breast milk and for chemicals in formula. In order to understand the full potential for infant dietary exposures to environmental chemicals in the United States, measurements of a wider variety of chemical types in breast milk as well as more comprehensive surveys of chemical levels in formula are needed. We also highlighted areas of potential uncertainty that may arise when using common risk assessment methods to estimate the potential for health risk to result from infant dietary exposures. Often, exposure–response information comes from studies of adult humans or laboratory animals, and the relevance of the observed health effects for humans exposed during a sensitive developmental period (i.e., infancy) is unclear. For many chemicals found in breast milk and/or formula, additional research is needed to gather data on potential impacts of developmental exposure on health during later life stages, extending into adulthood.

It is important to note that comparisons between chemical exposure levels and reference values are but one small element of a larger process for risk-based decision-making, which also includes consideration of risks from aggregate exposures as well as economic, technological, social, and legal factors (NRC 2009). Results of the types of comparisons described here may be interpreted within a more comprehensive framework acknowledging combined contributions to

health risk posed by multiple environmental stressors, including not only chemical exposures but also nonchemical stressors such as low socioeconomic status, lack of educational opportunities, low rates of employment, weak social support networks, and reduced access to health care (NEJAC 2004; U.S. EPA 2003).

This work is intended to encourage the scientific community to design studies to better characterize infant exposures to environmental chemicals in breast milk and infant formula as well as to improve our understanding of potential health consequences resulting from exposure to chemicals found in these foods. Further comparisons between breastfed and formula-fed infant exposures and relevant reference values may be useful for alerting us to potential health risks associated with this early life stage. In the meantime, it may be prudent to strengthen efforts to minimize the risk of potential health impacts in infants and children by reducing exposures to environmental chemicals and by minimizing the levels of environmental chemicals in infant formulas.

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