

Infant Dietary Exposures to Environmental Chemicals and Infant/Child Health: A Critical Assessment of the Literature

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BACKGROUND: The benefits of breastfeeding to the infant and mother have been well documented. It is also well known that breast milk contains environmental chemicals, and numerous epidemiological studies have explored relationships between background levels of chemicals in breast milk and health outcomes in infants and children.

OBJECTIVES: In this paper, we examine epidemiological literature to address the following question: Are infant exposures to background levels of environmental chemicals in breast milk and formula associated with adverse health effects? We critically review this literature *a)* to explore whether exposure–outcome associations are observed across studies, and *b)* to assess the literature quality.

METHODS: We reviewed literature identified from electronic literature searches. We explored whether exposure–outcome associations are observed across studies by assessing the quality (using a modified version of a previously published quality assessment tool), consistency, and strengths and weaknesses in the literature. The epidemiological literature included cohorts from several countries and examined infants/children either once or multiple times over weeks to years. Health outcomes included four broad categories: growth and maturation, morbidity, biomarkers, and neurodevelopment.

RESULTS: The available literature does not provide conclusive evidence of consistent or clinically relevant health consequences to infants exposed to environmental chemicals in breast milk at background levels.

CONCLUSIONS: It is clear that more research would better inform our understanding of the potential for health impacts from infant dietary exposures to environmental chemicals. A critical data gap is a lack of research on environmental chemicals in formula and infant/child health outcomes. <https://doi.org/10.1289/EHP1954>

Introduction

Infancy and early life stages are the foundation for a child's growth, maturation, and overall health throughout life. It is, therefore, essential that we understand the optimal environment and diet for a child's first months. Recent reviews affirm that breastfeeding confers numerous benefits to infants in comparison with formula feeding (AAP 2012; Hennet and Borsig 2016; Ip et al. 2007) and that exclusively breastfeeding infants for their first 6 mo, as recommended by the American Academy of Pediatrics (AAP) (AAP 2012) and the World Health Organization (WHO) (WHO 2011), provides additional benefits over exclusively breastfeeding for only the first 3 or 4 mo (AAP 2012; Kramer and Kakuma 2012).

Strong evidence supports the association between breastfeeding and reduced childhood risks for acute otitis media, severe lower respiratory infections, nonspecific gastroenteritis, atopic dermatitis, asthma, obesity, type 1 and 2 diabetes, sudden infant death syndrome (SIDS), neurodevelopmental problems, and childhood leukemia, as well as necrotizing enterocolitis in preterm infants (AAP 2012; Ip et al. 2007; Victora et al. 2016). Breastfeeding is also associated with maternal health benefits, including reduced risk of type 2 diabetes and breast and ovarian cancers (AAP 2012; Ip et al. 2007; Victora et al. 2016).

At the same time, breast milk and infant formula contain environmental chemicals to which infants are exposed (Baier-Anderson et al. 2006; Jensen and Slorach 1991; Lehmann et al. 2018). Epidemiological research has focused on exploring whether infant exposure to these environmental chemicals is associated with various health outcomes. The earliest epidemiological studies on environmental chemicals in breast milk were published in the late 1980s (Gladen et al. 1988; Rogan et al. 1987), and the literature has expanded since that time. In contrast, environmental chemicals in infant formula—reconstituted with drinking water or ready to use—and associated health outcomes in infants and children have not garnered the same attention.

Several reviews of epidemiological research on environmental chemicals in breast milk and potential adverse health effects in infants and children have been published (Jorissen 2007; Kacav 1994; LaKind et al. 2008; Landrigan et al. 2002; Massart et al. 2005; Pohl and Hibbs 1996; Ribas-Fitó et al. 2001; Schreiber 2001). Most examined one or a few classes of chemicals rather than attempting to examine all of the extant literature on environmental chemicals, and none included a formal examination of study quality in their assessments. For example, Goldman et al. (2007) evaluated the benefits and risks to the breastfeeding infant from a variety of potential risk factors, such as micronutrient deficiency, proinflammatory fatty acids, human immunodeficiency

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virus (HIV), pharmaceuticals, and environmental chemicals. Although some of these factors were associated with adverse clinical outcomes in infants, for environmental chemical exposures, the authors concluded that risks associated with breastfeeding were “largely undetermined.” In a risk–benefit assessment, van den Berg et al. (2017) found that dioxin-like chemicals in breast milk were above levels considered safe and that ΣDDTs (dichlorodiphenyltrichloroethane) are below or around safe levels but concluded that if “. . . potential adverse effects are balanced against positive health aspects for (breastfed) infants, the advantages of breastfeeding far outweigh the possible disadvantages.”

LaKind et al. (2004) reviewed the literature on environmental chemicals in human milk, including concentrations, infant exposures, epidemiological (six mother–infant cohort epidemiological studies) and risk assessment studies, and guidance for future research. For an in-depth case examination of the epidemiological literature on dioxins in breast milk, LaKind et al. (2008) used risk assessment methods as well as a review of the epidemiological evidence. Although some of the epidemiological studies found effects in breastfed infants exposed to dioxin-like compounds in breast milk, LaKind et al. (2008) noted that effects were generally within the range of normal and exposures in these study cohorts were higher than are typically found today. The authors also reported that, in most studies, it was not possible to separate the effects of prenatal and postnatal exposures (LaKind et al. 2008). They observed that “The essential conclusion. . . is that in studies of breastfed versus formula-fed infants across time, including times when levels of environmental chemicals such as dioxins were higher, beneficial effects associated with breastfeeding have been found.” Jorissen (2007) published an evaluation of epidemiological studies on postnatal exposure to polychlorinated biphenyls (PCBs) via breast milk and similarly concluded that although breastfed infants experienced higher exposures to PCBs in comparison with formula-fed infants, they “fared” better than formula-fed infants. Similarly, Aliyu et al. (2010) recommended breastfeeding despite the presence of PCBs in breast milk. Although these published reviews offer assessments of different aspects of the literature on infant exposures to environmental chemicals via diet (principally from breastfeeding) and associated health outcomes, none included a formal method for assessing the quality of the literature nor a strength-of-evidence assessment.

To our knowledge, a critical examination of information on—and approaches to—understanding associations between infant exposures to environmental chemicals in breast milk or infant formulas, including data strengths and weaknesses, has not been undertaken.

In this paper, we examine epidemiological literature and use a strength-of-evidence approach to address the following question: Are infant exposures to background levels of environmental chemicals in breast milk and formula associated with adverse health effects?

Methods

Using a Population, Exposure, Comparison, and Outcomes (PECO) framework (Higgins and Green 2011; Lam et al. 2014; Stephens et al. 2016), we define the boundaries of the review as follows:

Population: Infants and children (up to 18 y of age).

Exposure: Exposure to environmental chemicals via breastfeeding or consumption of infant formula as assessed using at least one measurement of levels of chemical(s) in breast milk or formula. We note that some epidemiological research-based exposure assessments have estimated postnatal exposure using measures in blood or hair, or by using questionnaire data. Here, we have included only studies that provided data from actual

measurements of chemicals in breast milk or formula. For the purposes of this review, we restrict the definition of environmental chemicals to those found in the environment with exposure sources, including air, soil, water, personal care products, food and drinks, clothes, or furniture. Research on pharmaceuticals and illicit drugs, alcohol, and tobacco has been described previously and is outside the scope of this paper [(Jansson 2009; Sachs and Committee on Drugs 2013); for a database on drugs and other chemicals to which breastfeeding mothers may be exposed, see U.S. NLM (2018)].

Comparison: Defined either by different levels of chemical exposure (e.g., tertiles of a cohort) or by a nonbreastfed comparison group.

Outcomes: Any health outcome assessed directly in the infant/child population except those existing at birth (e.g., birth weight, cryptorchidism). Studies that relied on risk calculations in the absence of actual observations of health outcomes were not considered.

The electronic data sources PubMed and Web of Science (WoS) were used to conduct the initial literature search for publications appearing at any time before 2 July 2017. 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 (“health” [All Fields] OR “growth” [All Fields] OR “development” [All Fields] OR “neurodevelopment” [All Fields]) AND (“humans” [All Fields] OR “epidemiology” [All Fields]) AND (“0001/01/01” [PDAT]: “2017/07/02” [PDAT]); and
- 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”) AND (“health” OR “growth” OR “development” OR “neurodevelopment”) AND (“humans” OR “epidemiology”)]. 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 (“health” [All Fields] OR “growth” [All Fields] OR “development” [All Fields] OR “neurodevelopment” [All Fields] AND (“humans” [All Fields] OR “epidemiology” [All Fields]) AND (“0001/01/01” [PDAT]: “2017/07/02” [PDAT])); and

- 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”) AND (“health” OR “growth” OR “development” OR “neurodevelopment”) AND (“humans” OR “epidemiology”)]. Indexes: SCI-EXPANDED, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, CCR-EXPANDED, IC.

Results were then manually screened to include only primary literature meeting the criteria outlined in the PECO statement above. Secondary references of relevant articles were reviewed to identify publications not captured by the electronic search. Two study authors (JSL and GML) conducted the search and selection of relevant studies.

Each study that met the inclusion criteria was examined, and the data from each study were tabulated. Information extracted from each study for the purposes of this review included the following:

1. Description of the study population (size, composition, source, and location)
2. Study design (cohort, cross-sectional, case-control, or other)
3. Number of samples and timing of sample collection
4. Outcomes
5. Results (original text summaries of results were reproduced verbatim or results were paraphrased) and
6. Description of study-specific chemical levels.

Studies of particular interest were those that considered the potential influence of prenatal exposure and/or beneficial effects associated with breastfeeding, either by inclusion of formula-fed infants in a comparison group, by comparing early exposure to later exposure (e.g., levels of chemical in cord blood or colostrum vs. mature milk), or by estimating cumulative dose and comparing dose groups.

In several of the cohort investigations, researchers used breast milk samples collected early in lactation to represent prenatal exposures (instead of using, for example, cord blood or blood from pregnant women as surrogates for prenatal exposures) and reported results as associations between prenatal exposures and outcomes. For this review, regardless of the study authors' interpretation, we considered any measures of environmental chemicals in breast milk to be measures of postnatal exposure relevant for understanding associations between breast milk chemicals and health outcomes.

To synthesize the literature, it is important to organize it in a way that allows for comparison of studies that examine the same or similar chemicals and outcomes. Therefore, we have organized the literature according to four broad categories of health outcomes or effects: growth and maturation, morbidity, biomarkers (thyroid, immune function, hematology, serum biochemistry, and reproductive and

growth biomarkers), and neurodevelopment. Within those categories, we organized the literature by chemical or chemical class.

We evaluated each study with a quality assessment tool—developed to enable a “systematic and transparent method of research synthesis in environmental health” by Woodruff and Sutton (2014). To improve the suitability of this tool for our review, we incorporated specific instructions for the exposure assessment and confounding domains and removed the conflict-of-interest domain. We used the following questions to assess the quality of a given study (detailed information regarding each of the following questions and the scientific foundation for responses to the questions are shown in Supplemental Material, Study Quality Evaluation Criteria):

1. Was the strategy for recruiting participants consistent across study groups?
2. Was knowledge of the exposure groups adequately prevented during the study?
3. Were the methods for assessing lactational exposures robust?
4. Was confounding from prenatal and postweaning exposures adequately addressed?
5. Were incomplete outcome data adequately addressed?
6. Are reports of the study free of suggestion of selective outcome reporting?
7. Were there other problems that would limit the value of the study for assessing strength of evidence?

Each study was assigned to a pair of authors for initial review, with all authors participating. One author (M.D.) subsequently reviewed all the study evaluations for consistency; differences in assessment for any item were discussed until consensus was achieved.

Results

The PubMed and WoS searches for studies of breast milk yielded 1,151 and 259 citations, respectively (https://public.tableau.com/views/EHP1954_HumanMilk/Dashboard1?embed=y&:display_count=yes&publish=yes). The citation titles and/or abstracts were reviewed to determine whether the articles met the inclusion criteria defined by the PECO statement. After removal of 108 duplicates as well as 1,228 articles that did not meet inclusion criteria based on titles/abstracts, 74 articles remained. These 74 publications were initially identified as potentially containing relevant information based on the criteria given in the PECO statement, and full articles were retrieved and reviewed. Review of publication bibliographies yielded an additional 11 citations (referred to as “other sources”), and those papers were retrieved. These 85 papers were reviewed to identify the associations between breast milk chemical levels and health outcomes evaluated in each study. Additional details (e.g., citations for each of the excluded studies) can be accessed via the online interactive figure: https://public.tableau.com/views/EHP1954_HumanMilk/Dashboard1?embed=y&:display_count=yes&publish=yes. An overview of the results of this review are presented in Figure 1.

Before developing summaries of the evidence for exposure–outcome associations, we narrowed the scope of our review to *a*) those exposures and outcomes with enough information to support conclusions, and *b*) exposures most relevant to the general U.S. population. Because it was clear from our initial review of the literature (Figure 1) that there was insufficient information available to support a weight-of-evidence evaluation for certain outcomes, the following were excluded from our evidence summaries: the presence of natal and/or neonatal teeth (Alaluusua et al. 2002), the development of demarcated hypomineralizations of developing teeth (Holttä et al. 2001), markers of oxidative stress (e.g., urinary 8-hydroxy-2'-deoxyguanosine and malondialdehyde) (Al-Saleh et al. 2013; Kippler et al. 2012), and markers of mutagenicity (e.g.,

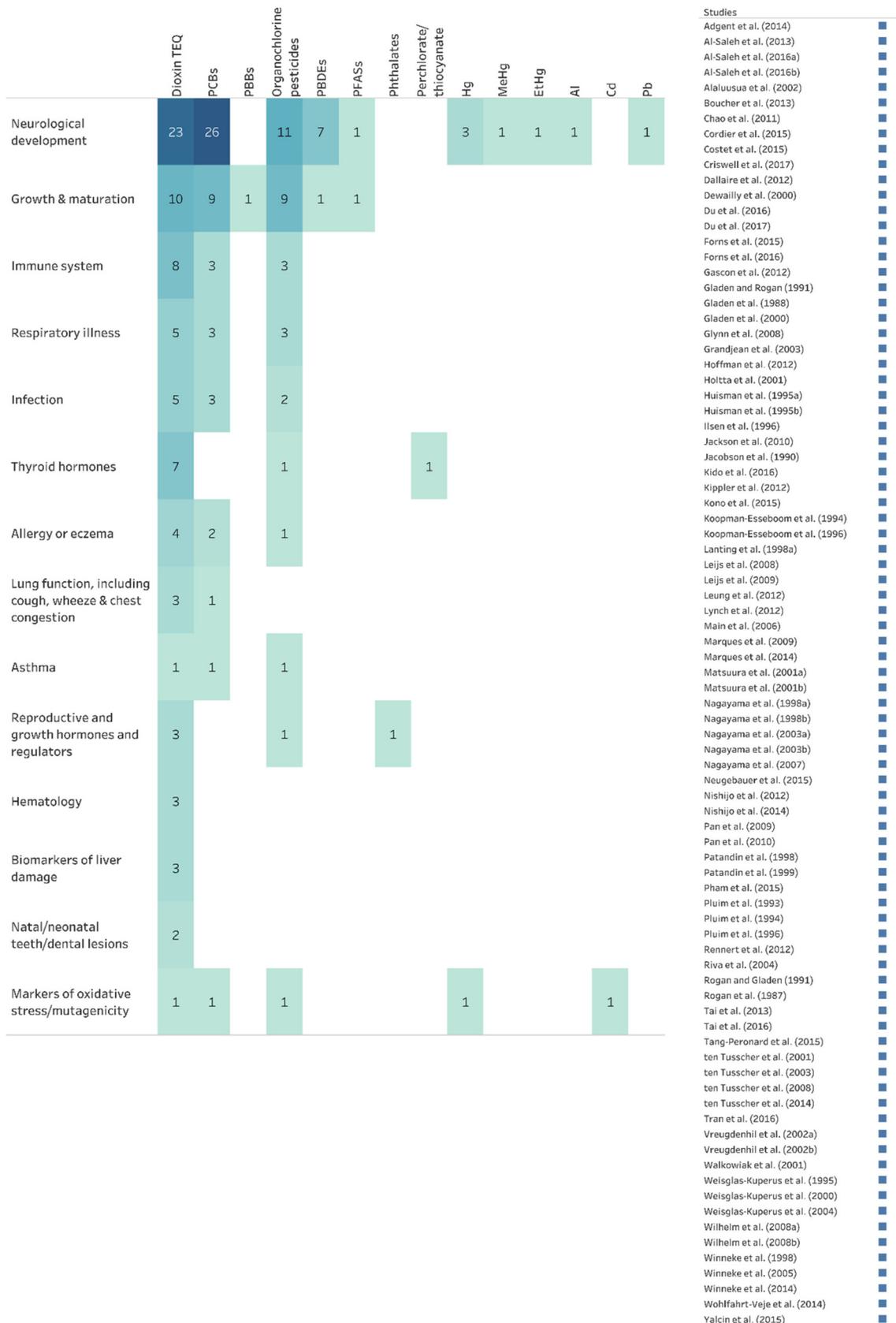


Figure 1. Exposure–outcome map of the database of studies evaluating associations between levels of environmental chemicals in breast milk and health outcomes in infants and/or children. The number of studies is given for each exposure–outcome combination in the database, and all 85 studies included in the map are listed on the right. Additional details (e.g., identification of which studies evaluated each exposure and outcome) can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_Inventory_2/Dashboard1?:embed=y&:display_count=yes.

sister chromatid exchanges in cultured lymphocytes) (Nagayama et al. 2003a, 2003b). Furthermore, studies that examined cohorts living in highly contaminated environments that are not representative of background exposures in the broader U.S. population were excluded from evidence summaries: studies of chlordecone exposure in Guadeloupe (Boucher et al. 2013; Cordier et al. 2015; Costet et al. 2015; Dallaire et al. 2012), studies of dioxin exposure in areas of Vietnam where Agent Orange was used (Kido et al. 2016; Nishijo et al. 2014; Nishijo et al. 2012; Pham et al. 2015; Tai et al. 2013, 2016; Tran et al. 2016), and studies of populations in Amazonian Brazil exposed to heavy metals by virtue of their residential proximity to smelters or kilns, their consumption of diets rich in fish from contaminated rivers, and receiving vaccinations that are still preserved with ethylmercury (thimerosal) (Marques et al. 2014, 2009). Although we believe that it is important to collect data from and assess health risk for highly exposed populations and others in the United States, the focus of this review is on studies that are more likely to be generalizable to the U.S. population as a whole.

Chlordecone (i.e., Kepone) contamination is a particular problem in the French Antilles because it was used extensively there until 1993 as an insecticide for banana weevil borer control (Boucher et al. 2013). The studies of Guadeloupean women listed above detected chlordecone in 71–100% of 68–159 breast milk samples at levels of <0.34–6.71 ppb (Boucher et al. 2013; Cordier et al. 2015; Costet et al. 2015; Dallaire et al. 2012). These current-day levels of breast milk chlordecone measured in Guadeloupe are similar to levels reported in the only study we could find of chlordecone in breast milk from women in the United States. That report was published in 1978, and chlordecone was detected in 9 of 298 samples at levels ranging from <1–6 ppb (U.S. EPA 1978). Chlordecone use in the U.S. was never as extensive as in Guadeloupe, and U.S. production of chlordecone ended in 1975 (ATSDR 1995). Because of differences in the patterns of use of this pesticide, it is unlikely that the general population of the U.S. currently has breast milk levels of chlordecone comparable to those reported in the studies of Guadeloupe; we did not include these studies in our evidence summaries.

During the Vietnam War, the U.S. military applied herbicide mixtures, including Agent Orange, to eliminate foliage that could conceal enemy forces, to clear areas around military installations, and to disrupt agricultural food production (Stellman et al. 2003). Agent Orange was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD); as a result, exposures in the areas that were sprayed consist predominantly of this most toxic dioxin congener. High levels of usage and spills not mirrored in the United States coupled with differences in congener patterns (Banout et al. 2014) make it unlikely that one would observe exposure patterns in the United States similar to those in hotspots in Vietnam. Therefore, we did not include studies of populations residing in those areas in our evidence summaries.

Marques et al. (2009) and Marques et al. (2014) explored associations between neurodevelopmental outcomes and exposures to methylmercury (via subsistence fish consumption), ethylmercury and aluminum (via thimerosal-containing vaccines), and lead (via breast milk) in Amazonian Brazil. Three groups of mother/infant pairs were included in these studies—two in rural villages of either fishermen or cassiterite miners and one in an urban center. In general, due to vaccinations, proximity to smelters and kilns, and subsistence fishing, this cohort is likely exposed to higher concentrations of heavy metals than would be found in the general U.S. population, and their overall life experience is quite different from the U.S. population. Therefore, this cohort was excluded from our evidence summaries.

Sixty-six publications were ultimately included in the evidence summaries. These included studies of organochlorine chemicals,

flame retardants, phthalates, perchlorate/thiocyanate, and per- and polyfluoroalkyl substances (PFASs).

A parallel effort to identify studies of health effects associated with exposure to environmental chemicals in infant formula was attempted. PubMed and WoS searches yielded 139 and 644 citations, respectively. After removal of 111 duplicates, 672 articles remained, none of which met the PECO criteria. Additional details (e.g., citations for each study) can be accessed via the online interactive version of the figure shown at https://public.tableau.com/views/EHP1954_InfFormula/Dashboard1?:embed=y&:display_count=yes&publish=yes.

General descriptions of the cohorts included in this review and their main findings are described in Supplemental Material, Study Summaries, and are organized by chemical class and study locations; information on studies grouped by chemical class is summarized in Table S1. The overall results from the study quality/risk-of-bias assessment are described in general terms below, and the details for each study are given in Table S2.

Study Quality Evaluation

Was the strategy for recruiting participants consistent across study groups? With the exception of three studies, recruitment strategy was judged by the authors of this review to be consistent across study groups within a cohort (Table S2). In general, these were prospective cohort studies with recruitment from hospitals or birthing centers. Both exposure levels and outcomes were determined after entry into the study.

Was knowledge of the exposure groups adequately prevented during the study? For studies included in this review, assessment of subjective outcomes most often included the use of neurodevelopmental assessment batteries or pubertal developmental staging; objective outcomes included measures of hormone levels or immunological factors in blood, or anthropometric measures, such as height and weight. Most studies either implemented adequate blinding or included only objective outcome measures unlikely to be influenced by knowledge of exposure level or group (Table S2). A judgment of inadequate blinding was generally made if blinding was not mentioned in the study and the outcome assessment was more subjective in nature.

Were the methods for assessing lactational exposures robust? Strong, exemplary breast milk exposure assessment methods were used in a number of studies. Researchers conducting a birth cohort study in North Carolina (Gladen et al. 1988) sampled breast milk four times by 6 mo postpartum and every 6 or 12 mo thereafter for as long as the mother was breastfeeding. This cohort, which informed numerous publications, stands out as nearly unique for the number of samples collected over time. In the Düsseldorf cohort, two samples were taken at 2 and 4 wk postpartum (Winneke et al. 1998), and the results of the chemical analyses of each individual sample were averaged together to provide the chemical concentration for the exposure estimation. In the Groningen/Rotterdam study, up to three milk samples per mother were collected until 3 mo postpartum (Huisman et al. 1995a); however, in publications reporting on the cohort, the researchers mention only one of the samples in connection with their analyses (at 2 wk postpartum). The cohort study conducted in Amsterdam and Zaandam, the Netherlands, pooled two samples from the same time period, at 3 wk postpartum. No other study included in our review reported collecting or using multiple breast milk samples in their analyses of post-natal exposures.

The Netherlands cohort (Pluim et al. 1994) provides a good example of estimating total exposures by including both volume of milk consumed and time of exclusive breastfeeding in their exposure assessment along with the concentrations of chemicals of interest at 3 wk postpartum. Not only did the North Carolina

cohort mentioned above collect multiple milk samples, but researchers also calculated exposures using the amount of milk consumed and length of time breastfeeding, completing what was one of the most comprehensive and complete postnatal exposure assessments in this database. Many studies included duration of breastfeeding in their exposure calculations, but some dichotomized duration data in their analyses (i.e., expressed duration as “≤ some number of weeks or months” or “> some number of weeks or months”), which poses increased risk of misclassification bias (Christensen et al. 2015). Others did not include any duration factor in their exposure estimations, relying solely on one chemical concentration in breast milk and not considering extent and duration of breastfeeding. Far fewer studies collected information about exclusivity of breastfeeding or appropriately adjusted volume of milk consumed in their exposure estimation or included this information in their statistical analyses for associations with the health outcome of interest.

Was confounding from prenatal and postweaning exposures adequately addressed? Any epidemiology study will have a multitude of confounders to consider, and we recognize that it may not be possible to account for every conceivable confounder. For the purposes of this review, we focus on two aspects of confounding that we view as critically important for assessing relationships between health outcomes and exposure to environmental chemicals in breast milk: consideration of *in utero* exposures and consideration of child dietary exposures outside of breastfeeding.

Only two studies reviewed in this paper included estimates of prenatal exposures in their analysis of associations between infant exposure to chemicals in breast milk and health outcomes. Huisman et al. (1995a) measured chemicals in cord blood and used these data to adjust analyses of associations between health outcomes (2–3 wk postpartum) and chemical concentrations in milk. The study by Walkowiak et al. (2001) included a chemical exposure assessment method that could potentially control for prenatal and postweaning exposures. The researchers measured PCBs in cord and children’s blood at 42 mo (the time of outcome assessment) and then used child blood levels at 42 mo in an effects model controlled for prenatal exposure. They did not note whether they created a model with prenatal, breast milk, and postweaning dietary exposures, though measurements of PCBs at the various time points would make such an analysis possible.

Aside from those two studies, others in this review separately analyzed the associations of a measure of prenatal exposure and postnatal breast milk exposure with the outcome of interest. Although not as robust as controlling for one exposure in the statistical model, this analysis provides an estimation of the relative strength of associations between the two routes of exposure and various developmental windows.

In terms of child dietary exposures, for many of the chemicals examined in the literature (e.g., dioxins and furans, PCBs, organochlorine pesticides), diet is a substantial pathway of exposure. For studies evaluating outcomes in infants or very young children who are still predominantly breastfed, exposures from other foods may not be an important issue. However, for many of the cohorts included in this review, children were followed for many years, well past the time of weaning. In these cases, dietary exposures outside of breast milk will likely play important roles, both in terms of exposure and outcome, and are thus confounding elements in these studies.

Only one study reviewed here (Walkowiak et al. 2001) analyzed associations between health outcomes (mental and motor development) and blood chemical (PCB) levels at the time of outcome assessment (42 mo of age) while also controlling for prenatal exposure levels. The researchers also analyzed associations of breast milk PCB levels with the same outcomes and compared

the strengths of association. That said, their data indicated a five-fold higher blood PCB level at 42 mo old in children breastfed for more than 4 mo in comparison with those children breastfed for less than 2 wk, which might indicate that the confounding effect of postweaning exposures is relatively minor at 42 mo of age. Other cohort studies that assessed outcomes at 8, 10, or 13 y of age (Table S1) did not report on chemical levels at the time of assessment. Most studies did not attempt to factor in postweaning exposures, even though more than a decade might have elapsed between weaning and outcome assessment. Years of dietary and environmental media exposures to the same chemicals found in breast milk would contribute to overall lifetime exposures to those chemicals, and, for many health outcomes studied, the sensitive window of development is not known, such that exposures during later life stages may be as important as exposures during infancy.

Were incomplete outcome data adequately addressed? Many of the studies we reviewed compared demographic characteristics or exposure levels for participants whose outcomes were assessed with those for the original cohort. Studies that did this were likely to be judged as having adequately addressed or probably adequately addressed missing outcome data. More than half of the studies were judged not to or probably not to have adequately addressed missing outcome data (Table S2).

Are reports of the study free of suggestion of selective outcome reporting? Generally, the researchers reported on the outcomes they had prespecified, and reports were free of suggestion of selective outcome reporting (Table S2). Few studies were identified as having some indication of a higher risk of reporting bias.

Were there other problems that would limit the value of the study for assessing strength of evidence? The final risk-of-bias criterion included any remaining issues that could potentially reduce study quality. We did not identify other problems in most studies (Table S2). Of the studies that we judged as not being or probably not being free of additional issues, the most frequent problem cited was using outcome assessments that have not been validated or may have been culturally biased.

In the following subsections, the strength of the epidemiological evidence of associations between environmental chemicals in breast milk and infant/child health outcomes is evaluated, with consideration of study quality and consistency of results.

Strength of Evidence of Associations between Environmental Chemicals in Breast Milk and Health Outcome

The results of the strength-of-evidence assessment are described for four broad categories of health outcomes or effects: growth and maturation, morbidity, biomarkers (thyroid, immune function, hematology, serum biochemistry, and reproductive and growth biomarkers), and neurodevelopment. We address the following questions: *a*) Are there multiple studies examining similar exposure–outcome associations (Table S1)? *b*) If yes, are the results across studies concordant? *c*) For studies grouped according to similar exposure–outcome associations, do study results differ according to study quality (Table S2)? *d*) What conclusions can be drawn from the overall available literature on each specific paired exposure–outcome?

Infant/child growth and maturation. Fifteen studies examined growth in infants and children using various metrics and covering age ranges from newborn infants to children 18 y of age. Chemicals studied included polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and/or PCBs (Criswell et al. 2017; Gladen et al. 2000; Grandjean et al. 2003; Ilsen et al. 1996; Jackson et al. 2010; Jacobson et al. 1990; Leijds et al. 2008; Pan et al. 2010; Patandin et al. 1998; Pluim et al. 1996; Rogan et al. 1987;

Wohlfahrt-Veje et al. 2014), PFASs (Wohlfahrt-Veje et al. 2014), polybrominated diphenyl ethers (PBDEs) (Wohlfahrt-Veje et al. 2014), and organochlorine pesticides, including DDT, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), aldrin, heptachlor, β -hexachlorocyclohexane (β -HCH), α -HCH, and heptachlor epoxide (Criswell et al. 2017; Du et al. 2016, 2017; Gladen et al. 2000; Pan et al. 2010; Rogan et al. 1987; Yalçin et al. 2015).

Growth measures from birth to approximately 4 years of age. Available studies reported inconsistent results (Figure 2). Rogan et al. (1987) observed that PCB or DDE exposure was not associated with infant weight up to 18 mo of age. Pan et al. (2010) found no association between PCB or DDE exposure and infant growth during the first year of life. DDE exposure was not associated with infant weight, length, head circumference, or percentage fat mass during the first year of life (Du et al. 2016, 2017). Similarly, Jacobson et al. (1990) found no association between height, weight, or head circumference and PCBs at 4 y of age. Pluim et al. (1996) measured body weight, body length, head circumference, and liver size in children up to 6 mo of age and found no difference between high- and low-exposure groups, defined according to concentrations of PCDDs/PCDFs in milk fat. At 31 mo of age, there were no significant differences in the size of the children associated with PCDD/PCDF exposure reported as toxic equivalents (TEQs), whether by concentration in breast milk or by cumulative lactational exposure (Ilsen et al. 1996). Wohlfahrt-Veje et al. (2014) found no association between PFASs and height gain, weight gain, or body mass index (BMI) up to 18 mo of age.

In contrast, five studies reported statistically significant findings for some aspects of growth with exposure to some chemicals in breast milk. Although Yalçin et al. (2015) found no relationship between levels of organochlorine pesticides in breast milk and z -scores of weight-for-age, height-for-age, weight-for-height, or BMI in 8-mo-old infants, they did find an inverse correlation between z -scores for head circumference and breast milk concentrations of β -HCH and DDT. Criswell et al. (2017) reported an association between increased levels of β -HCH in breast milk and a lower odds of rapid growth between the ages of 0 and 6 mo when their model was adjusted for maternal age, smoking, education, prepregnancy BMI, gestational weight gain, parity, child sex, cumulative breastfeeding, birth weight, gestational age, and preterm status; adjusted models revealed no significant associations between infant growth and exposure to HCB or PCB 74. Jackson et al. (2010) measured height, weight, weight for length, and head circumference in 24-mo-old children; although they found no significant associations between \sum PCBs and these anthropometric measures, they noted that PCB 77 was significantly inversely associated with length z -score. Wohlfahrt-Veje et al. (2014) found a significant positive association between a mixture of dioxins, PCBs, PBDEs, and other persistent chemicals in breast milk on height and weight gain. They further reported that total TEQs were associated with accelerated early height growth between 0 and 36 mo of age and early weight increase between 0 and 18 mo of age but not with changes in BMI. Patandin et al. (1998) observed no association between PCDDs, PCDFs, and PCBs with growth measures (i.e., changes in weight, length, and head circumference) up to 42 mo, except for a negative association with length gain, but not with weight gain or head circumference gain, from 3–7 mo of age. They also reported a statistically significant negative association in breastfed infants in comparison with formula-fed infants for growth rate for weight and length from 3–7 mo. Finally, Grandjean et al. (2003) found a significant negative association between PCB exposure and height and weight in 18-mo-old children, which was no longer observed at 42 mo of age.

Growth and maturation in cohorts of older children. Gladen et al. (2000) found no association between lactational exposures to PCBs or DDE and height, weight, or pubertal development in 10- to 16-y-old children. Leijds et al. (2008) also found no association between lactational exposures to PCDDs and PCDFs and weight, height, head circumference, axillary hair, age at pubic hair development, pubic hair stage, breast development, age of menarche, age at first ejaculation, male genital development, testicular volume, or BMI in 14- to 19-y-old individuals. They did, however, find a significant positive association between age at first breast development in girls and lactational exposures when exposure was estimated either by TEQs in breast milk or by cumulative lactational exposure. These two studies focused on different chemicals, and their results cannot be compared directly (Figure 3).

Assessment of study quality and risk of bias. The strongest studies were conducted by Ilsen et al. (1996), Pluim et al. (1996), Rogan et al. (1987), and Yalçin et al. (2015). These studies' relative strength across all features examined in the study quality assessment, and for exposure assessment in particular, lends more weight to their findings. Of these studies, only Yalçin et al. (2015) reported statistically significant associations between persistent chemical exposures from breast milk and differences in growth, and, even then, the only affected parameter was head circumference (decreased with increased breast milk β -HCH and DDT levels). Additional studies are needed to confirm these findings. Criswell et al. (2017) reported an association between breast milk β -HCH levels and infant growth rate but did not evaluate head circumference. Yalçin et al. (2015) is the only study of breast milk DDT levels and childhood growth, and studies of DDE have found no association between breast milk exposures and infant growth measures, including head circumference (Du et al. 2016, 2017; Gladen et al. 2000; Rogan et al. 1987). Both of the next-highest ranked studies (Jackson et al. 2010; Jacobson et al. 1990) also reported null findings, except that Jackson et al. (2010) noted that PCB 77 was significantly inversely associated with length z -score. Leijds et al. (2008) found significant results for age at first breast development in girls and exposure to dioxin TEQs in breast milk, but this study received only a midrange quality score; it neither included an assessment of various factors affecting growth and development after weaning, nor did it state whether outcome assessors were blinded. Other studies do not provide evidence supporting or refuting a potential association between exposure to dioxins in breast milk and age at first breast development. Although no other study included in our review analyzed associations with dioxins and pubertal development, Gladen et al. (2000) found no association with PCBs or DDE in breast milk and pubertal development.

In general, the literature does not reveal a consistent association between environmental chemical exposure via breastfeeding and growth and maturation in infants and children, and the strongest studies generally reported null findings.

Infant/child morbidity. Eight publications examined associations between lactational exposures to environmental chemicals and childhood morbidity or illness (Figure 4); these studies derive from five cohorts (Dewailly et al. 2000; Glynn et al. 2008; Rogan et al. 1987; ten Tusscher et al. 2001, 2003; Weisglas-Kuperus et al. 2000, 1995, 2004). Outcomes associated with organochlorine pesticides were assessed in three of the studies, with the remainder focused on PCDDs, PCDFs, and PCBs. The ages of the children at time of examination ranged from birth to approximately 12 y of age.

Morbidity in children up to approximately 42 months of age. Glynn et al. (2008) found significant associations between fewer respiratory infections and postnatal exposure to PCB 153



Figure 2. Growth measures from birth to 4 y of age. Study results are summarized according to outcome and chemical class. Each symbol represents a single evaluation of a potential association between exposure and outcome. Studies often evaluate multiple potential associations (e.g., at different time points, with exposures to different chemicals), so there may be multiple symbols shown for a single study. Symbol color represents the study or cohort in which the potential association was evaluated. Many cohorts are evaluated in multiple publications, so evaluations from multiple studies may be displayed in the same color. Symbol shape indicates whether a statistically significant association was observed for that evaluation and, if so, the direction of the observed association. Symbol size represents overall risk of bias, with larger symbols for evaluations conducted by studies judged to be at lower risk of bias (Table S2). Additional details about each evaluation (e.g., the age of study participants at outcome measurement, the specific chemical(s) measured in breast milk, the specific study corresponding with each evaluation, details of risk of bias determinations) can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure2?:embed=y&:display_count=yes. Note: DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCE, heptachlor epoxide; HCH, hexachlorocyclohexane; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; PFAS, per- and polyfluoroalkyl substance; TEQ, toxic equivalent.

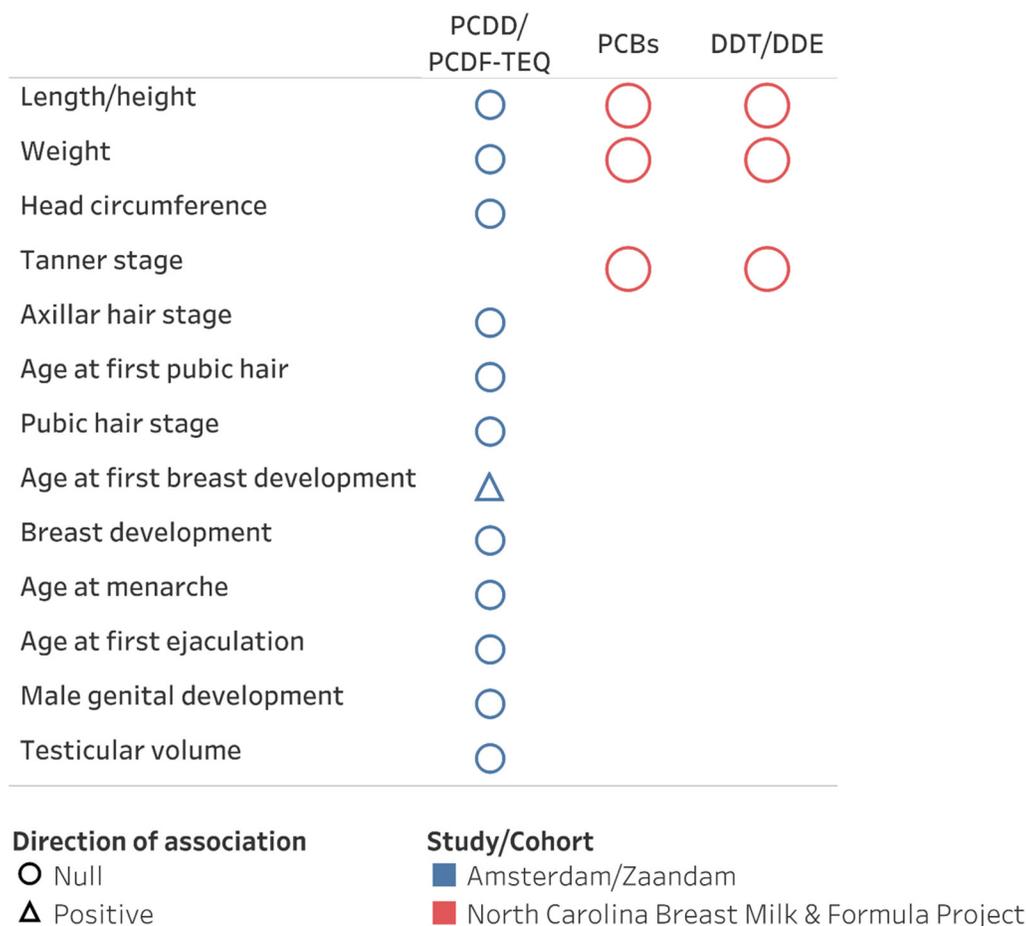


Figure 3. Growth and maturation in adolescents. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure3?:embed=y&:display_count=yes. Note: DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; TEQ, toxic equivalent.

and di-ortho PCBs in the highest exposed infants in comparison with the reference category. Associations for the other exposure groups for *p,p'*-DDE and mono-ortho PCB-TEQ suggested a U-shaped relationship. Rogan et al. (1987) reported a decrease in allergy with lactational exposure to DDE and a decrease in lower respiratory illness with exposure to PCBs, but no association between PCBs and DDE and upper respiratory illnesses, otitis media, gastroenteritis, eczema, or asthma in children up to 1 y of age. Dewailly et al. (2000) compared outcomes across exposure groups of breastfed children and reported a higher risk of acute otitis media with exposures to HCB, DDE, dieldrin, and mirex at 7 mo of age, and, until 12 mo of age, otitis media increased with tertiles of exposure to HCB and DDE. There was no association observed between otitis media and PCB exposure at any age; nor were there associations between lactational exposures to any of the measured chemicals and bronchitis or pneumonia (Dewailly et al. 2000). For children up to 1 y of age, Dewailly et al. (2000) found no significant difference between breastfed and formula-fed children in terms of organochlorine pesticide exposure and otitis media or bronchopulmonary disease; they also observed fewer pulmonary infections and lower risk of pneumonia in breastfed children.

Weisglas-Kuperus et al. (1995) found no association between lactational exposure to PCBs, PCDDs, and PCDFs (expressed as total TEQ) and rhinitis, bronchitis, tonsillitis, or otitis media in children up to 18 mo of age. At 42 mo of age, lactational

exposure to dioxin-like PCBs (expressed as PCB-TEQ) was significantly positively associated with otitis media, but not with pneumonia, scarlatina, chicken pox, asthma or bronchitis, coughing, chest congestion or phlegm, attacks of shortness of breath with wheeze, allergy, or eczema (Weisglas-Kuperus et al. 2000). Total TEQs (incorporating measurements of PCDDs and PCDFs) were not associated with any of these outcomes (including otitis media) at 42 mo, except for a positive association with coughing, chest congestion, and phlegm (Weisglas-Kuperus et al. 2000).

The significant association between lactational DDE exposure and otitis media reported by Dewailly et al. (2000) was not observed by Rogan et al. (1987). Similarly, the positive association between lactational exposures to PCBs and otitis media reported by Weisglas-Kuperus et al. (2000) was not found by Rogan et al. (1987). However, differences in study design complicate the interpretation of differences in the results of these studies. Rogan et al. (1987) assessed lactational exposure to total PCBs (including both dioxin-like and nondioxin-like PCB congeners) and evaluated effects in children during the first year of life. Weisglas-Kuperus et al. (2000) conducted their outcome assessment at 42 mo of age and found an association between otitis media and dioxin-like PCBs. Differences in both the chemicals analyzed and in the timing of outcome assessment could contribute to differences in study findings.

Morbidity in children at school age. All the studies on child morbidity at school age included PCDDs and PCDFs, whereas

	TEQ	PCBs	Organochlorine pesticides
Respiratory infection	▽	○▽▽	▽
Upper respiratory infection		○○○	○○○
Bronchitis	○○○○○	○○○	○○○○○○○○○○ ○○○○
Lower respiratory infection		▽	○
Pneumonia	○○○	○○○	○○○○○○○○○○ ○○○○
Coughing, chest congestion, or phlegm	○○△△		
Shortness of breath with wheeze	○○○○	○○	
FEV1/FVC ratio	▽		
Asthma	○○○	○	○
Rhinitis	○		
Otitis media	○○○○○△△	○●○○○●○○△	○○○●○○○○○○○ △△△△△△
Tonsillitis	○		
Gastroenteritis		○○○	○○○
Chicken pox	○○○○○	○○	
Scarlatina	○○○		
Allergy	○○○○○▽	○○○	▽
Eczema	○○○	○	○

Direction of association
○ Null
▽ Negative
△ Positive

Study/Cohort
■ Amsterdam/Zaandam
■ Dewailly et al. (2000)
■ Glynn et al. (2008)
■ North Carolina Breast Milk & Formula Project
■ Rotterdam/Groningen

Figure 4. Infant/child morbidity. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure4?:embed=y&:display_count=yes. Note: FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity; PCB, polychlorinated biphenyl; TEQ, toxic equivalent.

one also included PCBs. For children between the ages of 7 and 12 y, lactational PCDD and PCDF exposures (estimated both as TEQs in breast milk and as cumulative exposure over the breastfeeding duration) were significantly negatively associated with forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) and positively associated with chest congestion (for TEQs in breast milk only), but results were null for otitis media, allergy, and airway diseases such as bronchitis (ten Tusscher et al. 2001). The authors obtained data on other outcomes, including coughing spells, dyspnoea, asthma, pneumonia, chickenpox, measles, and atopy, reporting the results for several of these outcomes in a later publication (ten Tusscher et al. 2003). Lactational exposures to PCDDs/PCDFs were significantly negatively associated with allergies for both exposure metrics; findings were null for otitis media, pneumonia, and chicken pox. In the Rotterdam/Groningen cohort from preschool age to school age, Weisglas-Kuperus et al. (2004) found no association between PCDDs/PCDFs/PCBs in breast milk and chicken pox, allergic reaction, or shortness of breath/whoeze. There were significant positive associations with middle ear infection for PCBs (expressed as the sum of four PCB congeners in breast milk multiplied by the breastfeeding duration) and also for children breastfed less than 4 mo in comparison with children breastfed for more than 4 mo. As in ten Tusscher et al. (2001, 2003), no association was found between ear infections and TEQs in breast milk. Weisglas-Kuperus et al. (2004) also observed no significant difference in shortness of breath with wheeze between children breastfed less than 6 wk and greater than 4 mo. Children who had been breastfed for less than 4 mo had a higher risk of ear infection and less shortness of breath in comparison with those breastfed for greater than 4 mo.

It is difficult to interpret the results for the children of school age, because no information on various factors that influence morbidity in the years between weaning and outcome assessment was provided, and it is not clear if this information was obtained. There was only one study on lung function (ten Tusscher et al. 2001), so assessing overall strength of evidence across studies is not possible. The lung function study (ten Tusscher et al. 2001) and one other study (Weisglas-Kuperus et al. 2000) found statistically significant positive associations between TEQs in breast

milk and chest congestion in children 7–12 y old and 42 mo of age, respectively (although the latter study combined coughing, chest congestion, and phlegm). Results for allergy and ear infections were different across studies. Again, for ear infections, there were differences in the chemicals analyzed. Weisglas-Kuperus et al. (2004) found a positive association between middle-ear infection and lactational exposure to PCBs expressed as the sum of four congeners (PCBs 118, 138, 153, and 180). However, neither this study nor ten Tusscher et al. (2001) and ten Tusscher et al. (2003) observed such an association when exposure was expressed as total TEQs. For allergy, ten Tusscher et al. (2003) reported a negative association with lactational exposure to PCDDs/PCDFs expressed as total TEQ whereas Weisglas-Kuperus et al. (2004) found no association between total TEQ in breast milk and allergic reaction. These studies defined allergies and assessed their prevalence using similar methods. Even so, many factors could influence study results, including difference in exposures and exposure assessments, breastfeeding duration, and parental medical histories.

Assessment of study quality and risk of bias. The highest quality studies for this outcome category include Dewailly et al. (2000), Rogan et al. (1987), and ten Tusscher et al. (2003). Dewailly et al. (2000) and Rogan et al. (1987) reported contrasting findings for otitis media and DDE exposure. Weisglas-Kuperus et al. (2000) reported a significant, positive association between lactational exposures to dioxin-like PCBs and otitis media. Weisglas-Kuperus et al. (2004) found a significant, positive association between exposure to four PCB congeners and middle-ear infection, a negative association with being breastfed for greater than 4 mo, and no association between total TEQ exposure and allergic reaction. However, both of these studies had four lower rankings in quality categories (blinding, confounding, missing outcome data, and selective reporting), tempering their contribution to the strength of evidence. ten Tusscher et al. (2003), for which only one scoring criterion (confounding) was below the highest ranking, reported that TEQs in breast milk were not associated with otitis media but were inversely and significantly associated with allergy.

Overall, the literature reviewed here shows almost no consistent evidence supporting associations between exposure to various

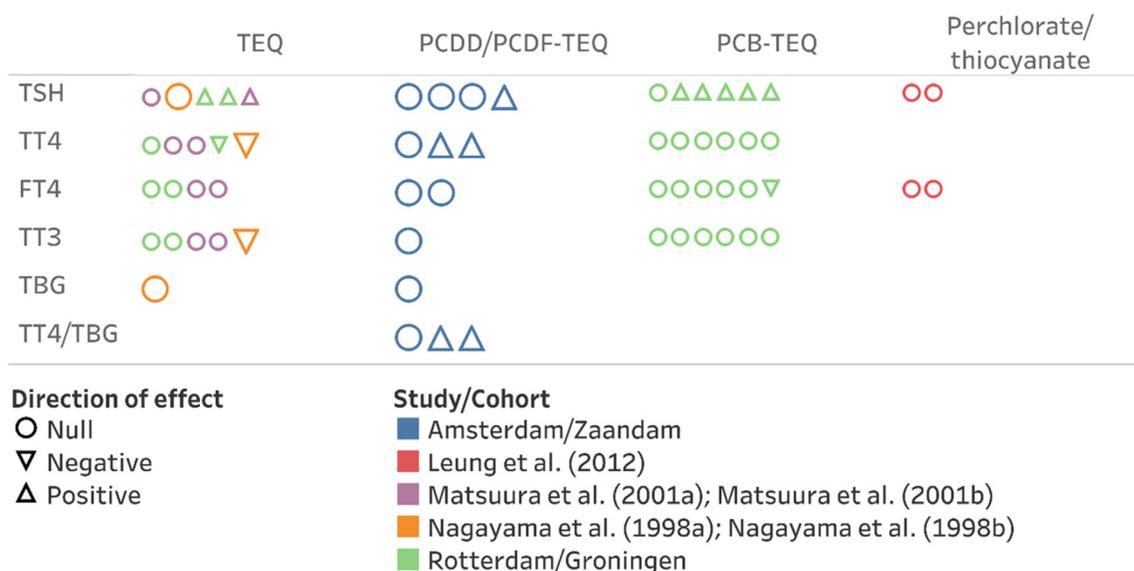


Figure 5. Thyroid hormones. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure5?:embed=y&:display_count=yes. Note: FT4, free thyroxine; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxin; PCDF, polychlorinated dibenzofuran; TBG, thyroxine binding globulin; TEQ, toxic equivalent; TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine.

environmental chemicals via breastfeeding and several health outcomes, such as otitis media, and allergic and infectious diseases, for ages ranging from infancy to school age. The ten Tusscher et al. (2001) study reported significant associations between the TEQs in breast milk and chest congestion in children at 7–12 y old, a finding that mirrors the findings that Weisglas-Kuperus et al. (2000) reported in younger children (42 mo), although the latter study combined coughing, chest congestion, and phlegm. Other study findings were not replicated in multiple studies, making this finding one of the more concordant results related to morbidity.

Biomarkers in infants and children. Nineteen studies used biomarkers to assess potential health outcomes or outcome pathways. In the following subsections, we evaluate the evidence regarding infant

exposure to organic environmental chemicals in breast milk and effects on thyroid hormone levels in infants and children (Figure 5), on biomarkers of the immune system in infants and children (Figures 6 and 7), on hematological parameters in infants and children (Figure 8), on liver function parameters in infants and children (Figure 8), and on reproductive and growth biomarkers in infants and children (Figure 9). Strength-of-evidence discussions are included in each subsection.

Thyroid hormones. Eight studies examined associations between chemicals in breast milk and thyroid hormone levels in infants and children (Ilsen et al. 1996; Koopman-Esseboom et al. 1994; Leung et al. 2012; Matsuura et al. 2001a, 2001b; Nagayama et al. 1998a; Pluim et al. 1993; ten Tusscher et al. 2008) (Figure 5). Seven of these studies included measurements

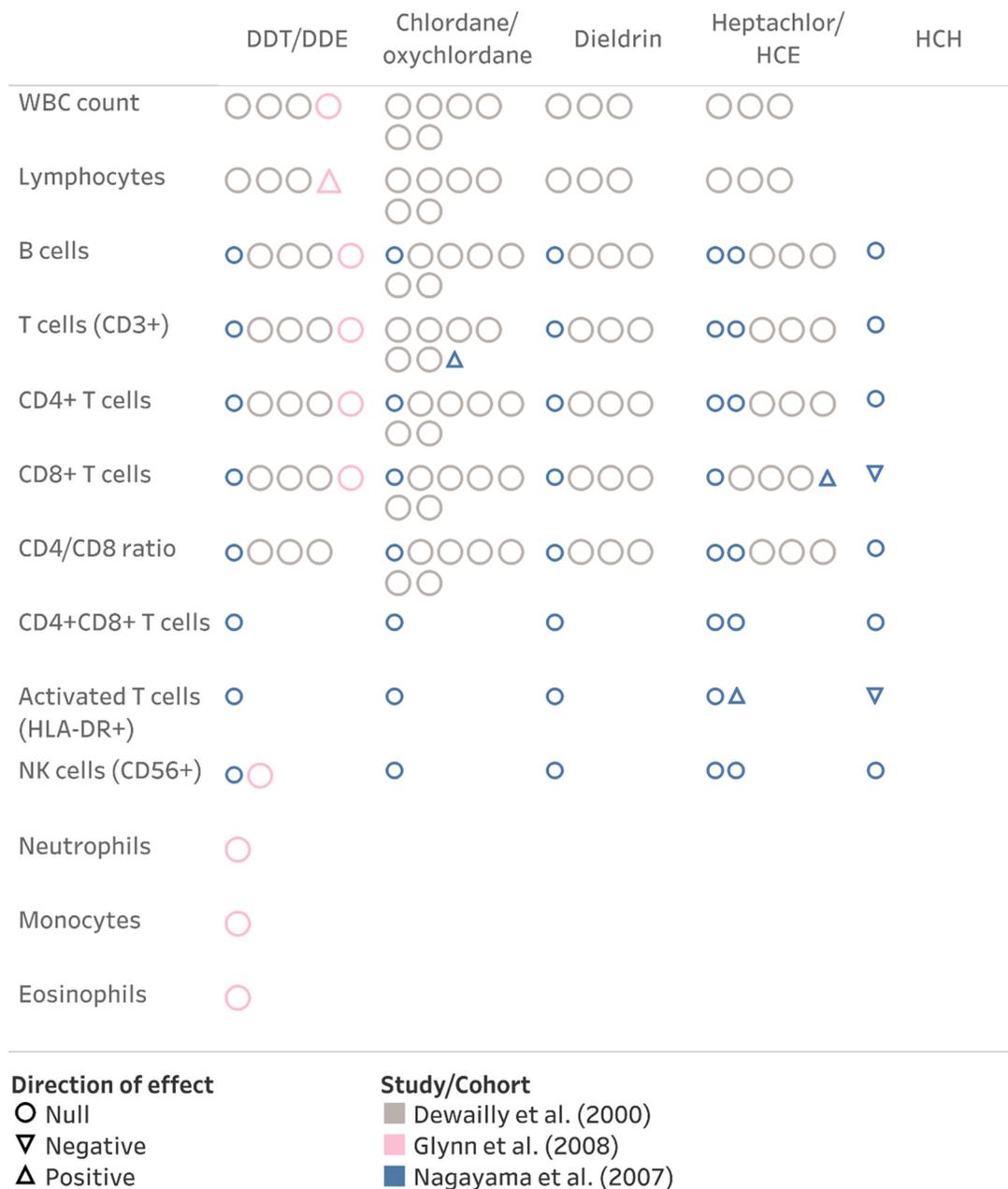


Figure 6. Immune biomarkers and exposure to organochlorine pesticides. Study results are summarized according to outcome and chemical. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure6?:embed=y&:display_count=yes. Note: DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCE, heptachlor epoxide; HCH, hexachlorocyclohexane; NK, natural killer; WBC, white blood cell.

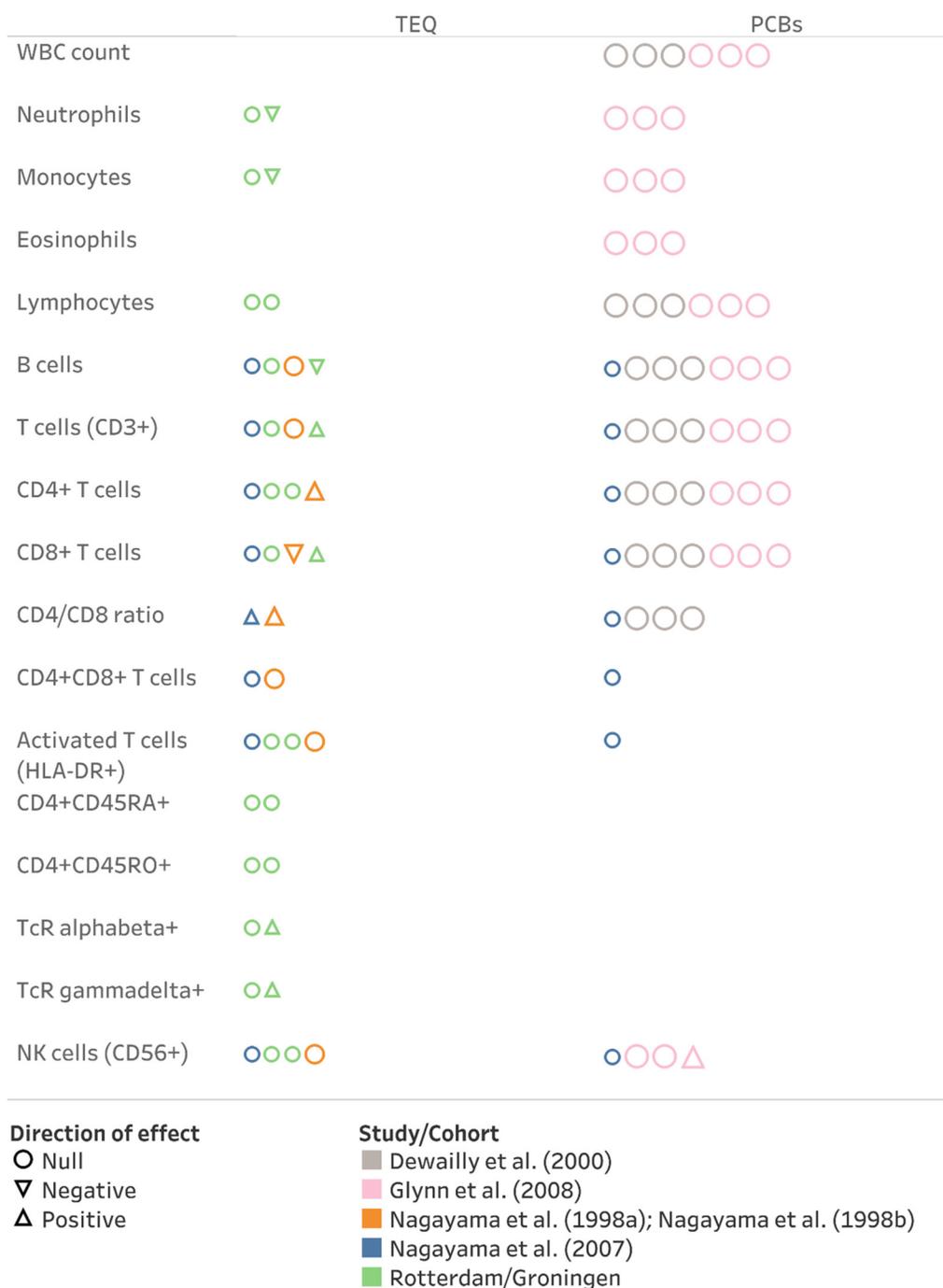


Figure 7. Immune biomarkers and exposure to dioxin-like chemicals and PCBs. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure7?:embed=y&:display_count=yes. Note: NK, natural killer; PCB, polychlorinated biphenyl; TEQ, toxic equivalent; WBC, white blood cell.

of dioxin-like chemicals; Leung et al. (2012) measured perchlorate and thiocyanate.

Results differed across studies of PCDDs, PCDFs, and PCBs. Ilse et al. (1996) and ten Tusscher et al. (2008) reported null results for all associations with PCDDs/PCDFs (expressed both as TEQs in breast milk and as cumulative exposure across the breastfeeding duration) and thyroid hormones: total triiodothyronine (TT3), total thyroxine (TT4), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroxine binding globulin (TBG), and TT4/TBG for Ilse et al. (1996), and TSH and FT4 for ten

Tusscher et al. (2008). The children in these two studies were 31 mo of age and 7–12 y of age, respectively, and thus experienced a longer postweaning duration in comparison with the other cohorts, which all comprised children around 1 y of age or younger.

Pluim et al. (1993) reported that for the group exposed to higher dioxin-TEQ levels in breast milk, there was a significant positive association with plasma TT4 and TT4/TBG at both 1 and 11 wk of age and with TSH at 11 wk. When the analysis was restricted to only infants who were breastfed for at least 11 wk, there were no significant differences in infant plasma levels of

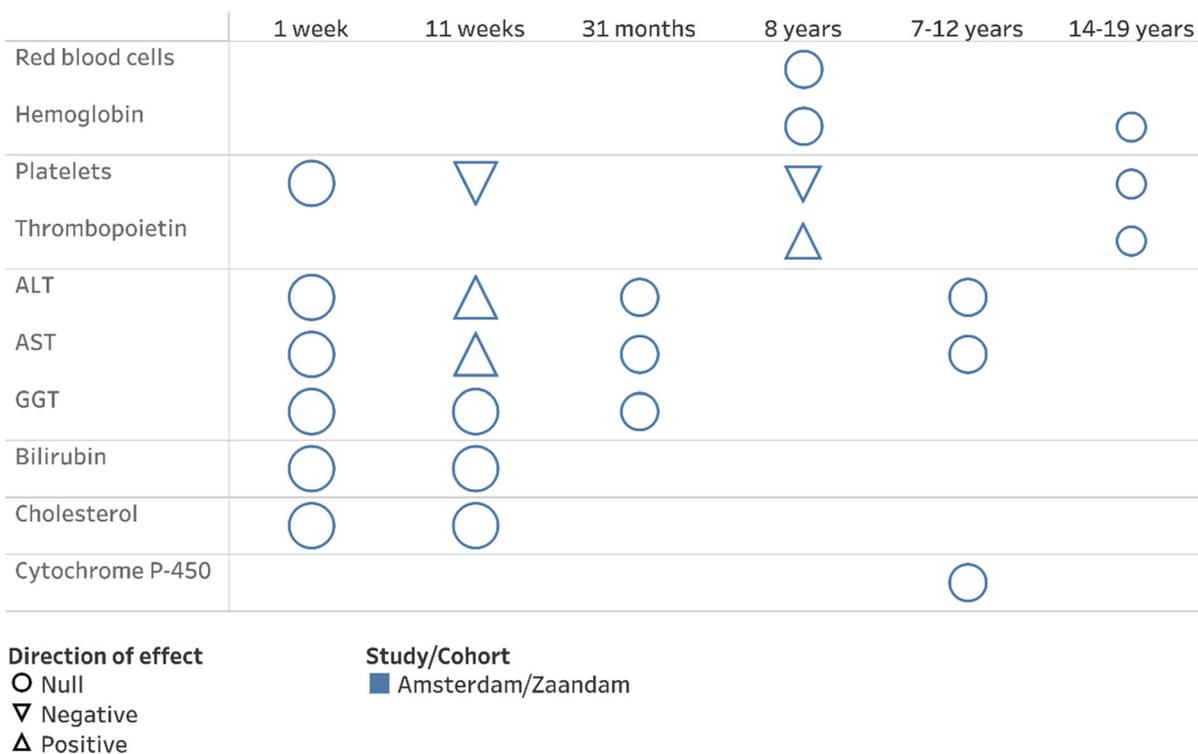


Figure 8. Hematology and biomarkers of liver function. Study results are summarized according to outcome and age at evaluation. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure8?:embed=y&:display_count=yes. Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

TT4, TBG, and TSH at 11 wk. However, TT4/TBG, which is a surrogate measure of FT4 levels, was still significantly higher in the higher exposure group. Koopman-Esseboom et al. (1994) assessed thyroid hormone levels at 2 wk and 3 mo of age, finding no significant associations between dioxin- or PCB-TEQ and TT3. However, there was a significant negative association between total dioxin-PCB-TEQ and both TT4 and FT4 at 2 wk only and a significant positive association with TSH at both 2 wk and 3 mo (Koopman-Esseboom et al. 1994). Matsuura et al. (2001a) and Matsuura et al. (2001b) found no association between total dioxin-PCB-TEQ and TT3, TT4, and FT4 in breastfed infants (and antithyroglobulin and antimicrosomal antibody tests were negative). TSH levels were significantly higher in breastfed infants compared to formula-fed infants in Matsuura et al. (2001b), but the result became null when data were analyzed from a larger group of infants (sample sizes increased from 55 in the breastfed group and 30 in the formula-fed group to 337 and 53, respectively) (Matsuura et al. 2001a). Nagayama et al. (1998a) observed a significant negative association between total dioxin-PCB TEQ in breast milk and TT4 and TT3 in infants at 1 y of age but found no association with TBG or TSH.

Although it is difficult to draw strength-of-association conclusions across these studies due to differences in study design, several of the study authors who reported significant findings placed their results in a child health context. For example, Pluim et al. (1993) stated that “the change in circulating TT4 and TSH concentration does not prove that functional thyroid status has been affected by pre- and postnatal exposure to dioxins.” Koopman-Esseboom et al. (1994) found that the thyroid hormone levels were in the normal range, but cautioned that the “small changes observed in this study might be of influence on the development of the fetus and infant.” Nagayama et al. (1998a) did not provide health context for the thyroid hormone levels in their study, but

LaKind et al. (2008) stated that the TSH levels generally fell within—and TT4 and TT3 levels were within or slightly higher than—published reference ranges.

One study examined the relationship between perchlorate and thiocyanate in breast milk and thyroid hormone levels in infants. Leung et al. (2012) conducted a cross-sectional study in 64 Boston-area mothers and their 1–3 mo-old infants. They found no correlations between infant TSH or FT4 and breast milk levels of perchlorate and thiocyanate. With only one study available for these chemicals, it is not possible to explore strength of association.

The studies with the highest rankings were Ilsen et al. (1996), ten Tusscher et al. (2008), and Pluim et al. (1993), with each study having only one lower score due to confounding, lack of information on postweaning exposures, or because prenatal exposures were not assessed in the lactational exposure effects model. None of the highest quality studies for this outcome category included exposure to PCBs in their analysis. Pluim et al. (1993) was the only one of these highest quality studies to evaluate thyroid hormone levels in young infants and the only one to observe an association between thyroid hormone levels and lactational exposure. The direction of this association was opposite that observed in some other studies of young infants (Koopman-Esseboom et al. 1994; Nagayama et al. 1998a), and it is possible that the difference in results may be explained by differences in study quality or by differences in the chemicals included in the analyses (dioxin TEQs vs. total dioxin/PCB TEQs). The other two highest quality studies found no associations in older children when considering dioxin TEQs (Ilsen et al. 1996; ten Tusscher et al. 2008). One study in young infants observed no association between lactational exposures to PCDDs/PCDFs/PCBs and changes in thyroid hormone levels (Matsuura et al. 2001a, 2001b), but that study had lower rankings in a number of quality categories, including recruitment strategy, exposure assessment, confounding, missing outcome

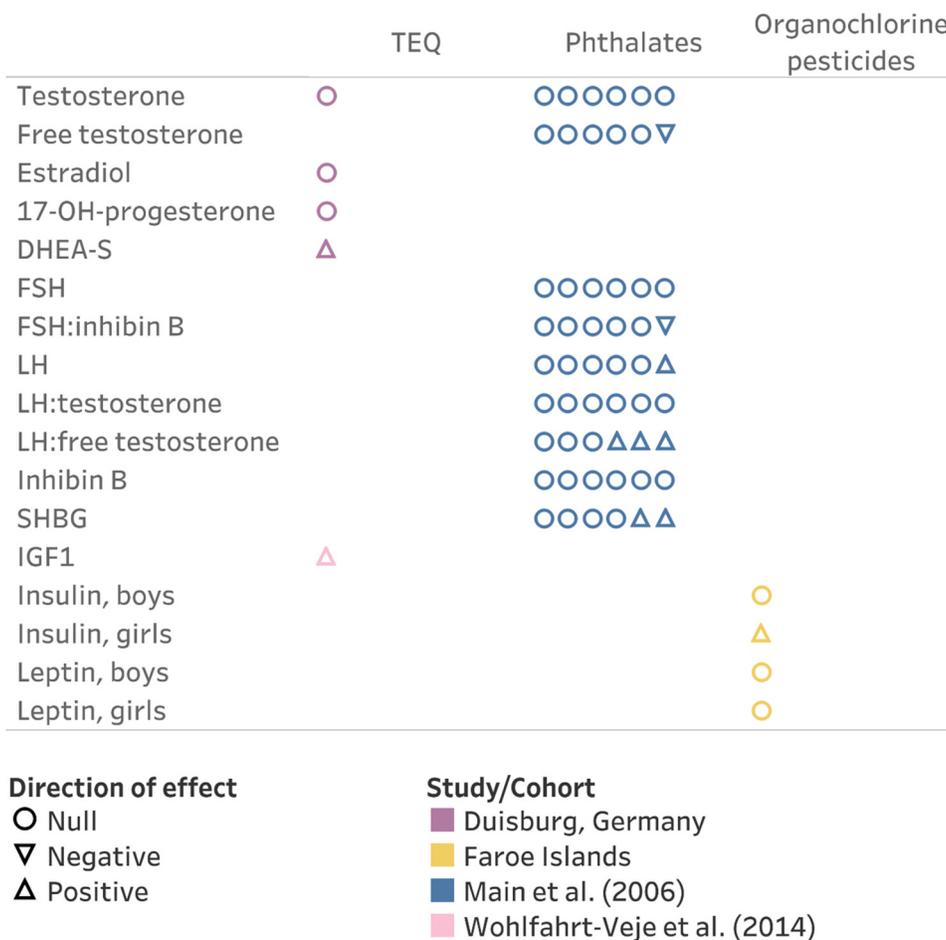


Figure 9. Reproductive and growth hormones and regulators. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure9?:embed=y&:display_count=yes. Note: DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; IGF 1, insulin-like growth factor 1; LH, luteinizing hormone; SHBG, sex-hormone binding globulin; TEQ, toxic equivalent.

data, and selective reporting. Two studies reported significantly higher TSH levels with higher total dioxin-PCB-TEQ levels in breast milk [Pluim et al. (1993) ($n = 38$), Koopman-Esseboom et al. (1994) ($n = 78$)], and one reported significantly higher TSH levels in breastfed infants in comparison with formula-fed infants [Matsuura et al. (2001b) ($n = 85$)]. However, that difference disappeared when the original, smaller cohort was included within a larger cohort ($n = 390$) (Matsuura et al. 2001a).

In general, there is a lack of consistent findings across studies supporting associations between infant exposure to environmental chemicals from breastfeeding and thyroid hormone levels in infants and children.

Immune system. Nine studies examined associations between environmental chemicals in breast milk and immunologic biomarkers (Dewailly et al. 2000; Glynn et al. 2008; Leijts et al. 2009; Nagayama et al. 1998b, 2007; Pluim et al. 1994; ten Tusscher et al. 2003; Weisglas-Kuperus et al. 2000, 1995). Three of these studies measured organochlorine pesticides (Dewailly et al. 2000; Glynn et al. 2008; Nagayama et al. 2007); all nine measured PCDDs, PCDFs, and/or PCBs.

Only DDE was evaluated in all three studies of organochlorine pesticides in breast milk and immunologic biomarkers (Figure 6). One of these studies (Glynn et al. 2008) reported an association between breast milk DDE levels and changes in white blood cell (WBC) populations: at 3 mo of age, infants in the highest postnatal DDE exposure group (determined using the DDE concentration in

breast milk 3 wk after delivery, the number of days of nursing, and the percentage of full nursing during the study period) had a significantly higher percentage of lymphocytes than infants with the lowest exposure in simple regression analysis. However, the difference was no longer significant when the means were adjusted for age of the mother, smoking and alcohol consumption during pregnancy, mother's education, vaccination of the infant, nursing of the infant, age of the infant, and the infant's history of respiratory infections. Dewailly et al. (2000) reported no association between DDE in breast milk and lymphocyte numbers in infants up to 12 mo of age. Although Nagayama et al. (2007) reported a lack of association between DDE exposure and lymphocyte subsets in 10-mo-old infants, they reported no information on the lymphocyte fraction as a whole.

Dieldrin and heptachlor epoxide were measured by Dewailly et al. (2000) and Nagayama et al. (2007). Neither study reported an association between breast milk dieldrin levels and changes in immunologic biomarkers. Nagayama et al. (2007) observed positive significant associations between heptachlor epoxide and CD8+ cells and HLA-DR+ cells. Dewailly et al. (2000) did not find an association between CD8+ cells and lactational exposure to heptachlor epoxide, and did not evaluate the abundance of HLA-DR+ cells. Although "chlordane" was evaluated by both Dewailly et al. (2000) and Nagayama et al. (2007), Dewailly et al. (2000) based their chlordane assessment on measurements of *cis*- and *trans*-chlordane, whereas Nagayama et al. (2007) measured

chlordan exposure as the sum of oxychlordan and *trans*- and *cis*-nonachlor. Dewailly et al. (2000) observed no association between immunologic biomarkers and chlordan levels in breast milk, whereas Nagayama et al. (2007) reported a positive significant association between chlordan and T cells.

Dewailly et al. (2000) found that infants who were breastfed at 3 mo of age had significantly lower levels of WBCs and lymphocytes, whereas at 7 and 12 mo of age, breastfed infants had significantly lower IgA levels in comparison with formula-fed infants [several chemicals in breast milk were measured (Table S1), but this comparison was simply for breastfed and formula-fed infants]; however, there were no clinically relevant differences between breastfed and formula-fed infants. Only one study explored associations between hexachlorocyclohexane in breast milk and immune system effects (Nagayama et al. 2007); negative associations were observed between hexachlorocyclohexane and CD8+ and HLA-DR+ cells in infants at 10 mo of age. Nagayama et al. (2007) further noted the importance of examining the effect of mixtures of chemicals on associations with immune system outcomes, reporting a positive association between CD8+ cells and co-exposure to heptachlor epoxide and chlordan in breast milk and a negative association between CD16+ cells and coexposure to DDT and PCBs.

In summary, three studies investigated organochlorine pesticides and immune system biomarkers (Dewailly et al. 2000; Glynn et al. 2008; Nagayama et al. 2007). All three evaluated DDE: Two of the three reported lymphocyte numbers, but only one of these found a significant association (Glynn et al. 2008). Neither of the two studies that measured dieldrin found an association (Dewailly et al. 2000; Glynn et al. 2008). One (Nagayama et al. 2007) of two studies evaluating heptachlor epoxide found associations with CD8+ and HLA-DR+ cell populations. However, the other study (Dewailly et al. 2000) did not count HLA-DR+ cells. The results of the two studies evaluating chlordan (Dewailly et al. 2000; Nagayama et al. 2007) are not directly comparable because they measured different components of the chlordan mixture.

Three of the studies that explored associations between PCDDs, PCDFs, and/or PCBs in breast milk and biomarkers of immune function conducted analyses of PCBs independent of their potential dioxin-like activity (Dewailly et al. 2000; Glynn et al. 2008; Nagayama et al. 2007); the remaining studies focused exclusively on analyses of TEQs (Figure 7). Although Glynn et al. (2008) reported mostly null results for associations between breast milk PCB levels and WBC and lymphocyte subsets in 3-mo-old infants, they reported a significant positive association with CD56+ cells in infants in the second highest exposure group of lactational PCB-153 exposure. Nagayama et al. (2007) did not observe an association between PCB exposure and CD56+ cells, and Dewailly et al. (2000) did not evaluate CD56 expression.

Of the remaining studies investigating relationships between dioxin-like activity (TEQ) in breast milk and immunologic biomarkers, five evaluated WBC differentials (Leijs et al. 2009; Pluim et al. 1994; ten Tusscher et al. 2003; Weisglas-Kuperus et al. 2000, 1995). No associations with breast milk TEQ were reported for WBC counts or percentages of lymphocytes. Weisglas-Kuperus et al. (1995) reported significant negative associations between TEQs in breast milk and monocytes and granulocytes in infants at 3 mo of age with results becoming null at 18 mo of age. When the children reached 42 mo of age, no significant associations were reported between TEQs and any WBC population (Weisglas-Kuperus et al. 2000). Pluim et al. (1994) observed a significant inverse relationship between the number of polynuclear neutrophils and breast milk TEQ in infants from the Amsterdam cohort at 1 wk of age. However, the association was no longer significant when gestational age was included as a confounding factor in the analysis, and no association was detected with or without

adjustment for confounders at 11 wk of age. Associations between lactational exposure to dioxin-like compounds and neutrophil and monocyte numbers were not observed in children at 8 y of age (ten Tusscher et al. 2003) or at 14–19 y of age (Leijs et al. 2009).

Five studies collected data on TEQs in breast milk and lymphocyte subsets in children at ages ranging from 3 mo to 8 y (Nagayama et al. 1998b, 2007; ten Tusscher et al. 2003; Weisglas-Kuperus et al. 2000, 1995). Weisglas-Kuperus et al. (1995) reported a significant negative association between TEQs in breast milk and B cells in infants at 3 mo of age. However, the association was no longer significant at 18 or 42 mo of age (Weisglas-Kuperus et al. 2000, 1995). Furthermore, no associations between lactational exposure to TEQs and B cell numbers were reported in children at 1 or 8 y of age (Nagayama et al. 1998b; ten Tusscher et al. 2003).

On the other hand, although Weisglas-Kuperus et al. (1995) reported no significant associations between TEQs and the numbers of T cells, CD8+ T cells, and TcR $\alpha\beta$ + and TcR $\gamma\delta$ + T cells at 3 mo of age, there were significant positive associations for all of these at 18 mo of age. When the children reached 42 mo of age (Weisglas-Kuperus et al. 2000), these associations were no longer significant. No associations between breast milk TEQs and T cell numbers were reported by Nagayama et al. (1998b, 2007) or by ten Tusscher et al. (2003). Nagayama et al. (1998b, 2007) reported a positive significant association between lactational exposure to TEQs and the ratio of CD4+ /CD8+ cells in infants around 10–12 mo of age. Although Nagayama et al. (1998b) reported a corresponding increase in CD4+ cells and a decrease in CD8+ cells with increasing breast milk TEQ, no significant associations between TEQ and CD4+ or CD8+ cells were observed in Nagayama et al. (2007). As mentioned above, Weisglas-Kuperus et al. (1995) observed a significant positive association between TEQs in breast milk and CD8+ T cells at 18 mo of age although there was no association with CD8+ T cells at 3 or 42 mo of age (Weisglas-Kuperus et al. 2000) and no association with CD4+ T cells at any time point in this cohort. However, cumulative lactational exposure to TEQs was significantly positively associated with CD4+ cell counts in children from the Amsterdam cohort at 8 y of age (ten Tusscher et al. 2003). ten Tusscher et al. (2003) also observed a significant positive association between lactational TEQ exposure and CD45RA+ cell counts in children at 8 y of age, which was not observed in children from 3–42 mo of age (Weisglas-Kuperus et al. 2000, 1995).

In general, it is once again difficult to draw strength-of-evidence conclusions from this set of studies. The results of studies that investigated PCDDs, PCDFs, and PCBs and immune system biomarkers were generally null or tended to become null as the age of the children increased. A possible exception is a positive association observed between lactational exposure to dioxin-like compounds and the number of CD4+ T cells, especially relative to CD8+ T cells, in infants at both 10–12 mo and 8 y of age (Nagayama et al. 1998b, 2007; ten Tusscher et al. 2003). However, this association was not observed in studies by Weisglas-Kuperus et al. (1995, 2000).

In terms of study quality, the study by Dewailly et al. (2000) received the highest rating for all criteria; only one criterion (confounding) was below the highest ranking for ten Tusscher et al. (2003) and Pluim et al. (1994). Dewailly et al. (2000) found no association between PCBs in breast milk and biomarkers of immune function, whereas ten Tusscher et al. (2003) found an increase in CD4+ T-helper cells with increasing lactational exposure to dioxin-like compounds, which is similar to findings by Nagayama et al. (1998b, 2007). However, it is important to interpret any potential changes in biomarkers of immune function in the context of overall infant health. Regarding the findings of Nagayama et al. (2007), the authors noted uncertainty regarding

the clinical significance of their results, and the reported values were similar to available reference ranges for healthy children (LaKind et al. 2008). For the results of ten Tusscher et al. (2003), LaKind et al. (2008) noted: "Because information on background levels of CD4+ in healthy children is sparse and since CD4+ levels are affected by the time of day of blood draw, fatigue and stress levels, infections, and time since recent vaccinations. . . , the significance of the CD4+ results for the clinician is unclear."

Because there is little consistent evidence supporting an increased risk of infectious disease or other alteration in immune function in infants exposed to organochlorine pesticides or PCDDs/PCDFs/PCBs in breast milk (see above section on environmental chemicals in breast milk and infant/child morbidity), slight changes in biomarkers of immune function associated with exposure to environmental chemicals in breast milk are likely to be of limited clinical significance.

Hematology. Data from one cohort have been used to assess potential relationships between hematological parameters and exposures to PCDDs/PCDFs in breast milk (Figure 8). Pluim et al. (1994) found a significant negative association between cumulative lactational exposure to dioxins and platelet number measured at 11 wk of age; this relationship was observed again at 8 y of age, along with a corresponding positive association between exposure and thrombopoietin concentration (ten Tusscher et al. 2003). These associations were no longer seen at ages 14–19 y (Leijts et al. 2009). No associations were observed between lactational dioxin exposures and red blood cell counts or red blood cell mean volume at 8 y of age, or hemoglobin at 8 or 14–19 y of age (Leijts et al. 2009; ten Tusscher et al. 2003).

All three studies examining hematological parameters had a low risk of bias, with two receiving one lower rating for the criterion of confounding (Pluim et al. 1994; ten Tusscher et al. 2003) and one with an additional lower score for missing outcome data (Leijts et al. 2009). It is worth noting that Pluim et al. (1994) observed a decrease in platelet counts in 11-wk old infants, and the platelet counts in the children at 8 y of age ranged from $248\text{--}449 \times 10^9/\text{L}$ in comparison with a normal platelet count for adults of $150\text{--}350 \times 10^9/\text{L}$ (ten Tusscher et al. 2003). Although increased lactational exposure to dioxins was related to decreased platelet counts, the decreases were not of a large enough magnitude to result in thrombocytopenia. The consistent finding of decreased platelets with increased lactational exposure in early life and at age 8 may be of note. However, all three studies evaluated the same small ($n=35$) cohort of children in the Netherlands, and strength-of-evidence assessment is not possible.

Serum biochemistry: liver function. Data from one cohort have been used to assess potential relationships between exposures to PCDDs/PCDFs in breast milk and biomarkers of liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ -glutamyl transferase (GGT)] (Figure 8). Pluim et al. (1994) found that cumulative exposure to PCDDs/PCDFs in breast milk was significantly associated with plasma activities of ALT and AST in infants at 11 wk of age. They found no relationship between lactational exposure and plasma GGT, cholesterol, or total and conjugated bilirubin. When the children reached 2.5 y of age, AST, ALT, and GGT levels were not significantly different between high and low exposure groups (Ilsen et al. 1996). By the age of 7–12 y, the previously observed associations between lactational exposures and AST or ALT in infancy were no longer found, and results for cytochrome P-450 activity were null as well (ten Tusscher et al. 2008).

Each of the three studies looking at liver function–related biomarkers was ranked as having a low likelihood of bias with a lower score only for the criterion of confounding. Although plasma activities of ALT and AST were observed to be positively associated

with lactational dioxin exposure in 11 wk old infants (Pluim et al. 1994), the authors of that study noted that "The clinical significance of our findings is as yet unclear, because AST and ALT plasma activities were in the normal range (normal <54 units/L) in all but three infants, who had slightly elevated AST . . . and ALT . . . plasma activities." They concluded that background levels of dioxins might have subclinical effects on infants. As with hematological outcomes, relationships between lactational exposures and liver function data have been evaluated in only one small cohort and for only one class of environmental chemicals, and the positive association was only observed at one of the three time points in the study; thus, the generalizability of these results is limited, and a strength-of-evidence assessment is not appropriate.

Serum biochemistry: reproductive and growth biomarkers. Two studies provided information on reproductive biomarkers (Main et al. 2006; Rennert et al. 2012); two studies included a biomarker for growth (Tang-Peronard et al. 2015; Wohlfahrt-Veje et al. 2014) (Figure 9). The results of these studies are summarized below for completeness, but because of a lack of comparability, they cannot be considered together for a true strength-of-evidence examination. One biomarker was evaluated in more than one of these studies: testosterone was measured in boys at 3 mo of age by Main et al. (2006) and in children at 6–9 y of age by Rennert et al. (2012). However, Main et al. (2006) evaluated associations with breast milk levels of phthalates whereas Rennert et al. (2012) focused on associations with breast milk levels of PCDDs/PCDFs/PCBs (expressed as TEQs).

Main et al. (2006) found significant positive associations between mono-ethyl phthalate (mEP) and mono-*n*-butyl phthalate (mBP) in breast milk and serum levels of sex-hormone binding globulin (SHBG) in 3-mo-old boys. Positive associations were also observed between the serum luteinizing hormone (LH):free testosterone ratio and mono-methyl phthalate (mMP), mEP, and mBP and between serum LH and mono-isononyl phthalate (miNP). Significant inverse associations were reported between mBP and free testosterone and between mono-2-ethylhexyl phthalate (mEHP) and the follicle-stimulating hormone (FSH):inhibin B ratio. No associations were observed between any of the measured phthalates, including mono-benzyl phthalate (mBzP), and serum levels of testosterone, FSH, inhibin B, or the LH:testosterone ratio.

Rennert et al. (2012) observed no associations between lactational exposure to PCDDs/PCDFs/PCBs and testosterone, estradiol or 17-OH-progesterone in older children from the Duisburg cohort (6–7- and 8–9-y-old children). However, a positive association with dehydroepiandrosterone sulfate (DHEA-S) was observed.

Tang-Peronard et al. (2015) reported an association between HCB in breast milk and increased levels of serum insulin (girls only), but not leptin in the Faroese Birth Cohort. They did not find mediating effects of insulin or leptin on later obesity.

Wohlfahrt-Veje et al. (2014) examined associations between serum levels of insulin-like growth factor I (IGF1) and lactational exposure to PCDDs/PCDFs/PCBs (expressed as TEQs), nondioxin-like PCBs, polybrominated biphenyls (PBBs), PBDEs, perfluorooctanesulfonic acid (PFOS), and perfluorooctanoic acid (PFOA) in 3-mo-old infants. Results were reported only for total TEQs, for which a significant positive association was found. Although as described above, Wohlfahrt-Veje et al. (2014) also found a significant positive association between dioxins in breast milk on height (from 0–36 mo of age) and weight gain (from 0–18 mo of age), other studies have observed negative or no associations between breast milk dioxins and growth in children of similar ages (Ilsen et al. 1996; Jackson et al. 2010; Patandin et al. 1998; Pluim et al. 1996). None of these or any other studies provided data on associations with IGF1.

Main et al. (2006) ranked as one of the studies with the highest risk of bias across all the papers included in this review,

which may temper the strength of any findings. In particular, several potential deficits related to exposure assessment were noted. The publications by Rennert et al. (2012) and Wohlfahrt-Veje et al. (2014) had only two categories with lower quality ratings and both ranked lower for the criterion of confounding. In addition, lower rankings were assigned to the study by Rennert et al. (2012) for incomplete outcome data and to the study by Wohlfahrt-Veje et al. (2014) for incomplete exposure characterization. Because these three studies each looked at different chemical exposures or different outcomes, no strength-of-evidence conclusions were drawn.

Infant/child neurodevelopment. Neurodevelopment is the most frequently studied outcome category in this body of literature. For the purposes of examining strength of association across studies, the research is divided into two groups. First, we describe research that used parent questionnaires for child behavior, language, and/or developmental milestones [e.g., tests such as the Infant Toddler Social and Emotional Assessment (ITSEA), Behavior Assessment System for Children (BASC), MacArthur-Bates Communicative Development Inventories (MacArthur CDI), Ages & Stages Questionnaire (ASQ), Pre-School Activities Inventory (PSAI), Child Behavior Checklist/Teacher's Report Form (CBCL/TRF)]. We then describe the literature that used standardized researcher-administered tests in two categories. The first includes studies that used researcher assessments of motor development for children under approximately 6 mo of age [e.g., tests such as Pechtl/Neurological Optimality Score (NOS), Hempel, Psychomotor Development Index/Bayley Scales of Infant Development (PDI/BSID), the motor portion of the McCarthy Scales of Children's Abilities (MSCA)]. The second used standardized researcher-administered assessments of broader neurodevelopment beyond the first 6 mo, including IQ (i.e., intelligence quotient), motor function, memory, reaction time, and/or language [e.g., tests such as BSID, Mullen Scales of Early Learning (MSEL), MSCA, Fagan Test of Infant Intelligence (Fagan), Kaufman Assessment Battery for Children (Kaufman), Test of Attentional Performance for Children (KiTAP), Wechsler Intelligence Scales for Children-Revised (WISC-R), Reynell Developmental Language Scales (Reynell)] [one study that is not replicated in the literature is not discussed further; visual function—Riva et al. (2004)]. For an overview of the various neurodevelopmental assessments and measures, see Youngstrom et al. (2010).

Parent questionnaires for assessment of behavior and development. Eleven studies used a parent questionnaire to evaluate child development. Three examined PBDEs (Figure 10), one evaluated PFASs (Figure 11), one evaluated mercury (Figure 11), two included organochlorine pesticides (i.e., HCB, β -HCH, oxy-chlordane, and/or DDT/DDE) (Figure 11), and seven reported on PCDDs/PCDFs and/or PCBs (Figure 11).

Thirty-month-olds were assessed with the ITSEA, and a “small, imprecise, yet consistent positive association” was found between BDEs 47, 99, and 100 and increased externalizing behaviors (i.e., activity/impulsivity) (Hoffman et al. 2012); no similar association was found for BDE 28 or 153, and no associations were observed between these five PBDE congeners and other social and emotional developmental domains. Children from the same cohort were examined at 36 mo of age with the PRS-P (Parent Rating Scales-Preschool) of the BASC-2. Statistically significant increases in anxiety scores were observed for fourth quartile vs. first quartile for BDE-28, BDE-99, and BDE-100, but not for BDE 47 or 153; withdrawal scores increased with increasing BDE-28 breast milk levels, but results were not statistically significant for the other four PBDEs included in the analysis (Adgent et al. 2014). Improved activity of daily living skills was associated with increased breast milk levels of BDE-153. Adgent et al. (2014) stated, “While we did observe modest associations between PBDEs and increased anxiety and

withdrawal, we also observed associations between PBDEs and improvement in certain adaptive behaviors and most cognitive outcomes. These results were imprecisely estimated, and few reached statistical significance, and therefore should be interpreted cautiously.”

Forns et al. (2016) used the Infant/Toddler Symptoms Checklist (ITSC) to assess behavioral problems in children at 12 and 24 mo of age and found no association between ITSC scores and breast milk concentrations of six PBDE congeners (PBDE 28, 47, 99, 100, 153, and 154). ITSC questions addressed issues associated with self-regulation, attention, sleep, eating or feeding, dressing-bathing-touch, and listening-language-sound. Children 8–12 mo of age were tested with the BSID-III, which uses parent-report questionnaires to assess social-emotional and adaptive behavior; no associations were observed between these scales and \sum PBDEs (14 congeners) in breast milk (Chao et al. 2011).

Two of the studies on PBDEs (Adgent et al. 2014; Hoffman et al. 2012) examined children from the same cohort at 30 and 36 mo of age. Results were mixed and, according to the authors, small and imprecise. Null results were reported in two studies of separate cohorts of younger children evaluated using different testing instruments (Chao et al. 2011; Forns et al. 2016). In the risk-of-bias evaluation, all four studies were ranked lower for confounding and incomplete outcome data (Table S2). Hoffman et al. (2012), Adgent et al. (2014), and Chao et al. (2011) were also ranked lower for exposure assessment; Forns et al. (2016) and Chao et al. (2011) were ranked lower for blinding. The available evidence does not point to an association of parent-assessed development to lactational PBDE exposures.

Forns et al. (2015) found no association between PFOS and PFOA concentrations in breast milk at around 1 mo of age and either ASQ-II scores at 6 and 24 mo of age or scores on the ITSC at 12 and 24 mo of age.

A positive association was observed between mercury levels in breast milk and scoring on the Parents' Evaluation of Developmental Status (PEDS) at 3 to 12 mo of age (Al-Saleh et al. 2016a, 2016b). However, that finding was no longer significant once the model was adjusted for variables that were significantly associated with both outcome and exposure, including z -scores of weight-for-age and weight-for-length, infant birth order, total number of full siblings, smoking status among other family members living in the same house, infant health status, mother's highest educational level, mother's working status, vaccination timing, infant taking supplements/vitamins, infant's sleeping problems, location of primary health care centers, father's smoking status, mother's taking medication, and mother's age.

Pan et al. (2009) used the MacArthur CDI with 12-mo-olds and found no association with lactational exposures to DDT or DDE. Forns et al. (2016) evaluated associations between breast milk concentrations of HCB, β -HCH, oxychlordane, DDE, and DDT at around 1 mo of age and ITSC scores at 12 and 24 mo of age. DDT levels in breast milk were found to be associated with higher ITSC scores, indicating greater behavioral problems, at 12 mo of age. This association was stronger among less-educated mothers and was no longer present at 24 mo of age, regardless of maternal education.

Two studies with different cohorts assessed neurodevelopment in children from 12–24 mo of age and reported mostly null results. The study by Pan et al. (2009) was relatively strong, receiving a lower ranking for the category of missing outcome data (Table S2). Forns et al. (2016) was ranked lower for blinding, confounding, and incomplete outcome data. Although both of these studies assessed DDT and DDE and used questionnaires completed by parents to evaluate behavioral parameters in 12-mo-old children, the specific behavioral parameters assessed in

		BDE 28	BDE 47	BDE 99	BDE 100	BDE 153	Sum of 5 PBDEs	Sum of 7 PBDEs	Sum of 14 PBDEs
Cognitive function	BSID: cognitive scale	○	○	○	○	○			○
	BSID: mental development		○	○	○	○		○	
	MSEL: composite	○	○	○	○	○	△		
Language	BSID: language scale	○	○	○	△	○			○
	MSEL: expressive language	△	○	△	○	○	△		
	MSEL: receptive language	○	○	△	○	○	○		
Perception	MSEL: visual reception	○	○	○	○	○	○		
Externalizing behavior	BASC-2 PRS-P: externalizing problems	○	○	○	○	○	○		
	ITSEA: externalizing domain	○	○	△	△	△	○		
	ITSEA: activity/impulsivity	△	△	△	△	○	△		
	ITSEA: aggression/defiance	○	○	○	○	○	○		
	ITSEA: peer aggression	○	○	○	○	○	○		
Behavioral symptoms	ITSC: behavioral problems	○○	○○	○○	○○	○○			
	BASC-2 PRS-P: behavioral symptoms	○	○	○	○	○	○		
	BASC-2 PRS-P: hyperactivity	○	○	○	○	○	○		
	BASC-2 PRS-P: aggression	○	○	○	○	○	○		
	BASC-2 PRS-P: atypicality	○	○	▽	○	○	○		
	BASC-2 PRS-P: withdrawal	△	○	△	○	△	○		
	BASC-2 PRS-P: attention	○	○	○	○	○	○		
Internalizing behavior	ITSEA: internalizing domain	○	○	○	○	○	○		
	BASC-2 PRS-P: internalizing problems	○	○	○	○	○	○		
	BASC-2 PRS-P: anxiety	△	○	△	△	○	○		
	BASC-2 PRS-P: depression	○	○	○	○	○	○		
	BASC-2 PRS-P: somatization	○	○	○	○	▽	○		
Social-emotional competence	BSID: social-emotional scale	○	○	○	○	○			○
	ITSEA: social-emotional competence	○	▽	○	○	○	○		
	ITSEA: compliance	○	○	○	○	○	○		
	ITSEA: attention regulation	○	○	○	○	○	△		
	ITSEA: imitation and pretend play skills	○	○	△	○	○	○		
	ITSEA: mastery motivation	○	○	○	○	○	○		
	ITSEA: empathy	○	○	△	○	○	○		
	ITSEA: prosocial peer relations	○	○	○	○	○	○		
Dysregulation	ITSEA: dysregulation	○	○	○	○	○	○		
	ITSEA: problems with sleeping	○	○	○	○	○	○		
	ITSEA: problems with eating	○	○	○	○	○	○		
	ITSEA: negative emotionality	○	○	△	○	○	△		
	ITSEA: sensory sensitivity	○	△	○	○	○	○		
Adaptive behavior	BSID: adaptive behavior scale	○	○	○	○	○			○
	BASC-2 PRS-P: adaptive skills	○	○	○	○	○	○		
	BASC-2 PRS-P: activities of daily living	○	○	○	○	△	○		
	BASC-2 PRS-P: adaptability	○	○	○	○	○	○		
	BASC-2 PRS-P: functional communication	○	○	△	○	○	○		
	BASC-2 PRS-P: social skills	○	○	○	○	○	○		
Motor function/development	BSID: motor scale	○	○	○	○	○			○
	BSID: psychomotor development		○	○	○	○		○	
	MSEL: fine motor	○	○	○	○	△	○		

Direction of effect
○ Null
▽ Negative
△ Positive

Study/Cohort
■ Chao et al. (2011)
■ Gascon et al. (2012)
■ Norwegian Human Milk Study
■ Pregnancy, Infection, and Nutrition Babies Study

Figure 10. Infant/child neurodevelopment and exposure to PBDEs. Study results are summarized according to outcome and chemical. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure10?:embed=y&:display_count=yes. Note: BASC-2, Behavior Assessment System for Children; BDE, brominated diphenyl ether; BSID, Bayley Scales of Infant Development; ITSC, Infant/Toddler Symptoms Checklist; ITSEA, Infant Toddler Social and Emotional Assessment; MSEL, Mullen Scales of Early Learning; PBDE, polybrominated diphenyl ether; PRS-P, Parent Rating Scales - Preschool.

		TEQ	PCBs	Organochlorine pesticides	PFASs	Metals
Neuropsychological development	ASQ domain score				OOOO	
	PEDS					O
Behavioral symptoms	ITSC: behavioral problems		OOOOOOOO OOOOOOOO OOOOOOOO OO	OOOOOOOO OΔ	OOOO	
Social cognition, and externalizing and internalizing behaviors	CBCL (social problems; anxious/depressed feelings)	Δ				
	SDQ	OO				
	TRF (social problems; aggressive behavior; thought problems)	Δ				
ADHD	FBB-ADHS (overall ADHD)	OO	O			
Activity level	FBB-ADHS (hyperactivity)	OO	O			
Attention/inattention	FBB-ADHS (inattention)	OO	O			
Impulsivity	FBB-ADHS (impulsivity)	OO	▽			
Behavioral sexual dimorphism	PSAI (femininity; females)	OOOO▽▽Δ	OO			
	PSAI (femininity; males)	OOOΔΔΔ	OO			
	PSAI (masculinity; females)	OOOOO▽▽	OΔ			
	PSAI (masculinity; males)	OOOOOO	OO			
Language	MacArthur CDI (vocabulary comprehension)		OO	OO		

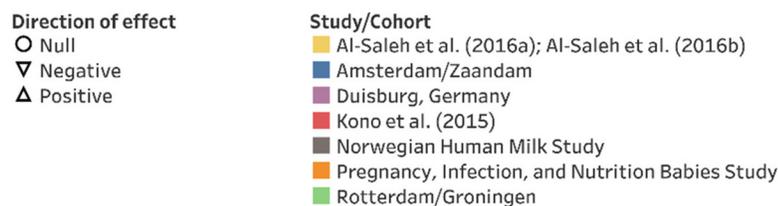


Figure 11. Parent questionnaires for assessment of behavior and development: dioxin-like chemicals, PCBs, organochlorine pesticides, PFASs, and metals. Study results are summarized according to outcome and chemical class. Symbol interpretation is as described in the legend for Figure 2. Additional details about each evaluation can be accessed via the online interactive version of this figure: https://public.tableau.com/views/EHP1954_v12/Figure11?:embed=y&:display_count=yes. Note: ADHD, attention deficit hyperactivity disorder; ASQ, Ages and Stages Questionnaire; CBCL, Child Behavior Checklist; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; FBB-ADHS, Disability Deficiency-Hyperactivity Disorder Assessment Sheet; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; ITSC, Infant/Toddler Symptoms Checklist; MacArthur CDI, MacArthur-Bates Communicative Development Inventories; PCB, polychlorinated biphenyl; PEDS, Parents' Evaluation of Developmental Status; PFAS, per- and polyfluoroalkyl substance; PSAI, Preschool Activities Inventory; SDQ, Social Difficulties Questionnaire; TEQ, toxic equivalent; TRF, Teacher's Report Form.

these studies were different. The MacArthur CDI, used by Pan et al. (2009), provides a measure of a child's vocabulary, while the ITSC, used by Forns et al. (2016), assesses a wider variety of behavioral aspects, including those related to self-regulation and temperament. The only association reported between breast milk organochlorine pesticide levels and parent-assessed development was between DDT and ITSC scores at 12 mo of age, and this association was transient, disappearing by 24 mo (Forns et al. 2016).

Pan et al. (2009) used the MacArthur CDI with 12-mo-olds and found no association with lactational exposures to PCBs. Similarly, Forns et al. (2016) found no associations between breast milk concentrations of PCBs at around 1 mo of age and ITSC scores at 12 and 24 mo of age. The Duisberg cohort children were assessed with the PSAI at 6–8 y of age and Winneke et al. (2014) observed a statistically significant association between lactational TEQ-weighted sum of PCDD/F + PCB exposures and reported femininity [positive for boys and negative for girls; there were also statistically significant results for masculinity (negative for girls for PCDDs/PCDFs and PCDDs/PCDFs/PCBs)]. The children in the Rotterdam cohort were assessed at 7.5 y of age using the PSAI to determine whether exposures to PCDDs/PCDFs/PCBs were associated with sex-related differences in childhood play behavior (Vreugdenhil et al. 2002b). \sum PCBs in milk were associated with more masculine play behavior in girls, whereas dioxin TEQ levels in milk were associated with more feminized play behavior in both sexes; lactational exposures assessed as chemical concentrations in breast milk multiplied by the number of weeks of breastfeeding were not associated with play behavior in children who had been breastfed or in boys and girls separately. The Amsterdam-Zaandam cohort was assessed with the CBCL and TRF at ages 7–12 y (ten Tusscher et al. 2014). The authors reported that the TRF showed a statistically significant increase in social problems, aggressive behavior and thought problems—as well as an increase in total TRF and total externalizing scores—associated with cumulative lactational PCDD/PCDF exposures. The CBCL showed a statistically significant increase in social problems with increasing cumulative lactational PCDD/PCDF exposures. A borderline positive significant association was seen with increasing aggressive behavior. Parents reported increased anxious/depressed feelings and social problems with increased TEQ in breast milk. Kono et al. (2015) used the Social Difficulties Questionnaire (SDQ) to evaluate associations between lactational exposure to dioxins and social and behavioral problems in children between the ages of 6 and 13 y. They found no significant association between the SDQ “total difficulties score” and estimated dioxin exposure through breastfeeding in boys or girls, or in children aged 6–10 y or 11–13 y. The Duisberg cohort was studied at 8–11 y of age using a parent rating scale for attention-deficit hyperactivity disorder (FBB-ADHS) (Neugebauer et al. 2015); a reduced FBB-ADHS impulsivity score was observed for \sum PCBs exposure through breastfeeding but not for TEQ-weighted PCBs or PCDDs/PCDFs.

These studies of different cohorts yielded mixed results for influence on feminine/masculine behavior and on outcomes such as social problems. The only similar finding was for increased reported femininity behavior in older boys with increasing exposure to TEQs as discussed earlier. However, direct comparisons of the results of the studies of social problems are problematic because of differences in the testing instruments used. In addition, it is difficult to draw conclusions about associations between breastfeeding and effects in older children without examining multiple possible confounders for the intervening years. Nonreplication of outcomes for other findings make strength-of-evidence assessments difficult. Pan et al. (2009) had the highest quality ranking in this group of outcomes, receiving

only one lower rating, for the category of missing outcome data (Table S2).

Standardized researcher-administered assessments (motor development in children approximately 6 months of age and younger). In the cohorts that examined young children for motor development, the chemicals studied were PCDDs, PCDFs, PCBs, DDE, and mercury (Figure 12). Gladen et al. (1988) found no association between lactational exposures to PCBs or DDE and Bayley scores at 6 mo of age in a U.S. cohort. Winneke et al. (1998) found no association between \sum PCBs and motor development (PDI of the BSID-II) or visual recognition memory (Fagan Test of Infant Intelligence) at 7 mo of age. This observation held after these data were reanalyzed to adjust for variables known to affect mental or motor development [i.e., parental education, maternal IQ, infant sex, and Home Observation for Measurement of the Environment (HOME) score] and variables found to correlate with both exposure and outcome (i.e., parity, maternal smoking during pregnancy, and maternal BMI) (Walkowiak et al. 2001). Similarly, Pluim et al. (1996) found no significant influence of PCDDs/PCDFs on the neurological optimality score according to Prechtl, mean number of abnormal reflexes, and tonus scores at 1 wk and 6 mo of age, and Wilhelm et al. (2008b) found no association between lactational exposures to PCDD/PCDF/PCB-TEQ and neurological optimality at 2 wk of age. No statistically significant association was found between breast milk mercury and infant performance on the Denver Developmental Screening Test II (DDST-II) at 3 to 12 mo of age (Al-Saleh et al. 2016a, 2016b).

In contrast, Huisman et al. (1995a) also used the Prechtl scoring for 10- to 21-d-old infants and found that higher levels of PCDDs/PCDFs/PCBs in breast milk were significantly associated with reduced neonatal neurological optimality, and higher breast milk levels of planar PCBs were statistically significantly associated with a higher incidence of hypotonia. Although Koopman-Esseboom et al. (1996)—with the same cohort—found no significant differences between breastfed and formula-fed infants at 3 mo of age for the PDI test of the BSID, at 7 mo of age, breastfed infants scored significantly higher than formula-fed infants. However, there was a negative association between lactational exposure to PCDDs/PCDFs/PCBs, with the highest exposed breastfed infants' PDI results comparable to formula-fed infants.

Three of the five studies examining early life motor development reported null findings with lactational exposures to DDE, PCBs, or PCDDs/PCDFs (Gladen et al. 1988; Pluim et al. 1996; Winneke et al. 1998). The two studies that reported statistically significant associations with DDE, PCBs, or PCDDs/PCDFs exposure involved the Rotterdam/Groningen cohort. The authors of these studies provided health context to their findings. Huisman et al. (1995a) noted that reflexes and responses were normal and described the observed hypotonia as a “minor dysfunction.” It is also worth noting that when these children were tested for neurologic conditions (Hempel Neurological Examination) at 18 mo, Huisman et al. (1995b) no longer observed an association with PCDDs/PCDFs/PCBs in breast milk and found better fluency of movements in breastfed infants. Koopman-Esseboom et al. (1996) noted that although exposure via breastfeeding was negatively associated with the PDI at 7 mo of age, the breastfed infants never scored lower than the formula-fed infants.

All five studies on children younger than about 6 mo of age that focused on dioxins, furans, PCBs, and/or DDE had relatively high quality ratings (Table S2), with only one or two lower-ranked categories. One study cohort was from the United States, while the others were from the Netherlands and Germany. These cohorts were recruited in the 1990s at a time when exposures to these chemicals were generally higher than levels found in the

children ages 1–5 y, save one marginally significant finding for reduced motor development at 4 y of age (Gladen and Rogan 1991).

Overall, evidence for an effect on children's neurodevelopment related to lactational exposures to DDT/DDE is weak to nonexistent. In terms of risk of bias in these studies, Pan et al. (2009) was ranked relatively high across all criteria, as were the three studies from the North Carolina cohort (Table S2). For all four of these studies, only one or two categories were scored below the highest ranking. Particularly of note were high rankings on all for robust exposure assessment methods.

A multitude of studies used researcher-administered function tests to explore associations between lactational exposures to PCDDs/PCDFs and/or PCBs and neurodevelopment (Figure 13). In the United States, Pan et al. (2009) found no association with PCBs (median sum of 18 congeners, 77 ng/g lipid; median PCB 153, 17 ng/g lipid) using the MSEL, whereas for the North Carolina Breast Milk and Formula cohort, three separate assessments (Gladen and Rogan 1991; Gladen et al. 1988; Rogan and Gladen 1991) revealed no associations between PCBs and the BSID or MSCA (children ranged in age from 1–5 y for these four studies). In contrast, Jacobson et al. (1990) found that reduced activity in 4-y-olds was associated with PCBs in breast milk, although they note that “effects on activity are negligible unless the infant has breast fed for at least 1 y. . . . The effect seen here was relatively subtle, and its clinical significance is uncertain” (mean PCB concentration = 835.9 ng/mL lipid). Lynch et al. (2012) used the BSID-II to examine potential effects of lactational exposures to PCBs (median PCB concentration = 162.4 ng/g lipid) in 24-month-old children and found no statistically significant associations with child neurodevelopment; however, breast milk PCB 153 levels (median = 27.6 ng/g lipid) were associated with a decrease in the PDI score (statistically significant only for the highest levels; the authors note the possibility that the finding was due to chance).

Of these six U.S.-based cohort studies focused on PCBs, four reported null findings, one found subtle reduced activity in 4-y-olds (Jacobson et al. 1990), and one found reduced psychomotor scores in 2-y-olds exposed at the highest PCB 153 levels (Lynch et al. 2012). All of these studies were found to be of relatively high quality (Table S2), with only one or two categories scored below the highest ranking. Although exposure levels cannot be directly compared across cohorts (e.g., different methods of PCB analysis were used for each cohort, measuring different sets of congeners for each), it is of interest to note that breast milk PCB levels in two studies that recruited women in the early 1990s, and reported significant findings, were 835.9 ng/mL lipid (mean) and 162.4 ng/g lipid (median) for Jacobson et al. (1990) and Lynch et al. (2012), respectively. In contrast, median levels of PCBs in breast milk from samples collected in the United States since 2000 [including Pan et al. (2009)] ranged from approximately 70–100 ng/g lipid (Table S1).

Two German cohorts included researcher-administered assessments of neurodevelopment. In the Düsseldorf cohort, at 7 mo of age, after adjustment for mother's BMI, age, education, vocabulary, and breastfeeding duration as well as infant birth weight, HOME score, Apgar score, and cord blood lead levels, a significant negative association was observed between lactational exposure to PCBs 138, 153, and 180 and the mental development index (MDI) part of the BSID-II; no associations with motor development were observed (Winneke et al. 1998). Walkowiak et al. (2001) reanalyzed the data from infants at 7 mo of age together with data gathered when the children reached 18, 30, and 42 mo of age, adjusting for variables known to impact mental or motor development (i.e., parental education, maternal IQ, infant sex, and HOME score) as well as variables found in their analysis to correlate with

both exposure and outcome (i.e., parity, maternal smoking during pregnancy, and maternal BMI). They reported negative associations for both mental and motor scores that were statistically significant at 30 mo of age and older (using the BSID at 18 and 30 mo and the Kaufman Assessment Battery for Children at 42 mo). At 72 mo of age, the Kaufman Assessment Battery for Children scores were no longer associated with lactational exposure to these PCBs (Winneke et al. 2005); the authors postulate that “early PCB-exposure at current environmental background levels possibly induces transient delay in cognitive development rather than irreversible deficit.” Further evidence for a potential reduction in impact associated with lower exposure levels comes from the Duisberg cohort, with no reported associations between BSID-II scores in 12- to 24-month-olds and lactational exposures to either PCDD/PCDF/PCB-TEQ (Wilhelm et al. 2008b) or the sum of PCB congeners 138, 153, and 180 (Wilhelm et al. 2008a). There was also no association identified between lactational exposures to PCDD/PCDF/PCB-TEQ and neurological optimality at 18 mo of age (Wilhelm et al. 2008b). In a follow-up study when the children reached 8–11 y of age (Neugebauer et al. 2015), results of the KiTAP were null except for a slower reaction time in the distractibility part of the test with increasing lactational exposures.

The results from these two cohorts were again mixed, with some null and some statistically significant negative results. The Düsseldorf cohort showed statistically significant negative associations between PCB exposures and neurodevelopment at early ages, but not at school age (Walkowiak et al. 2001; Winneke et al. 1998, 2005). In contrast, there were no associations between PCB or TEQ exposures and neurodevelopment at early ages in the Duisberg cohort (Wilhelm et al. 2008a, 2008b)—associations were observed when the children were school age (Neugebauer et al. 2015). In terms of risk of bias, the studies by Wilhelm et al. (2008a), Wilhelm et al. (2008b), and Neugebauer et al. (2015) received lower scores on the confounding criterion because they did not include prenatal exposures in their effects model for lactational exposures, and for Neugebauer et al. (2015), there was no information on postweaning exposures in the intervening years. Two of the Düsseldorf papers—Walkowiak et al. (2001) and Winneke et al. (2005)—were considered to be at low risk of bias, with all high rankings for the criteria in Table S2.

Two Dutch cohorts provide information on lactational exposures and researcher-administered function tests: the Amsterdam-Zaandam cohort and PCDDs/PCDFs, and the Rotterdam/Groningen cohort and PCDDs/PCDFs/PCBs. In the Amsterdam-Zaandam cohort, the BSID administered at 2 years of age (Ilsen et al. 1996) and the WISC-R administered at 7–12 y of age (ten Tusscher et al. 2014) yielded null results for both estimates of TEQs in breast milk and measures of cumulative exposures via breastfeeding. Ilsen et al. (1996) observed fewer suboptimal scores on the Hempel neurological exam at 31 mo of age in children exposed to higher TEQ levels in breast milk. The children in the Rotterdam/Groningen cohort were tested with the BSID at 18 mo (Koopman-Esseboom et al. 1996), the Kaufman Assessment Battery for Children and Reynell Language Development Scales (Patandin et al. 1999) and the Touwen/Hempel test for neurological optimality (Lanting et al. 1998a, 1998b) at 42 mo, and the Dutch version of the MSCA for cognitive and motor abilities at 6.5 y of age (Vreugdenhil et al. 2002a). All results were null.

These Dutch cohorts yielded null results except for improved neurological optimality in 31-month-olds with exposures measured as TEQ in the Amsterdam-Zaandam cohort (Ilsen et al. 1996). Regarding risk of bias, Ilsen et al. (1996) was highest ranked in this group, with only one lower score for confounding, while Koopman-Esseboom et al. (1996) additionally scored lower on exposure assessment. Other studies in this grouping had three or

four lower scores, and all scored lower on confounding in part due to lack of postweaning exposure information (Table S2).

Overall, the various studies on multiple cohorts using researcher-administered function tests indicate mixed results for associations between lactational exposures to PCDDs/PCDFs and/or PCBs and various neurodevelopmental outcomes. Age of the children at assessment varied across the studies, and some indicated lower neurodevelopment scores associated with higher exposure to PCDDs/PCDFs and/or PCBs at the same age as other studies indicating no association. For example, Walkowiak et al. (2001) found statistically significant decreases in developmental scores associated with exposure to PCBs in children at 42 mo and Jacobson et al. (1990) found subtle reduced activity at 48 mo, but more than five studies reported null results for similar ages, outcomes, and chemicals.

Discussion

Examining associations between environmental chemicals in breast milk and infant/child health is extremely complex for several reasons. First, environmental chemicals in breast milk are also present in the mother during gestation, a particularly vulnerable life stage for many health end points. Thus, depending on study design, it is either difficult or impossible to disentangle the two exposure periods when ascribing any effects observed in children to environmental chemical exposure; studies that compare breastfed infants across different dose groups as well as formula-fed infants and include a measure of chemical levels in each pregnant mother offer an opportunity to separate possible effects from exposures during these two life stages. Second, we can only attempt to evaluate potential links between exposure and outcome for those chemicals actually measured, as most studies limit their focus to one or a few chemicals. Third, breastfeeding in and of itself confers many health benefits to infants, requiring an assessment of decreased optimality rather than simply examining risk alone. This type of complexity mirrors that of assessing risk/benefits associated with fish consumption; i.e., how to assess the benefits associated with consuming omega-3 fatty acids vs. the risks associated with environmental chemicals in fish. Finally, there are numerous end points related to growth and development that could be examined; however, due to resource-, time- and burden-related limitations, most studies can only focus on at most one or a few outcomes. Therefore, although there is a body of literature related to health outcomes and environmental chemicals in breast milk, all studies suffer from at least some of the limitations described here. Despite this, there is information to be gleaned from the literature as well as lessons learned that can inform future research.

In this examination of the environmental epidemiology literature on associations between environmental chemicals in breast milk and infant/child outcomes, we sought to identify aspects of the literature that, taken together, would inform public health discussions about this critical life stage. Although a relatively large number of cohorts have been studied, and many studies reported no associations between exposure and outcome, the number of chemicals that have been addressed by the body of research is relatively small. The only studies with similar study design yielding concordant results were two studies that reported inverse associations with cognitive outcome and BDE-209, although the exposure assessments were not conducted in the same way (i.e., colostrum vs. milk samples collected one mo postpartum). Two studies reported statistically significant positive associations between chest congestion and TEQs in breast milk, though in children of different ages and using different questions to ascertain that health outcome. Similarly, two other studies reported negative associations in

children of different ages with different neurodevelopmental function tests and higher PCB levels.

Results varied for studies that evaluated effects of chemicals in breast milk on growth in infants and young children. Some differences may stem from variations in study design (e.g., chemicals measured, age of children at the time of outcome assessment, types of anthropometric measurements taken). For studies that compared growth in breastfed infants with those not breastfed [e.g., Grandjean et al. (2003)], it must be recognized that these efforts are complicated by the differences observed for growth curves between breastfed and formula-fed infants (CDC 2015). For example, at 18 mo of age, breastfed babies in a cohort in Davis, California, were shown to weigh less than formula-fed babies (Dewey et al. 1992). The difference in weights of breastfed babies and those not breastfed in the Faroe Islands (Grandjean et al. 2003) and in Davis, California was almost identical; assuming that infants in Davis had lower PCB exposures than the Faroese children because of the Faroese consumption of fish and marine mammals with high levels of environmental chemicals (Weihe and Joensen 2012), this would reinforce the hypothesis that other nutritional factors drive the difference in weight gain for the two different forms of infant nutrition. Further, *in utero* exposures to PCBs may be associated with delayed infant growth. Grandjean et al. (2003) point out the challenge of disentangling the highly correlated pre- and post-natal exposures.

Similar to the results for studies of effects on growth in infants and young children, statistically significant findings were not replicated across studies with similar exposure–outcome hypotheses for health outcomes, such as otitis media, and allergic and infectious diseases (for ages ranging from infancy to school-age children; the strongest studies provided contrasting findings), or thyroid hormone levels in infants and children. Although small changes in immune function biomarkers were observed in more than one study, there was little consistent evidence supporting an increased risk of infectious disease or other alteration in immune function in infants. For neurodevelopmental outcomes, the literature once again offers mixed results in terms of outcome and study quality, with limited replication of study design. Although these issues are particularly evident for the literature on PBDEs, these chemicals have been studied more recently in comparison with the organochlorine chemicals. Additional studies will be useful to determine whether the reported significant outcomes—some of which were variously described by the study authors as “small,” “imprecise,” or “modest”—are consistently observed.

To interpret the information in this review, several issues must be addressed. First, we limited our assessment to cohorts with background levels of exposure similar to those encountered by the general population of the United States. For the studies included in our evaluation, it is uncertain whether the convenience sampling conducted covered the entire range of possible background exposures—particularly those experiencing the highest levels of background exposure—during the studies’ respective time periods. Some of the cohorts may have included individuals in the general population that may have been more highly exposed based on their consumption of game fish [e.g., cohorts of anglers in Michigan (Jacobson et al. 1990) and New York (Jackson et al. 2010; Lynch et al. 2012)], or Arctic marine mammals [e.g., a population from Arctic Quebec, the Inuit Cohort (Dewailly et al. 2000)]. Longnecker et al. (2003) compared the PCB exposures of mothers (as characterized by their milk and serum levels) from 10 different cohort studies evaluating neurodevelopmental impacts. Their analysis highlighted similarities as well as differences seen across the cohorts: “a) the distribution of exposure in the majority of studies overlapped substantially, b) exposure levels in the Faroe Islands study was about 3 to 4 times higher

than in most other studies, and c) the exposure levels in the more recent United States studies were one-third or more lower than in the earlier United States studies or more recent European and northern Québec studies.” Our current review included two of the studies (Patandin et al. 1999; Walkowiak et al. 2001) and half of the cohorts assessed by Longnecker et al. (2003). Pan et al. (2009) found no associations between neurodevelopmental impacts in infants at 12 mo of age and lactational exposure to PCB 153, and observed that “the median PCB 153 concentration (in breast milk) in our study population would be much lower than in the study with the lowest PCB 153 concentration that was previously reviewed” (Longnecker et al. 2003).

Second, various issues with study design must be acknowledged. For example, three important factors drive the overall level of exposure: the concentration of the chemical in the medium of interest, and the extent and duration of exposure. In an ideal study seeking to explore associations between exposures to environmental chemicals in breast milk and infant and child health outcomes, the chemical(s) of interest would be measured in multiple breast milk samples over the duration of lactation, and data would be collected on exclusive versus partial breastfeeding and the number of weeks that the infant was breastfed. Collection of this type of information places demands on the new mother as well as on the resources available to the investigators. However, without these data, exposure misclassification is more likely, and it is not known in which direction the misclassification could bias the results; either direction is possible.

In terms of physicochemical properties, two general classes of environmental chemicals in breast milk have been explored for their associations with health outcomes in infants and children: those with short physiological half-lives (i.e., hours to days or weeks) and those with long half-lives (i.e., years). For the former, it is well established that variability in chemical concentrations in the body can be quite high and that one measurement may be insufficient for characterizing longer-term exposures (Braun et al. 2012; Johns et al. 2015; LaKind et al. 2014; Meeker et al. 2013). Although most of the studies on variability in levels of short-lived chemicals have used urinary biomarkers, there is no reason to assume that this variability will not be observed in breast milk samples as well.

For chemicals with long half-lives, the conventional wisdom is that concentrations in breast milk would slowly decline over the duration of breastfeeding as historically accumulated levels in the mother would be mobilized and depurated (LaKind 2007; LaKind et al. 2004, 2000). However, recent research conducting careful examinations of levels of these types of chemicals over the course of lactation has revealed a more complex picture, with some concentrations remaining relatively constant in breast milk over time and others either increasing or decreasing at variable rates (Hooper et al. 2007; LaKind et al. 2009; Thomsen et al. 2010a). At this time, it is not known what drives these differences, although women’s current dietary exposures may play a role (LaKind 2007) as may proximity to products containing these chemicals, particularly for flame retardants. Regardless, for both classes of chemicals, it is highly unlikely that one measurement of a chemical from one sample of milk will be able to fully capture infant exposure. An exception to this would be an early life study in which the sample was collected shortly postpartum and the health outcome was assessed at the same time or soon thereafter.

The extent and duration of breastfeeding provides information on the total amount of breast milk consumed over the course of lactation until weaning is complete. According to estimates by the U.S. EPA (2008), an exclusively breastfed infant consumes approximately 600–900 mL breast milk/day over the first 6 mo of life. In contrast, an infant who is partially breastfed might

consume on the order of 60% of that amount. Further, knowing the duration of breastfeeding is essential to estimating overall exposure to a chemical of interest. Therefore, a robust exposure assessment incorporates information on whether and for how long an infant was exclusively breastfed.

We are unaware of any chemical included in this assessment that would involve exposures via breastfeeding to the exclusion of *in utero* exposures. Because of this complication, it is necessary to account for potential impacts of *in utero* exposures when attempting to ascribe a particular health outcome to exposures via breastfeeding. Some of the studies reviewed in this paper attempted to distinguish between these two exposure pathways by determining *in utero* exposures using cord blood measures or maternal blood measures during pregnancy or immediately postpartum and using this information in their analyses. However, many studies made no attempt to assess *in utero* exposures, making it virtually impossible to determine which window of exposure, or whether both, might be related to an observed outcome. Identifying the sensitive window(s) of development and exposure is important for understanding potential impacts of chemicals in breast milk and for providing information to doctors and parents about infant nutrition.

Given the paucity of data characterizing background exposures at any given point in time in the countries where studies were conducted, we are not able to place the cohorts’ exposure levels within contemporary and geographically relevant distributions of background exposures. However, many of the cohorts described in this paper were recruited decades ago at a time when some classes of chemicals such as dioxins, furans, and PCBs were present in the environment and in humans at much higher concentrations than today. Our review’s findings may be less certain or pertinent for exposures above or below the range of exposures in the included studies. Wilhelm et al. (2008a) specifically addressed this question and reported that while in the Düsseldorf birth cohort both mental and motor development were negatively associated with PCBs in breast milk, this finding was not repeated in a cohort recruited some years later (the Duisburg cohort), suggesting that more recent levels of PCBs “no longer apparently impair neurodevelopment of infants.” Pan et al. (2009) noted that their cohort had much lower *p,p'*-DDE levels compared to Rogan et al. (1987), and generally found no association between exposure to persistent chemicals and neurodevelopment at 12 mo of age, except between *p,p'*-DDE exposures and decreased gross motor score in boys. Of the studies reporting unfavorable, non-transient effects associated with organochlorine chemicals in breast milk, most were studies of cohorts recruited in the early 1990s (Table S1).

There have been few attempts to collect population-wide data on environmental chemicals in breast milk, and no comprehensive data are available for the United States (LaKind et al. 2001). In the absence of data, it is challenging to establish a baseline range of “background” levels of chemicals in breast milk in this country or to identify individuals or populations that may experience exposures above that range. Although data on concentrations of most chemicals in U.S. breast milk are generally lacking, concentrations of dioxins and furans have declined from 1975 to 2005 (LaKind 2007). Further, the Centers for Disease Control and Prevention has reported that serum concentrations of dioxins, furans, and dioxin-like PCBs in the United States have decreased by more than 80% since the 1980s (CDC 2017), and it is reasonable to assume that breast milk concentrations have similarly decreased (Marchitti et al. 2013). This finding provides some assurance that current concentrations for some of the chemicals discussed in this review are lower than concentrations observed in the cohorts that were recruited in the 1980s and 1990s. Similar

data for the same timeframe for organochlorine pesticides are not available. However, regarding PBDE flame retardants, penta-BDE products were phased out in 2004, and mean serum concentrations of PBDEs decreased from 2003–2004 to 2005–2008, although the differences for most congeners were not statistically significant (Sjodin et al. 2014). More recently, Guo et al. (2016) found that between 2003–2005 and 2009–2012, total PBDEs in the milk of women in California declined by approximately 39%.

Other study design limitations commonly encountered in this body of literature include small sample size or lack of demonstrated adequacy of statistical power, narrow focus with regard to health outcomes, and incomplete exposure assessment (e.g., lack of data on breastfeeding duration and/or exclusivity, additional exposure sources during and after infancy).

A third issue critical to interpreting the information in this review relates to whether statistically significant findings in the epidemiological literature reviewed here are of clinical significance. Subclinical effects should be placed into context when describing study results to health care providers and families because these results, although meaningful at the population level and potentially important from an overall public health perspective, should be interpreted together with information on health benefits associated with breastfeeding and potential risks associated with environmental chemicals in formula when informing personal decisions regarding infant nutrition. For several of the studies that reported a statistically significant association between exposures from breastfeeding and health or biomarker outcomes, the results were characterized by the authors as subtle and/or with uncertain clinical significance [see, for example, Huisman et al. (1995a); Jacobson et al. (1990); Koopman-Esseboom et al. (1996); Pluim et al. (1993, 1994); ten Tusscher et al. (2001, 2003); Walkowiak et al. (2001); Winneke et al. (2005)]. Further, statistically significant findings were sometimes reported in an early assessment of a specific cohort but were no longer observed when the cohort was reassessed at a later age [e.g., Winneke et al. (2005)], suggesting transiency in effect.

Fourth, in attempting to understand windows of exposure that may be related to a specified outcome, the infant stage presents a particularly complex exposure problem. Even with a detailed exposure assessment with serial sampling from time of conception throughout infancy (which none of the studies reviewed here conducted), it can be extremely difficult to separate out potential effects of prenatal, perinatal, and postnatal exposures. Although one could argue that, for public health protection efforts, it is important to understand early life exposures during all of these periods, it may be especially important to separate effects resulting exclusively from prenatal exposure from those that may also result from exposure during breastfeeding as this has implications for advice provided by health care practitioners regarding infant nutrition.

Fifth, although it would be useful to be able to compare cohort exposures across studies, infant lactational exposure is related not only to chemical levels in breast milk but also to duration and exclusivity of breastfeeding. Almost none of the studies evaluated these aspects of exposure. Cross-study interpretation is also generally hindered by differences in the numbers/types of chemicals measured across different studies (e.g., differences in congeners assessed within a chemical class), and by differences in the range of exposures represented in different study populations, which led to differing definitions of “low” and “high” exposure levels between studies.

Sixth, from a public health perspective, shifts in infant/child health outcomes associated with environmental chemicals in breast milk are important to recognize and can be used to support recommended reductions in exposures in the general population.

However, recommendations to limit infant exposure to breast milk would be short-sighted without also considering the health benefits of breastfeeding and potential risks associated with exposure to environmental chemicals in formula in addition to comparisons of *in utero* exposures. For example, research would be needed to confirm that any negative outcomes observed in exposed breastfed infants exceeded negative outcomes in a similar formula-fed cohort of infants. Unfortunately, the literature on this is extremely sparse. However, in an overview of the literature on PCBs in breast milk and infant outcomes, Jorissen (2007) concluded that although breastfed infants experienced higher exposures to PCBs in comparison with formula-fed infants, they fared better than formula-fed infants in terms of neurological development, physical growth, and immunological status. For dioxin-like compounds, although Koopman-Esseboom et al. (1996) observed a transient significant negative association between postnatal dioxin/PCB exposure and psychomotor development at 7 mo of age at the two highest exposure levels, they noted that breastfed infants never scored significantly lower than formula-fed infants. Formula-fed comparison groups are needed in epidemiological studies to inform this discussion.

Seventh, aspects of study design in this body of literature limited our ability to interpret the results. For example, many of the studies included measurements of several chemicals and assessments of many outcomes; if such a study reports one or two significant findings in their examination of what can be 20 or more associations, it becomes more likely that significant findings were due to chance (i.e., multiple comparison issue). This was highlighted by Lynch et al. (2012) in their discussion of a significant association between PCB-153 and decrements in motor development; they note “we cannot rule out that our findings are due to chance alone, given the number of hypothesis tests that were performed as a part of this study.” Also, for studies that follow a cohort over a long time period (e.g., for years after weaning), there is a lack of information on possible confounding factors that may influence outcomes in older children. Although in some cases, measures of persistent environmental chemicals (e.g., PCBs) in older children were included, as noted by Engel and Wolff (2013), use of these measures “cannot be used as a surrogate for perinatal exposure because body size changes dramatically during early life, and similarly dramatic and unpredictable changes in child PCB levels occur due to breastfeeding, weight gain, and continued dietary exposure.”

Finally, there is also a larger design issue that applies to the literature as a whole: Despite the large number of epidemiological studies that have investigated associations between environmental chemicals in breast milk and health outcomes, there has been very little replication of study design across studies, and limited replication of study results even for studies with similar designs, which limits our ability to draw confident conclusions.

Conclusions

In this paper, we provide a critical examination of the environmental epidemiological literature on associations between environmental chemicals in breast milk and infant/child health outcomes. Our goal was to draw information from the literature that can be used to inform public health discussions about a sensitive life stage (i.e., infancy and early childhood). This review revealed that, although a relatively large number of cohorts has been studied, the number of chemicals addressed by the body of research is relatively small. Further, the number of high-quality studies (for example, those with rigorous exposure assessments) is limited, as is the number of studies that have replicated findings from earlier studies.

It is clear from this review that more research is needed to fully inform our understanding of the potential for lactational exposures to environmental chemicals to impact health outcomes during infancy or at later life stages. This research needs to include properly powered studies and adequate recruitment of study participants from the high and low ends of the exposure distributions. Clearly, to synthesize literature and examine the weight of the evidence—in particular for observational research—more than one study on a given exposure–outcome assessment (i.e., study replication) is also needed. Our review highlighted the general lack of study replication in the current body of literature. We strongly recommend that future study designs include sufficiently similar components to previous studies such that evidence synthesis can be conducted.

Although the research needs identified above are essential, we note that exposure assessment can be considered the Achilles heel of environmental epidemiology, and many of the data gaps described in this review attest to this. We therefore describe here in detail exposure assessment-related gaps and research needs:

- **Chemical mixtures:** Very few studies examine chemical mixtures beyond particular groups of congeners, such as dioxins, furans, and PCBs. Assessment of mixtures is a difficult but necessary step forward in understanding chemical–outcome associations. As new chemicals are introduced into the marketplace, resources and tools are needed to analyze breast milk for their presence. For the mixtures that are currently the subject of study, agreement on a consistent approach to reporting will be vital to conducting interstudy comparisons. For example, all future studies of PCBs could include congener-specific analyses as well as summing of congeners, and studies focused on dioxin-like chemicals could include a TEQ assessment.
- **Chemicals in infant formula:** There is a dearth of U.S.-specific data on concentrations of environmental chemicals in infant formula powder and reconstituted formula. A full picture of potential effects of postnatal exposures to environmental chemicals is incomplete without epidemiological studies on environmental chemicals in infant formula (reconstituted with drinking water or ready to use) and infant/child health outcomes. Further, epidemiology studies of environmental chemicals in breast milk should include a comparison formula-fed group (with measures of prenatal exposures via cord blood) to increase the ability to explore separate associations between health outcomes and exposures at different life stages.
- **Distinguishing between prenatal and lactational exposures:** It can be a challenge to assess the relative contributions of prenatal and breastfeeding exposures to associated health outcomes. Some studies have included a comparison group of formula-fed infants to observe potential effects of prenatal chemical exposure in the absence of lactational exposure. However, interpreting the results from comparisons between breastfed and formula-fed infants can be complicated, especially when the outcomes of interest may differ between these two groups independent of specific chemical exposures. Other approaches to address this issue involve the incorporation of *in utero* exposure data (e.g., cord blood or maternal blood chemical levels) into analyses of associations between breastfeeding exposures and health outcomes. Studies might also use pharmacokinetic models to estimate exposures at different life stages and to distinguish effects resulting from prenatal exposure from effects resulting from exposure during infancy (Verner et al. 2010). Additional studies implementing approaches such as these would allow for a much more precise determination of the likelihood for

potential health outcomes of exposure during the breastfeeding period.

- **Changes in chemical concentrations during lactation:** To accurately assess infant exposures to persistent, lipophilic chemicals via breastfeeding, data on the concentrations over the entire duration of lactation are needed (Fenton et al. 2005). An early synopsis of the literature on changes in concentrations of persistent chemicals indicated that concentrations declined over the course of lactation, in accordance with the hypothesis that the levels of these chemicals are primarily a reflection of the lifetime exposures of the mother; thus, with continued lactation, the accumulated stores of chemicals in the mother's lipids would be eliminated, and concentrations in her milk would decline accordingly (a process referred to as depuration) (LaKind et al. 2011). This hypothesis also found support in the literature indicating that multiparous women have lower concentrations of persistent chemicals in breast milk than primiparous women (LaKind et al. 2004), although not all studies have observed this decline with increasing parity (Harris et al. 2001). More recent longitudinal studies designed to quantify the rates of depuration for several types of persistent lipophilic chemicals (dioxins, furans, PCBs, PBDEs, organochlorine pesticides) (Hooper et al. 2007; LaKind et al. 2009) found no consistent evidence of substantial—or in some cases any—depuration. In contrast, Thomsen et al. (2010b) reported decreasing concentrations of PBDEs, hexabromocyclododecane, PFASs, and PCBs in breast milk over 12 mo of lactation. Changes in physiology during pregnancy and postpartum complicate this analysis (e.g., blood loss at delivery). Further, the relative impact of the mothers' current exposure versus lifetime exposure on breast milk chemical concentrations is not understood (LaKind 2007). Thus, a full understanding of changes in concentrations of these chemicals in breast milk over the course of lactation will ultimately require a longitudinal exposure/bio-monitoring study that captures changes in mothers' exposures during lactation while also measuring concentrations of lipophilic environmental chemicals in the mother's adipose tissue, serum, and milk.
- **Even fewer data are available on variability in breast milk chemical concentrations for short-lived chemicals.** Based on measurements of the chemicals in serum and urine, large day-to-day or even hour-to-hour variability is anticipated (LaKind et al. 2014; Teeguarden et al. 2011), making estimates of infant exposures highly uncertain. Studies on temporal variability of breast milk concentrations of short-lived chemicals are needed.

Based on this review, the overall strength of the evidence—though weak—did not reveal any consistency in health outcomes associated with exposures to environmental chemicals in breast milk at general population background levels. Our overall conclusion must be weighed with various uncertainties, including differences in background levels across studies that may not have captured the high or low end of the exposure distributions, the clinical meaning of reported outcomes, the difficulty of differentiating effects of pre- and postnatal exposures, and the lack of statistical power in some of the studies. Regardless of the chemical concentrations in breast milk, breastfed children have generally fared at least as well as formula-fed children in these studies (when formula-fed control groups were available for comparison). This speaks to the benefits of breastfeeding, even in light of evidence that exposures to some chemicals are higher in breastfed infants as compared to formula-fed infants.

Although our initial goal was to conduct a parallel assessment of environmental chemicals in infant formula and health consequences associated with those exposures, this was not possible due

to a dearth of pertinent epidemiological literature on this topic. Because research on environmental chemicals in breast milk has the potential to affect decisions regarding infant nutrition, it is essential that epidemiological research on environmental chemicals in infant formulas and associations with various health outcomes be conducted. Researchers need to design studies that will help to better characterize infant exposures to environmental chemicals in breast milk and infant formula. Further, epidemiologists and risk assessors should incorporate those improved exposure characterizations in their efforts to examine health outcomes.

In conclusion, the evidence compiled and evaluated here does not provide conclusive evidence of consistent or clinically relevant health consequences to infants exposed to environmental chemicals in breast milk at population background levels. Further, there is epidemiological evidence suggesting that some subtle effects observed in earlier studies when levels of persistent organic chemical levels in breast milk were higher than today's levels are no longer observed (Wilhelm et al. 2008a). However, based on comparisons between breastfed infant exposure levels and current reference values and some epidemiological evidence of potential health risk from early life (including prenatal) exposures, it may be prudent to consider measures that would reduce maternal chemical exposures.

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