Journal of Toxicology and Environmental Health, Part B, 11:373–517, 2008

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937400801921320

Taylor & Francis
Taylor & Francis Group

EPIDEMIOLOGIC EVIDENCE OF RELATIONSHIPS BETWEEN REPRODUCTIVE AND CHILD HEALTH OUTCOMES AND ENVIRONMENTAL CHEMICAL CONTAMINANTS

Donald T. Wigle[1], Tye E. Arbuckle[2], Michelle C. Turner[1], Annie Bérubé[3], Qiuying Yang[4], Shiliang Liu[5], Daniel Krewski[1]

[1]McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, [2]Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, [3]Vulnerable Populations Division, Safe Environments Program, Health Canada, Ottawa, Ontario, [4]OMNI Research Group, Department of Obstetrics and Gynecology, Faculty of Medicine, University of Ottawa and Ottawa Health Research Institute, Ottawa, Ontario, and [5]Centre for Healthy Human Development, Public Health Agency of Canada, Ottawa, Ontario, Canada

This review summarizes the level of epidemiologic evidence for relationships between prenatal and/or early life exposure to environmental chemical contaminants and fetal, child, and adult health. Discussion focuses on fetal loss, intrauterine growth restriction, preterm birth, birth defects, respiratory and other childhood diseases, neuropsychological deficits, premature or delayed sexual maturation, and certain adult cancers linked to fetal or childhood exposures. Environmental exposures considered here include chemical toxicants in air, water, soil/house dust and foods (including human breast milk), and consumer products. Reports reviewed here included original epidemiologic studies (with at least basic descriptions of methods and results), literature reviews, expert group reports, meta-analyses, and pooled analyses. Levels of evidence for causal relationships were categorized as sufficient, limited, or inadequate according to predefined criteria. There was sufficient epidemiological evidence for causal relationships between several adverse pregnancy or child health outcomes and prenatal or childhood exposure to environmental chemical contaminants. These included prenatal high-level methylmercury (CH_3Hg) exposure (delayed developmental milestones and cognitive, motor, auditory, and visual deficits), high-level prenatal exposure to polychlorinated biphenyls (PCBs), polychlorinated dibenzofurans (PCDFs), and related toxicants (neonatal tooth abnormalities, cognitive and motor deficits), maternal active smoking (delayed conception, preterm birth, fetal growth deficit [FGD] and sudden infant death syndrome [SIDS]) and prenatal environmental tobacco smoke (ETS) exposure (preterm birth), low-level childhood lead exposure (cognitive deficits and renal tubular damage), high-level childhood CH_3Hg exposure (visual deficits), high-level childhood exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (chloracne), childhood ETS exposure (SIDS, new-onset asthma, increased asthma severity, lung and middle ear infections, and adult breast and lung cancer), childhood exposure to biomass smoke (lung infections), and childhood exposure to outdoor air pollutants (increased asthma severity). Evidence for some proven relationships came from investigation of relatively small numbers of children with high-dose prenatal or early childhood exposures, e.g., CH_3Hg poisoning episodes in Japan and Iraq. In contrast, consensus on a causal relationship between incident asthma and ETS exposure came only recently after many studies and prolonged debate. There were many relationships supported by limited epidemiologic evidence, ranging from several studies with fairly consistent findings and evidence of dose-response relationships to those where 20 or more studies provided inconsistent or otherwise less than convincing evidence of an association. The latter included childhood cancer and parental or childhood exposures to pesticides. In most cases, relationships supported by inadequate epidemiologic evidence reflect scarcity of evidence as opposed to strong evidence of no effect. This summary points to three main needs: (1) Where relationships between child health and environmental exposures are supported by sufficient evidence of causal relationships, there is a need for (a) policies and programs to minimize population exposures and (b) population-based biomonitoring to track exposure levels, i.e., through ongoing or periodic surveys with measurements of contaminant levels in blood, urine and other samples. (2) For relationships supported by limited evidence, there is a need for targeted research and policy options ranging from ongoing evaluation of evidence to proactive actions. (3) There is a great need for population-based, multidisciplinary and collaborative research on the many relationships supported by inadequate evidence, as these represent major knowledge gaps. Expert groups faced with evaluating epidemiologic evidence of

Funding for this review was provided by the National Collaborating Centre for Environmental Health. The authors acknowledge Robert Cushman for providing helpful comments. Daniel Krewski is the NSERC/SSHRC/McLaughlin Chair in Population Health Risk Assessment at the University of Ottawa.

This work does not necessarily reflect the views of Health Canada and the Public Health Agency of Canada and no official endorsement should be inferred. The findings and conclusions of this report are those of the authors and do not necessarily represent the views of Health Canada and the Public Health Agency of Canada.

Address correspondence to Donald T. Wigle, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Room 318B, One Stewart Street, Ottawa, ON K1N 6N5, Canada. E-mail: don.wigle@sympatico.ca

potential causal relationships repeatedly encounter problems in summarizing the available data. A major driver for undertaking such summaries is the need to compensate for the limited sample sizes of individual epidemiologic studies. Sample size limitations are major obstacles to exploration of prenatal, paternal, and childhood exposures during specific time windows, exposure intensity, exposure–exposure or exposure–gene interactions, and relatively rare health outcomes such as childhood cancer. Such research needs call for investments in research infrastructure, including human resources and methods development (standardized protocols, biomarker research, validated exposure metrics, reference analytic laboratories). These are needed to generate research findings that can be compared and subjected to pooled analyses aimed at knowledge synthesis.

Epidemiologic research conducted mainly since 1970 has demonstrated several causal relationships and many possible associations between parental or childhood environmental exposures and adverse pregnancy, childhood, and adult health outcomes. Toxicologic research supports assessment of biologic plausibility, one of the major criteria for evaluating cause-effect relationships in humans since first applied by the U.S. Surgeon General in assessing human health effects of smoking (U.S. Department of Health, 1964). Epidemiologic studies also draw on toxicologic research for clues as to possible causes of human diseases and functional deficits and for biomarkers of exposure, susceptibility, and adverse health effects.

Findings from epidemiologic and toxicologic studies have shown that the risk of adverse pregnancy, child, and delayed health outcomes depends not only on the dose and potency of a given toxicant, but also on the occurrence of exposure during critical developmental time periods (Selevan et al., 2000). Such evidence of critical exposure windows is congruent with biomolecular research showing the dependence of fetal and child development on a complex orchestration of genes in specific cell types at different times (National Academy of Sciences, 2000b). Disruption of prenatal and early childhood developmental processes can produce permanent disability and functional deficits, as well as delayed effects such as cancer later in life.

Children may have relatively high exposures to some environmental contaminants because of their behavior, diet and metabolic and physiologic characteristics (Moya et al., 2004). Hand–mouth behavior is common among young children and increases exposure to contaminants in soil, house dust, and toys. Children eat relatively high amounts of certain foods that may contain pesticide residues or other toxicants and take in more air, water, and food per unit body weight per day than adults. They also have age-dependent differences in the absorption, distribution, metabolism, and excretion of chemicals (National Academy of Sciences, 1993). For instance, breast-fed infants have relatively high exposures to polychlorinated biphenyls (PCBs) and certain other lipid-soluble toxicants at a time of rapid growth and development (Berlin et al., 2002). Children in disadvantaged households (low-income and/or low parental education) are at increased risk of exposure to many environmental hazards, including lead (Bernard & McGeehin 2003), tobacco smoke (Lund & Helgason 2005), cockroach allergens (Cohn et al., 2006), and outdoor air pollutants (Chaix et al., 2006).

Several recent reports or books provide high-level summaries of current knowledge of relationships between child health and the environment (American Academy of Pediatrics Committee on Environmental Health, 2003; European Environment Agency and the WHO Regional Office for Europe [Copenhagen], 2002; Wigle, 2003; Wigle et al., 2006). In this review, we survey the level of epidemiologic evidence for relationships between adverse reproductive and child health outcomes and preconceptual, prenatal, and childhood exposures to environmental chemical contaminants. Wherever possible, we rely on peer-reviewed expert group reports supplemented by subsequently published original studies. We occasionally cite original studies included in an expert group report to illustrate the strengths or weaknesses of supporting evidence. Space limitations precluded comprehensive discussion of each of the many exposure–outcome relationships reviewed here. Thus our review is a survey of the current state of knowledge in this field, as opposed to a collection of exhaustive evaluations. Our goal was to categorize the level of evidence for many exposure–outcome relationships to support public health research and policy planning (further discussed in the Conclusion). We defined three basic categories for level of evidence (see Methods). Many relationships were supported by limited evidence; it was beyond the scope of this review to define a fourth category such as suggestive evidence, as this would have entailed substantial lengthening of the article.

Discussion is organized by health outcomes, including functional deficits, disability, and structural abnormalities. These include fetal loss, intrauterine growth restriction, preterm birth, birth defects, cancer (including certain adult cancers linked to prenatal or childhood exposures—note that prenatal exposure is defined throughout the text as prenatal maternal exposure), asthma, other childhood diseases, neuropsychological deficits, and premature or delayed sexual maturation. Environmental exposures considered here include chemical toxicants in air, water, soil, house dust, foods, and consumer products. Evidence of health effects at high exposure levels is briefly summarized, but the major focus is on potential health effects at relatively low background exposure levels to which the majority of the population is likely exposed. The tables summarize key findings for relationships supported by limited or sufficient epidemiologic evidence (see definitions in Methods). Additional information on the epidemiologic evidence published up to 2004 for these relationships is available elsewhere (Wigle, 2005).

METHODS

This review included peer-reviewed English-language publications and government reports identified from PubMed and TOXNET searches and other reports identified from bibliographies of retrieved articles published by December 31, 2006. Search strategies included key words for various combinations of health outcome and environmental exposure. The PubMed "related articles" function was used to search for other relevant articles not retrieved in initial key word searches. Key words for adverse health outcomes included (but were not limited to) fertility, conception, pregnancy, spontaneous abortion, stillbirth, fetal death, birth weight, gestation length, preterm birth, birth defect, congenital anomaly, chromosomal abnormality, sudden infant death syndrome, asthma, otitis media, bronchitis, bronchiolitis, pneumonia, allergy, growth, milestone, cognitive, psychomotor, auditory, visual, hyperactivity, attention, childhood cancer, leukemia, lymphoma, brain cancer, Wilms, neuroblastoma, germ cell, bone cancer, sarcoma, retinoblastoma, testicular cancer, breast cancer, lung cancer, chloracne, teeth, enamel, dentin, renal, menarche, puberty, and Tanner stage. For exposure, key words included (but were not limited to) environment, chemical, metal, lead, mercury, cadmium, manganese, arsenic, polybrominated biphenyl (PBB), polychlorinated biphenyl (PCB), dioxin, pesticide, environmental tobacco smoke, air pollution, smoke, particulate matter, carbon monoxide, polycyclic aromatic hydrocarbon (PAH), ozone, volatile, water, disinfection by-product (DBP), nitrate, nitrite, bisphenol, and phthalate. Other searches were done using names of authors of relevant articles. Terms such as case-control, cohort, review, and meta-analysis were used to narrow some searches. Reviewed reports included original epidemiologic studies (with at least basic descriptions of methods and results), literature reviews, expert group reports, meta-analyses, and pooled analyses. When authoritative review articles were available, consideration of original reports was generally limited to those published since the year before the most recent review was published. Excluded papers included case reports, analytic studies with fewer than five exposed cases or case parents, studies published more than a year before a recent authoritative review, and preliminary reports of subsequently published studies. All included papers are cited in the text.

Levels of evidence for causal relationships were defined as: (i) sufficient—at least one expert group has reviewed the available evidence and published a peer-reviewed report indicating a consensus view that there is a causal relationship, (ii) limited—evidence is suggestive of an association between the agent and the outcome but is limited (and may or may not represent a causal relationship) because chance, bias and confounding cannot be ruled out with confidence, e.g., at least one high-quality study shows a positive association but the results of other studies are inconsistent and, (iii) inadequate—available studies are of insufficient quality (e.g., available studies have failed to adequately control for confounding or have inadequate exposure assessment), consistency or statistical power to permit a conclusion regarding the presence or absence of an association *or* no studies exist that examine the relationship. We did not attempt to identify exposure–outcome associations for which there is limited or sufficient epidemiologic evidence of no causal relationship as the limitations of available studies precluded firm conclusions about the absence of any risk. The definitions of limited and inadequate epidemiologic evidence are those used recently by the U.S. National Academy of Sciences (National Academy of Sciences, 2000a)

RESULTS

Adverse Pregnancy Outcomes

The level of epidemiologic evidence for associations between delayed conception and fetal growth and survival and environmental factors is summarized in Table 1.

Delayed Conception (Time to Pregnancy) Couple fecundability is defined as the probability of conception in a menstrual cycle exposed to unprotected intercourse and can be an indicator of a wide range of reproductive processes from gametogenesis to survival of the conceptus up to the time of detection (Baird et al., 1986). The number of menstrual cycles it takes for a couple to conceive (time to pregnancy) can be used to assess fecundability. Delayed conception may be assessed as a continuous (e.g., number of weeks of unprotected intercourse before conception) or categorical variable (e.g., duration of unprotected intercourse before conception greater than 6 or 12 mo). Time to pregnancy studies are most often retrospective; however, prospective studies that recruit couples at the start of their attempt at pregnancy and incorporate regular testing and follow-up (as in studies of early pregnancy loss described below) are becoming more feasible (Joffe et al., 2005).

Lead Male partner occupational exposure, inadequate evidence: While sperm concentration has been found to be reduced among men with a blood lead concentration above 44 μg/dl (Bonde et al., 2002), results of well-designed time to pregnancy studies have been inconsistent. In a large multicountry European study, no clear pattern of association of time to pregnancy with short-term lead exposure, with duration of lead exposure or with cumulative exposure to lead was observed (Joffe et al., 2003). A more recent study of time to pregnancy among lead battery workers in Taiwan reported a dose-response relationship with significant decreases in the likelihood of conception at blood lead levels of 30–39 and ≥40 μg/dl (respective hazard ratios of 0.50, 95% CI 0.34–0.74, and 0.38, 95% CI 0.26–0.56) (Shiau et al., 2004).

Unspecified heavy metals Male partner occupational exposure, inadequate evidence: Studies of occupational exposures to other heavy metals are limited. A study of workers in a smelter reported a nonsignificant dose response relation with shorter median waiting times if only one parent worked in the smelter compared to couples where both were employed in the smelter (Wulff et al., 1999). Other studies have reported that male welders had lower fecundability ratios than nonwelding metal workers (Hjollund et al., 1998), and suggest that male exposure to metal fumes and solvents in a mint is associated with an increase in time to pregnancy (Figa-Talamanca et al., 2000).

PCBs Female partner exposure, inadequate evidence:PCB exposure via fish consumption has been examined as a risk factor for longer time to pregnancy in several cohorts. A recent review of these studies has concluded that no firm conclusions can be drawn due to uncertainties in the exposure estimation and inconsistencies in the results (Toft et al., 2004). One study has reported a weak and inconclusive association between serum levels of PCBs and time to pregnancy (Law et al., 2005), while another provided no evidence of an adverse effect related to serum PCB–153 levels (Axmon et al., 2004).

Pesticides Male partner exposure, specific pesticides, inadequate evidence: Studies from Finland and Canada have examined risks associated with specific pesticides. The only statistically significant finding was for unprotected use of pyrethroids (fecundability density ratio [FDR] = 0.40, 95% CI = 0.19–0.85) (Sallmen et al., 2003); however, both studies suggested that fecundability might be reduced for fungicides (Curtis et al., 1999; Sallmen et al., 2003). One study has suggested that dichlorodiphenyltrichloroethane (DDT) exposure may be associated with reduced fecundability (Cocco et al., 2005).

Female partner exposure, specific pesticides, inadequate evidence: Although none of the results were statistically significant, one study has reported that preconceptual pesticide use was associated with reduced fecundability for dicamba, glyphosate, 2,4-dichlorophenoxyacetic acid (2,4-D), organophosphates, and thiocarbamates (Curtis et al., 1999). Two studies have used biomonitoring data to establish exposure. One study reported that DDT exposure of mothers was associated with decreased fecundability of their daughters but dichlorodiphenyldichloroethylene (DDE) exposure was linked with increased fecundability of their daughters (Cohn et al., 2003). Another study found that only at the highest concentration (≥60 μg/L) was preconceptual serum

TABLE 1. Role of Environmental Toxicants in Delayed Conception and Fetal Growth and Survival

Toxicant	Exposure	Delayed concep[a]	Spont. abor[b]	Stillbirth[c]	Preterm birth[d]	FGD[e]
Lead	Prenatal		**L**	I	**L**	**L**
	Paternal	I	**L**	I	I	I
Mercury	Prenatal		I	I		
Arsenic	Prenatal		**L**	Drinking water—I Airborne—I	Drinking water—I Airborne—I	Drinking water—I Airborne—I
	Paternal			Airborne—I	Airborne—I	Airborne—I
Cadmium	Prenatal			I	I	I
Other and unspecified metals	Paternal	I				
PCBs	Prenatal	I	High-level—I Low-level—I	High-level—I Low-level—I	Environ—I Occup—I	Environ—I Occup—I
PBBs	Prenatal		I			
TCDD	Prenatal		I			I
	Paternal		I	I	I	I
2,4,5-T, chlorophenate wood preservatives	Paternal		I	I	I	I
Other chlorophenoxy herbicides	Prenatal	I (2,4-D, dicamba)	I (2,4-D, 2,4-DB, MCPA)		I	I
	Paternal		**L** (2,4-D, MCPA, dicamba)		I	I
Other or unspecified herbicides	Prenatal	I (glyphosate)	I (atrazine, glyphosate)	I		I (atrazine, metolachlor, cyanazine)
	Paternal		I (carbaryl, thiocarbamate, atrazine, glyphosate)		I (atrazine)	
DDT/DDE	Prenatal	I	**L**	**L**	**L**	**L**
	Paternal	I	I			
Organophosphate insecticides	Prenatal	I	I	I	I	I
	Paternal		I			
Other or unspecified insecticides, repellents	Prenatal		I (DEET, organochlorine)	I (pyrethroids, organochlorine, unspecified)	I (organochlorine, DEET, pyrethroids)	I (DEET, propoxur, organochlorine)
	Paternal	I (pyrethroids)	I (carbaryl, unspecified insecticdes)			
Fungicides (any)	Prenatal		I	I	I	I
	Paternal	I	I			
Ethylene oxide	Prenatal		**L**			
	Paternal		I			
Unspecified pesticides	Prenatal	I	I	I	I	I
	Paternal	I	I	I	I	I

(Continued)

TABLE 1. *(Continued)*

Toxicant	Exposure	Delayed concep[a]	Spont. abor[b]	Stillbirth[c]	Preterm birth[d]	FGD[e]
Active smoking	Prenatal	S	**L**	**L**	**S**	**S**
	Paternal	I				
Environmental tobacco smoke	Prenatal	I	**L**	I	**S**	**L**
Outdoor air pollution[f] near residence	Prenatal	I		I	**L**	**L**
Airborne industrial emissions	Prenatal				I	I
Drinking water DBPs	Prenatal		**L**	**L**	I	**L**
Drinking water nitrate	Prenatal			I	I	**L**
Hazardous waste disposal sites	Prenatal		I	I	I	
Chlorinated solvents	Prenatal		**L**		I	I
Glycol ethers	Prenatal	I	**L**			
	Paternal		I			
Other or unspecified solvents	Prenatal	I	**L**	I	I	I
	Paternal	I	**L**	I	I	I
Bisphenol A	Prenatal		I			
Oil, oil products	Paternal	I				
Plastics	Paternal	I				

Note. TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. S, Sufficient evidence—based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed. L, Limited evidence—includes relationships for which several epidemiologic studies, including at least one case-control or cohort study, found fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders. I, Inadequate evidence—relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or found little or no evidence of exposure-risk relationships.

[a]For delayed conception, prenatal or paternal exposure, respectively, refer to preconceptual female or male partner exposure.

[b]Clinically apparent pregnancy loss before gestation week 20.

[c]Currently defined as fetal death after gestation week 20; previously defined as fetal death after gestation week 28.

[d]Gestation length <37 wk.

[e]Fetal growth deficit comprises small for gestational age (birth weight below 10th percentile based on gestation length) and term low birth weight (birth weight <2500 g for infants born at 37 or more weeks gestation).

[f]Major pollutants from fossil fuel combustion.

DDE concentration associated with reduced fecundability (FDR = 0.65, 95% CI 0.32–1.31) (Law et al., 2005).

Female partner occupations, unspecified pesticides, inadequate evidence: Two studies have reported that work in flower production was associated with impaired fecundability, but did not attempt to determine risks for specific pesticides (Abell et al., 2000; Idrovo et al., 2005).

Male partner occupations, unspecified pesticides, inadequate evidence: A number of European studies have investigated the role of occupations involving pesticide use on time to pregnancy with conflicting results (de Cock et al., 1994; Larsen et al., 1998; Petrelli & Figa-Talamanca 2001; Thonneau et al., 1999). While none of these studies examined risk associated with specific pesticides, some studies attempted to qualify exposures by employing crude measures of intensity of exposure (e.g., use of protective equipment, duration of exposure) with higher exposures associated with longer time to pregnancy (de Cock et al., 1994; Petrelli & Figa-Talamanca 2001; Sallmen et al., 2003).

Tobacco smoke Female partner, active smoking, sufficient evidence: Female smokers have a dose-related increased risk of delayed conception (Bolumar et al., 1996; Curtis et al., 1997; Hassan & Killick 2004). The U.S. Surgeon General concluded there was sufficient evidence of a causal relationship between female partner active smoking and reduced fertility (U.S. Department of Health and Human Services, 2004).

Female partner ETS exposure, inadequate evidence: There have been few epidemiologic studies of the role of environmental tobacco smoke (ETS) exposure in delayed conception. The U.S. Surgeon General reviewed the four available studies and found inadequate evidence for an association between reduced female fertility and female partner ETS exposure alone or in combination with active smoking (U.S. Department of Health and Human Services, 2006). In the Avon Longitudinal Study of Pregnancy and Childhood Study, however, delayed conception was associated with prenatal active smoking (OR = 1.23, 95% CI 0.98–1.49, for delay of over 6 mo; OR = 1.54, 95% CI 1.19–2.01, for delay of over 12 mo) and, independently, with prenatal ETS exposure (OR = 1.17, 95% CI 1.02–1.37 and OR = 1.14, 95% CI 0.92–1.42, respectively) (Hull et al., 2000).

No consistent pattern has been observed between male partner smoking and fecundability; it appears that no published studies have assessed male partner ETS exposure and delayed conception.

Outdoor air pollution Male or female partner exposure, inadequate evidence: One study has reported an association between ambient sulfur dioxide (SO_2) levels and fecundability in the first unprotected menstrual cycle (Dejmek et al., 2000).

Indoor air pollution Female partner exposure, inadequate evidence: Frequent occupational exposure to nitrous oxide for midwives has been associated with longer time to pregnancy (FDR = 0.64, 95% CI 0.44–0.95) (Ahlborg et al., 1996).

Solvents Female partner exposure, glycol ethers, inadequate evidence: There are some data showing that females occupationally exposed to ethylene glycol ethers have longer time to pregnancy (FDR = 0.59, 95% CI 0.37–0.94) (Chen et al., 2002b).

Female partner exposure, organic solvents, inadequate evidence: Decreased fecundity was associated with female partner solvent exposure (FDR = 0.79, 95% CI 0.68–0.93), particularly those using acetone (FDR = 0.72, 95% CI 0.53–0.97) (Wennborg et al., 2001). One study reported that daily toluene exposure was associated with reduced fecundity in women (FDR = 0.47, 95% CI 0.29–0.77) (Plenge-Bonig & Karmaus 1999). Similarly, female exposure to formaldehyde at work may have an adverse effect on fecundity (FDR = 0.64, 95% CI 0.43–0.92) (Taskinen et al., 1999). The Agricultural Health Study (AHS) cohort, a large study of licensed pesticide applicators in Iowa and North Carolina, reported that the likelihood of not becoming pregnant after 12 mo of unprotected intercourse was elevated for women (OR = 1.42, 95% CI 1.15–1.75) with at least monthly exposure to solvents (Sallmen et al., 2006). Stronger associations were apparent when solvent exposure was defined as either partner (OR = 1.62, 95% CI 1.20–2.17) or both partners (OR = 2.10, 95% CI 1.22–3.60).

Male partner exposure, organic solvents, inadequate evidence: Men with frequent occupational solvent exposure experienced decreased fecundity (FDR = 0.80, 95% CI 0.57–1.11) (Sallmen et al., 1998), but studies reported no effect (Luderer et al., 2004; Spinelli et al., 1997). Toluene exposure

was not associated with reduced fecundity in men (Plenge-Bonig & Karmaus 1999). The Agricultural Health Study (AHS) cohort, a large study of licensed pesticide applicators in Iowa and North Carolina, reported that the likelihood of not becoming pregnant after 12 mo of unprotected intercourse was elevated for men (OR = 1.21, 95% CI 0.93–1.57) with at least monthly exposure to solvents (Sallmen et al., 2006). Stronger associations were apparent when solvent exposure was defined as either partner (OR = 1.62, 95% CI 1.20–2.17) or both partners (OR = 2.10, 95% CI 1.22–3.60).

Other toxicants Male partner exposure, plastics, inadequate evidence: One study reported no association between workers highly exposed to di(2-ethylhexyl)phthalate and time to pregnancy (Modigh et al., 2002). While reduced fecundity (FDR = 0.79, 95% CI 0.59–1.05) was observed in styrene-exposed workers, no dose response was observed in relation to tasks indicating higher exposure (Kolstad et al., 2000).

Male partner exposure, oil and oil products, inadequate evidence: One study has reported no major influence of exposure to hydrocarbons on time to conception (Bull et al., 1999).

Summary Except for female partner active smoking (sufficient evidence), epidemiologic evidence for the role of environmental toxicants in delayed conception is inadequate.

Early Pregnancy Loss Early pregnancy loss is defined as pregnancy detected by daily urinary human chorionic gonadotrophin (hCG) monitoring with loss occurring less than 6 wk after onset of the last normal menstrual period (LNMP). Early pregnancy loss occurs in about 10–20% of conceptions and is usually not recognized or reported (Ellish et al., 1996; Hjollund et al., 2000; Wang et al., 2003b). As there have been very few studies of early pregnancy loss and environmental exposures, this field remains largely unexplored.

Pesticides Maternal exposure, inadequate evidence: A cohort study of newly married Chinese female textile workers monitored for conception using daily urinary hCG measurements revealed a dose-response relationship between early pregnancy loss (gestation length <6 wk, confirmed by hCG) and maternal preconceptual serum DDT levels (2nd vs. 1st tertile, OR = 1.07, 95% CI 0.58–1.99; 3rd vs. 1st tertile, OR = 1.71, 95% CI 0.93–3.12, *p*-trend = .06); there were similar results when serum DDE was modeled (Venners et al., 2005).

Spontaneous Abortion (Gestation Week <20) Spontaneous abortion is defined as unintentional fetal loss before gestation week (GW) 20. This is the definition used in most recent epidemiologic studies, but some studies have included fetal deaths up to GW 24 or 28. Because early pregnancy loss is rarely recognized and reported, clinically recognized spontaneous abortions virtually all occur after GW 6.

Lead Maternal exposure, limited evidence: A recent review concluded that high-level prenatal occupational lead exposure during the 19th and early 20th centuries likely increased the risk of spontaneous abortion and that limited evidence supports an association at prenatal blood lead levels below approximately 30 μg/dl (Hertz-Picciotto 2000). In particular, a birth cohort study in Mexico City revealed a monotonic dose-response relationship between spontaneous abortion and prenatal blood lead (respective odds ratios for 5–9, 10–14, and ≥15 μg/dl were 2.3, 5.4, and 12.2, *p*-trend = .03) (Borja-Aburto et al., 1999).

Paternal occupational exposure, limited evidence: Reviewers noted limited evidence for an association between spontaneous abortion and paternal occupational lead exposure (Anttila & Sallmen, 1995; Bellinger, 2005). Spontaneous abortion was associated with preconceptual blood lead levels of at least 39 μg/dl in a Finnish cohort of occupationally exposed men (OR = 3.0, 95% CI 1.0–8.7) (Lindbohm et al., 1991b). A similar study in British Columbia found no association with paternal blood lead levels; selection bias is possible as only 38% of workers participated in this study (Alexander et al., 1996). A retrospective cohort study of Norwegian men reported an elevated risk of 2nd trimester spontaneous abortion and likely lead exposure based on job titles (OR = 2.4, 95% CI 0.8–6.9) (Kristensen et al., 1993).

Inorganic and elemental mercury Maternal exposure, inadequate evidence: Case-control studies in Massachusetts revealed an association of borderline statistical significance between spontaneous abortion and detectable drinking water mercury levels in the community of prenatal residence (OR = 1.5, 95% CI 1.0–2.3) (Aschengrau et al., 1989). In a small retrospective cohort study, spontaneous abortion risk was not elevated among women occupationally exposed to elemental mercury (OR = 1.07, 95% CI 0.27–4.56, calculated from data in paper) (Elghany et al., 1997).

Inorganic arsenic Maternal exposure, limited evidence: A case-control study In Massachusetts observed no association between spontaneous abortion and maternal residence in communities with detectable arsenic in drinking water supplies (≥1.4 μg/L vs. undetectable, OR = 1.5, 95% CI 0.4–4.7); the highest level detected was 1.9 μg/L, well below the current U.S. Environmental Protection Agency (EPA) drinking water arsenic maximum contaminant level (10 μg/L) (Aschengrau et al., 1989). A retrospective cohort study in Bangladesh revealed an increased risk of spontaneous abortion in a town with average drinking-water arsenic levels of 240 μg/L, relative to a comparison town with arsenic levels below 20 μg/L (RR = 2.82, 95% CI 1.12–7.36, calculated from data in report) (Ahmad et al., 2001). Spontaneous abortion risk was slightly elevated among women working in a Swedish copper smelter (OR = 1.33, 95% CI 0.94–2.08) (Wulff et al., 2002). Reviewers found limited epidemiologic evidence and sufficient toxicologic evidence of fetal deaths after prenatal arsenic exposure (Golub et al., 1998).

PCBs PCB congeners have half-lives in humans or monkeys of about 3–20 yr (Masuda, 2001; Mes et al., 1995). As their concentrations per unit weight of lipid in maternal or cord blood, breast milk, or adipose tissue samples are highly correlated, PCB levels in any of these samples provide an index of prenatal and fetal exposure. For breast-fed infants, they also reflect lactational exposure, especially when combined with duration of breast feeding. Although most epidemiologic studies report serum or plasma PCB concentrations adjusted for lipid content (based on total cholesterol and triglycerides), a substantial proportion of serum organochlorines are not associated with lipid (Longnecker et al., 2002). Thus use of lipid-adjusted serum PCB levels may contribute to misclassification of exposure levels and reduce the chance of observing true associations with health outcomes.

Maternal high-level exposure, inadequate evidence: A retrospective cohort study of women who consumed cooking oil contaminated by high levels of PCBs, polychlorinated dibenzofurans (PCDFs) and related toxicants during the Yucheng incident in Taiwan revealed no association between spontaneous abortion and maternal preconceptual serum PCB levels (baseline maternal serum PCB >46 vs. ≤46 μg/g lipid, crude OR = 1.12, 95% CI 0.34–3.70) (Yu et al., 2000).

Maternal low-level exposure, inadequate evidence: Reviewers found inadequate evidence for an association between spontaneous abortion and background environmental PCB exposure (Longnecker et al., 1997). In a Swedish retrospective cohort study of fishing families, spontaneous abortion was not associated with residence in a region with fish contaminated by relatively high PCB concentrations (1st trimester fetal death, OR = 0.51, 95% CI 0.27–0.96; 2nd trimester, OR = 0.90, 95% CI 0.44–1.83) (Axmon et al., 2000). In the absence of body-burden data, interpretation of these results is difficult. A case-control study nested within a cohort of Chinese textile workers revealed no association between spontaneous abortion and prenatal serum PCB (per 1 ng/100 g serum increment, OR = 0.96, 95% CI 0.87–1.05) (Korrick et al., 2001). In a small Japanese case-control study, spontaneous abortion was not associated with prenatal serum PCB concentration (mean serum PCB, cases vs. controls, 263.7 ± 136.9 vs. 319.9 ± 189.7 ng/g lipid) (Sugiura-Ogasawara et al., 2003). In an Australian birth cohort study, pregnancy loss (spontaneous abortion or stillbirth) was not associated with breast milk PCB levels (≤50 μg/kg lipid vs. undetectable, OR = 0.60, 95% CI 0.17–2.14; >50 μg/kg, OR = 1.07, 95% CI 0.34–3.35, p-trend = 0.65) (Khanjani & Sim, 2007).

PBBs Maternal exposure, inadequate evidence: A retrospective cohort study of women in Michigan who ate meat from livestock accidentally poisoned by polybrominated biphenyls (PBBs) revealed no association between spontaneous abortion and maternal serum PBBs at baseline soon after exposure (>2 ppb vs. <LD, OR = 0.73, 95% CI 0.47–1.13) (Small et al., 2007).

TCDD Maternal environmental exposure, inadequate evidence: A cohort study of women living in Seveso at the time of the 1976 factory explosion that released substantial amounts of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) found no association between spontaneous abortion and maternal preconceptual serum TCDD levels (per 10-fold increment of maternal serum TCDD, OR = 1.0, 95% CI 0.6–1.6) (Eskenazi et al., 2003).

Paternal occupational exposure, inadequate evidence: Reviewers found insufficient evidence for an association between spontaneous abortion and paternal occupational exposure to phenoxy herbicides potentially contaminated with TCDD (National Academy of Sciences, 2003). This review focused mainly on health risks for Vietnam veterans potentially exposed to Agent Orange (a 50:50

mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) known to be contaminated with TCDD). A retrospective cohort study of veterans revealed no association between spontaneous abortion and paternal serum TCDD levels defined as background (current serum TCDD < 10 pg/g lipid), low (current serum TCDD ≥ 10 and baseline level 10–109 pg/g lipid) and high (current serum TCDD ≥ 10 and baseline level ≥ 110 pg/g lipid) (Wolfe et al., 1995). The respective odds ratios for spontaneous abortion, calculated from data in the paper, were background (OR = 1.13, 95% CI 0.81–1.59), low (OR = 1.32, 95% CI 0.94–1.86) and high (OR = 0.99, 95% CI 0.68–1.43). A subsequent study of wives of men highly exposed to TCDD during production of Agent Orange revealed no association between spontaneous abortion and paternal serum TCDD (per 10-fold increment of paternal serum TCDD at conception, OR = 0.97, 95% CI 0.88–1.09) (Schnorr et al., 2001).

Pesticides Reviewers noted limited but somewhat inconsistent evidence for associations between fetal deaths (spontaneous abortions or stillbirths) and maternal or paternal pesticide exposure indices (Arbuckle & Sever, 1998; Sever et al., 1997). They noted methodologic issues, especially inadequate exposure assessment and limited statistical power of epidemiologic studies. A more recent review examined evidence from epidemiologic studies of pregnancy outcome that assessed pesticide class, family, and/or active ingredient (Weselak et al., 2006). These reviewers found limited epidemiologic evidence for associations between fetal death and DDT and inadequate evidence for associations with other pesticide categories including chlorophenoxy herbicides, triazine herbicides, or thiocarbamate fungicides.

Maternal exposure, chlorophenoxy herbicides, inadequate evidence: Chlorophenoxy herbicides comprise many closely related chemical entities including 2,4-dichlorophenoxyacetic acid (2,4-D[1]), 2,4-dichlorophenoxybutyric acid (2,4-DB), 2-methyl–4-chlorophenoxyacetic acid (MCPA), and 2-methyl–4-chlorophenoxypropionic acid (MCPP, mecoprop) (Wood, 2007). The Ontario farm family study reported no association between spontaneous abortion at GW <20 and prenatal farm use of any chlorophenoxy herbicide (OR = 1.1, 95% CI 0.6–2.1) or subtypes including 2,4-D (OR = 1.0, 95% CI 0.5–2.0), 2,4-DB (OR = 0.7, 95% CI 0.3–1.7) or MCPA (OR = 0.9, 95% CI 0.4–2.0) (Arbuckle et al., 1999). The Ontario study also found no association between these herbicides and spontaneous abortions before GW 12 or during GW 12–19. A subsequent report of this study confirmed no association between prenatal farm use of chlorophenoxy herbicides and spontaneous abortion at GW <12 (OR = 0.6, 95% CI 0.4–1.0) or GW 12–19 (OR = 1.3, 95% CI 0.8–2.0) (Arbuckle et al., 2001). However, there were associations of borderline statistical significance between late spontaneous abortion (GW 12–19) and prenatal farm use of 2,4-D (crude OR = 1.6, 95% CI 0.9–2.7) or dicamba (crude OR = 1.6, 95% CI 0.8–3.2). A case-only analysis within this study showed that early spontaneous abortion (GW <12) was more likely after preconceptual compared to postconceptual (prenatal) chlorophenoxy herbicide use (OR = 1.9, 95% CI 1.1–3.3). In the Ontario study, pesticide exposure reflected both pesticide use by the farm operator spouse (80% males) and indirect exposure of the other spouse since the study was limited to couples on operating farms.

Maternal exposure, other herbicides, inadequate evidence: The Ontario farm family study reported no association between spontaneous abortion before GW 20 and prenatal farm use of atrazine (OR = 0.8, 95% CI 0.5–1.2) or glyphosate (OR = 1.1, 95% CI 0.7–1.7) (Arbuckle et al., 2001). There was also no association between these pesticides and spontaneous abortions before GW 12 or during GW 12–19.

Maternal exposure, DDT/DDE, limited evidence: A recent review found limited evidence based on five studies that reported associations between fetal death and biomarkers of prenatal DDT/DDE exposure (Weselak et al., 2006). Among recent studies cited in their review, a large U.S. nation-wide study found a nonmonotonic dose-response relationship between fetal death at any gestation length and prenatal serum DDE (maternal serum DDE increment of 60 μg/L, OR = 1.4, 95% CI 1.1–1.6) but not DDT levels (Longnecker et al., 2005). Among newly married Chinese female textile workers monitored for conception using daily urinary hCG measurements, there was no association between clinical spontaneous abortion (GW 6–19) and maternal preconceptual serum DDT levels (2nd vs. 1st tertile, OR = 1.22, 95% CI 0.51–2.92; 3rd vs. 1st tertile, OR = 1.28,

[1]First used in 1948.

95% CI 0.53–3.10, *p*-trend = .61); there were similar results when serum DDE was modeled (Venners et al., 2005). In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk DDT or DDE levels (2nd vs. 1st tertile DDE, OR = 0.81, 95% CI 0.0.47–1.42; 3rd vs. 1st tertile, OR = 0.76, 95% CI 0.41–1.39) (Khanjani & Sim, 2006).

Maternal exposure, organophosphate insecticides, inadequate evidence: A nested case-control study in the San Francisco Bay Area revealed a weak association between spontaneous abortion before GW 28 and prenatal residence in areas treated with aerially applied malathion less than a week before the outcome (OR = 1.20, 95% CI 0.94–1.52) but not for such use 1–4 wk before the outcome (OR = 0.91, 95% CI 0.75–1.12) (Thomas et al., 1992). A retrospective cohort study of Ontario farm families reported no association between spontaneous abortion (GW <20) and postconceptual farm use of organophosphate insecticides (OR = 0.6, 95% CI 0.4–1.0) (Arbuckle et al., 2001).

Maternal exposure, other specified insecticides or repellents, inadequate evidence: In a randomized controlled trial of *N,N*-diethyl-*m*-toluamide (DEET) to prevent malaria during pregnancy, spontaneous abortion risk was not increased among exposed women (OR = 1.52, 95% CI 0.49–4.85) (McGready et al., 2001). In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk dieldrin, heptachlor epoxide or oxychlordane levels (Khanjani & Sim. 2006).

Maternal exposure, fungicides, inadequate evidence: Hexachlorobenzene (HCB) is an organochlorine fungicide used as a seed treatment, especially on wheat. A small case-control pilot study nested within a cohort of Chinese textile workers revealed an association of borderline statistical significance between spontaneous abortion and prenatal serum HCB (per 1 ng/100 g serum increment, OR = 1.06, 95% CI 1.00–1.14) (Korrick et al., 2001). A small study of Turkish women poisoned as children (average age 6 yr) by consumption of hexachlorobenzene-contaminated wheat seed grain (or by breastfeeding if mothers were exposed) revealed an association between spontaneous abortion and maternal serum hexachlorobenzene levels (per log HCB (μg/L), $\beta = 2.88 \pm 0.91$, $p < .001$) but did not assess or adjust for potential confounders (Jarrell et al., 1998). There was no association between repeated spontaneous abortion (3 or more) and maternal serum HCB levels (mean HCB ± SD, cases vs. controls, 17.6 ± 10.2 vs. 21.2 ± 10.0 ng/g lipid, $p > .05$) in a small Japanese case-control study (Sugiura-Ogasawara et al., 2003). In an Australian retrospective cohort study, fetal death (any gestation length) was not associated with breast milk HCB levels (2nd vs. 1st tertile, OR = 1.03, 95% CI 0.61–1.75; 3rd vs. 1st tertile, OR = 0.49, 95% CI 0.26–0.90) (Khanjani & Sim, 2006). The Ontario farm family study reported no association between spontaneous abortion (GW <20) and postconceptual farm use of the broad class of fungicides (OR = 0.8, 95% CI 0.5–1.1) (Arbuckle et al., 2001).

Ethylene oxide Maternal exposure, limited evidence: Ethylene oxide is used as a grain fumigant but epidemiological studies have assessed occupational exposures in other settings. Among Finnish nurses, spontaneous abortion was not associated with exposure to anaesthetic gases (Hemminki et al., 1985). In a retrospective cohort study of most recent pregnancies among female dental assistants in California who conceived while working full-time, spontaneous abortion was associated with self-reported occupational ethylene oxide exposure (OR = 2.5, 95% CI 1.0–6.3) and was independent of age and exposure to nitrous oxide or preparation of mercury amalgams (Rowland et al., 1996). A South African retrospective cohort study revealed a strong association between spontaneous abortion and occupational exposure to ethylene oxide in hospital sterilizing units while working full-time during the relevant pregnancy (high vs. low exposure, OR = 20.8, 95% CI 2.1–199); this estimate was based on only 4 spontaneous abortions among 19 highly exposed pregnancies and 1 among 78 pregnancies of women with relatively low exposure (Gresie-Brusin et al., 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: Reviewers found limited evidence for associations between spontaneous abortion and maternal employment in agriculture or other occupational exposure to unspecified pesticides, including dose-response relationships with number of pesticides used and nonuse of protective equipment (Arbuckle & Sever, 1998). Recently, a Chinese retrospective cohort study reported that spontaneous abortion was associated with maternal use of drinking water from sources subject to runoff from pesticide-treated cotton fields (OR = 1.63, 95% CI 1.11–2.39) but not with occupational pesticide exposure (OR = 0.60, 95% CI 0.43–0.84) (Cho et al., 1999). In a retrospective cohort study of licensed pesticide applicators in

Minnesota, spontaneous abortion was associated with prenatal mixing, loading or application of pesticides (OR = 1.81, 95% CI 1.04–3.12) (Garry et al., 2002). Although suggestive, the heterogeneity of exposure indices precludes firm conclusions and more research is needed to examine specific pesticides, critical exposure windows and dose-response relationships.

Paternal occupational exposure, TCDD-free, inadequate evidence: Reviewers found insufficient evidence for an association between spontaneous abortion and paternal occupational exposure to chlorophenoxy herbicides potentially contaminated with TCDD (National Academy of Sciences, 2003). See also discussion of paternal occupational TCDD exposure above.

Paternal occupational exposure, TCDD-contaminated chlorophenoxy herbicides, chlorophenoxy herbicides, limited evidence: An initial report of the Ontario farm family cohort showed no association between spontaneous abortions before GW 20 and preconceptual use (mainly paternal) of 2,4-D (OR = 1.3, 95% CI 0.8–2.1), MCPA (OR = 1.1, 95% CI 0.6–1.8) or dicamba (OR = 1.1, 95% CI 0.6–2.1) (Savitz et al., 1997a). Further analysis revealed an association between preconceptual agricultural use (mainly paternal) of chlorophenoxy herbicides and spontaneous abortion before GW 12 (OR = 2.5, 95% CI 1.0–6.4) but not with those at GW 12–19 (OR = 0.4, 95% CI 0.2–1.0) (Arbuckle et al., 1999). The Ontario study also revealed statistically nonsignificant elevated risks of early spontaneous abortion (GW < 12) related to preconceptual paternal use of 2,4-D (OR = 1.9, 95% CI 0.7–4.8) or MCPA (OR = 2.3, 95% CI 0.8–6.5). A subsequent report indicated that spontaneous abortion at GW < 12 was associated with preconceptual chlorophenoxy herbicide use (crude OR = 1.5, 95% CI 1.1–2.1) and weakly with 2,4-D use (crude OR = 1.3, 95% CI 0.9–2.0) (Arbuckle et al., 2001). Although there was no association between spontaneous abortion at GW <20 and preconceptual farm use of dicamba (OR = 1.1, 95% CI 0.7–1.9, 95% CI 0.7–1.7), there was a statistically nonsignificant elevated risk of early spontaneous abortion (GW < 12) related to such exposure (OR = 1.6, 95% CI 0.8–3.2). In a case-only analysis, early spontaneous abortions (GW < 12) were more likely after preconceptual compared to postconceptual exposure chlorophenoxy herbicide use (OR = 3.1, 95% CI 1.4–6.4) (Arbuckle et al., 2001). A retrospective cohort study in Minnesota revealed a statistically nonsignificant association between spontaneous abortion before GW 13 among the subset of pregnancies conceived during the spring spray season and use of any chlorophenoxy herbicide (relative to use of any other pesticides, OR = 1.59, 95% CI 0.77–3.27) (Garry et al., 2002). However, there was an association between spontaneous abortions conceived during spring and paternal combined use of chlorophenoxy, sulfonylurea, and benzothiodazole herbicides (relative to use of any other pesticides, OR = 2.94, 95% CI 1.40–6.16). In Minnesota, herbicides are generally applied to crops in spring, and insecticides in summer and fungicides as needed in summer and fall (Garry et al., 2002).

Paternal occupational exposure, other herbicides, inadequate evidence: The Ontario farm family study reported that spontaneous abortion before GW 20 was associated with preconceptual use (mainly paternal) of carbaryl (OR = 1.9, 95% CI 1.1–3.1) and thiocarbamate crop herbicides (OR = 1.9, 95% CI 1.1–3.3); there were also associations of borderline statistical significance with atrazine (OR = 1.5, 95% CI 0.9–2.4) and glyphosates (OR = 1.5, 95% CI 0.8–2.7) (Savitz et al., 1997a). A subsequent report of the Ontario study revealed no association between spontaneous abortion at GW <20 and preconceptual farm use of atrazine (OR = 0.8, 95% CI 0.5–1.2) or glyphosate (OR = 1.1, 95% CI 0.7–1.7) (Arbuckle et al., 2001). The latter report indicated a statistically nonsignificant elevated risk of early spontaneous abortion (GW <12) related to preconceptual farm use of glyphosate (OR = 1.4, 95% CI 0.8–2.5). The Minnesota retrospective cohort study revealed associations between spontaneous abortion before GW 13 among the subset of pregnancies conceived during the spring spray season and use of herbicides including sulfonylurea (relative to use of any other pesticides, OR = 2.11, 95% CI 1.09–4.09) and imidizolinone (OR = 2.56, 95% CI 1.11–5.87) (Garry et al., 2002). Further studies are needed to assess specific herbicides, critical exposure windows, and dose-response relationships.

Paternal occupational exposure, DDT/DDE, inadequate evidence: Spontaneous abortion before GW 20 was associated with paternal employment using backpacks to apply DDT and other insecticides on cotton crops in India (exposed vs. unexposed men, RR = 2.00, 95% CI 1.77–2.26) (Rupa et al., 1991). A retrospective cohort study of male malaria control workers in Mexico

reported a weak and statistically nonsignificant association between spontaneous abortion and paternal DDE body burden estimated from self-reported information on timing, intensity, and duration of DDT exposure (4th vs. 1st quartile estimated paternal DDE, OR = 1.24, 95% CI 0.91–1.70) (Salazar-Garcia et al., 2004).

Paternal occupational exposure, organophosphate insecticides, inadequate evidence: The Ontario farm family study reported that spontaneous abortion before GW 20 was not associated with preconceptual use (mainly paternal) of organophosphate crop insecticides (OR = 1.3, 95% CI 0.7–2.3) (Savitz et al., 1997a). A more recent report of this study also revealed no association between preconceptual organophosphate insecticide use and early (GW <12) (OR = 1.0, 95% CI 0.6–1.6) or late (GW 12–19) spontaneous abortion (OR = 1.0, 95% CI 0.6–1.7) (Arbuckle et al., 2001). In a case-only analysis, the Ontario study showed that early spontaneous abortion was associated with preconceptual organophosphate insecticide use (compared to postconceptual use, OR = 3.8, 95% CI 1.1–13.4). The significance of the latter finding is not clear but supports the need for research to clarify the role of preconceptual organophosphate insecticide exposure.

Paternal occupational exposure, other or unspecified insecticides, inadequate evidence: The Ontario farm family study reported that spontaneous abortion before GW 20 was associated with preconceptual carbaryl use (OR = 2.1, 95% CI 1.1–4.1) (Savitz et al., 1997a). In a large retrospective cohort of licensed pesticide applicators in Minnesota, spontaneous abortion was not associated with insecticide use (insecticide and herbicide vs. herbicide only use, OR = 1.27, 95% CI 0.68–2.36) (Garry et al., 2002).

Paternal occupational exposure, fungicides, inadequate evidence: The Ontario farm family study reported that spontaneous abortion before GW 20 was not associated with preconceptual use (mainly paternal) of fungicides (OR = 1.2, 95% CI 0.7–2.1) (Savitz et al., 1997a). In a subsequent report, there were statistically nonsignificant associations between preconceptual fungicide use and spontaneous abortion before GW 12 (OR = 1.3, 95% CI 0.9–1.9) or during GW 12–19 (OR = 1.4, 95% CI 0.9–2.1) (Arbuckle et al., 2001). In a case-only analysis, spontaneous abortion before GW 12 (but not those at GW 12–19) was associated with preconceptual farm fungicide use (compared to postconceptual use, OR = 3.9, 95% CI 1.4–10.3). The Minnesota study revealed associations between spontaneous abortion and application of the fungicides mancozeb and/or maneb (compared to unexposed men, OR = 1.77, 95% CI 1.11–2.83) and organotin fungicides (OR = 1.55, 95% CI 1.01–2.37) (Garry et al., 2002).

Ethylene oxide Paternal exposure, inadequate evidence: In a Finnish retrospective cohort study based on linkage of national databases on pregnancy outcome and census information, spontaneous abortion was associated with paternal occupations likely exposed to ethylene oxide (based on job-exposure matrix) (OR = 4.7, 95% CI 1.2–18.4) (Lindbohm et al., 1991a).

Paternal occupational exposure, unspecified pesticides, inadequate evidence: Retrospective cohort studies reported associations between spontaneous abortion and paternal occupational exposure to unspecified pesticides in semi-enclosed Columbian greenhouses (exposure vs. preexposure period, OR = 1.79, 95% CI 1.16–2.77) (Restrepo et al., 1990b) and backpack application of multiple pesticides in India (OR = 2.00, 95% CI 1.82–2.66) (Rupa et al., 1991). In another retrospective cohort study, Norwegian farm families had an elevated risk of spontaneous abortion (GW 16–27) compared to nonfarm families living in agricultural communities (OR = 2.18, 95% CI 1.67–2.85) (Kristensen et al., 1997a). This study could not distinguish between maternal and paternal pesticide exposure; 57% of men and 34% of women worked at least 500 h/yr on their farms. A small retrospective cohort study in Italy reported an association between spontaneous abortion and paternal occupation as a pesticide applicator (OR = 3.8, 95% CI 1.2–12.0) (Petrelli et al., 2000). In a cohort of Italian greenhouse workers, there was a strong association between spontaneous abortion and paternal occupational pesticide exposure (compared to unexposed greenhouse workers, crude OR = 3.70, 95% CI 1.04–13.3, calculated from data in paper) (Petrelli et al., 2003). A retrospective cohort study of wives of agricultural pesticide aerial applicator pilots revealed no increased risk of spontaneous abortion (crude OR = 0.65, 95% CI 0.41–1.03, calculated from data in paper) (Roan et al., 1984). Although the collective evidence from these studies is suggestive, the heterogeneity of exposure indices precludes firm conclusions.

Tobacco smoke Prenatal active smoking, limited evidence: The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between spontaneous abortion and maternal active smoking (U.S. Department of Health and Human Services, 2001).

Prenatal ETS exposure, limited evidence: Reviewers concluded that the three available epidemiologic studies provided limited evidence of an association between spontaneous abortion and prenatal ETS exposure (Lindbohm et al., 2002). An expert panel found limited evidence of a causal association between spontaneous abortion and prenatal ETS exposure independent of paternal smoking (California Environmental Protection Agency, 2005). The panel noted limited evidence of a causal association between spontaneous abortion and paternal active smoking (an important source of prenatal ETS exposure) but noted that this could arise from preconceptual paternal germ-cell mutations rather than postconceptual maternal ETS exposure. The U.S. Surgeon General reviewed five available studies and concluded that there was inconsistent evidence of an association between spontaneous abortion and prenatal ETS exposure (U.S. Department of Health and Human Services, 2006). A subsequently published original case-control study of spontaneous abortions at GW 6–12 revealed an association with maternal ETS exposure (OR = 1.67, 95% CI 1.17–2.38) (George et al., 2006). This study was unusually robust in that both the outcome and exposure were confirmed using biomarkers (hCG to confirm pregnancy and cotinine to verify exposure status).

Drinking-water disinfection by-products Most epidemiologic studies of DBPs and potential adverse health outcomes have used drinking-water trihalomethane (THM) concentrations as an indicator of total disinfection by-product (DBP) concentrations in chlorinated drinking water. DBP concentrations tend to be highest in chlorinated surface waters that contain relatively high amounts of natural organic material that reacts with chlorine to generate THMs and many other by-products. The mutagenic activity of raw drinking water is generally very low but may increase substantially after chlorination.

Maternal exposure, limited evidence: Reviewers noted limited and fairly consistent evidence for an association between spontaneous abortion and drinking water disinfection by-products (Bove et al., 2002; Graves et al., 2001; Nieuwenhuijsen et al., 2000). In experimental animals, high-dose prenatal exposure to chloroform, bromodichloromethane (BDCM), haloacetonitriles, or haloacetic acids (HAAs) caused fetal toxicity, including fetal resorptions and reduced fetal weight and survival (Graves et al., 2001; Nieuwenhuijsen et al., 2000).

Hazardous waste disposal sites Maternal exposure, inadequate evidence: Reviewers found inadequate evidence for an association between fetal deaths and prenatal residential proximity to hazardous waste landfill sites or incinerators; there were few extant studies of spontaneous abortion and such exposure (Johnson & DeRosa, 1995; Vrijheid, 2000). Subsequently published studies revealed no association between spontaneous abortion and maternal residential proximity to high-dioxin emission incinerators (OR = 0.82, 95% CI 0.54–1.20, p-trend = .97 (over ten 1-km increments)) (Tango et al., 2004) or hazardous waste disposal sites (high vs. low/moderate hazard sites, OR = 0.75, 95% CI 0.28–1.99) (Gilbreath & Kass, 2006a).

Solvents Prenatal occupational exposure, chlorinated solvents, limited evidence: Spontaneous abortions were associated with prenatal occupational exposure to tetrachloroethylene in Scandinavia (≥1 h/d, OR = 2.88, 95% CI 0.98–8.44) (Olsen et al., 1990), California (OR = 4.7, 95% CI 1.1–21.1) (Windham et al., 1991), and the United Kingdom (dry-cleaning operator, OR = 1.63, 95% CI 1.01–2.66) (Doyle et al., 1997), trichloroethylene in California (OR = 3.1, 95% CI 0.92–10.4) (Windham et al., 1991), and with occupational chloroform use in Swedish laboratories (preconceptual exposure, OR = 2.3, 95% CI 0.9–5.9) (Wennborg et al., 2000).

Prenatal occupational exposure, glycol ethers, limited evidence: Employment in U.S. semiconductor industry fabrication rooms during early pregnancy was associated with medical-record-confirmed spontaneous abortion in a national cohort study (clinical spontaneous abortion, OR = 1.43, 95% CI 0.95–2.09; clinical spontaneous abortion plus early pregnancy loss confirmed by daily urinary hCG tests, OR = 1.25, 95% CI 0.63–1.76) (Schenker et al., 1995). This study showed that spontaneous abortion risk increased with level of exposure to glycol ethers and other photoresist and developer chemicals (highly exposed vs. unexposed, OR = 2.70, 95% CI 1.40–4.55) (Swan et al., 1995). In a cohort study in two eastern U.S. semiconductor plants, spontaneous abortion was associated with

high exposure to ethylene glycol ether exposure during the month of conception (compared to unexposed women, OR = 2.8, 95% CI 1.4–5.6) (Correa et al., 1996). A small case-control study nested within a cohort of UK semiconductor industry female employees revealed no association between spontaneous abortion and prenatal work in semiconductor fabrication (OR = 0.64, 95% CI 0.27–1.51); there were too few cases to assess specific solvent exposures (Elliott et al., 1999).

Prenatal occupational exposure, other or unspecified solvents, limited evidence: A meta-analysis of 5 studies published during 1988–1992 indicated a modest association between spontaneous abortion and maternal occupational exposure to organic solvents (summary OR = 1.25, 95% CI 0.99–1.58) (McMartin et al., 1998). In subsequently published studies, spontaneous abortion was associated with prenatal occupational exposure to unspecified solvents in Finland (high vs. low 1st trimester exposure, OR = 2.3, 95% CI 1.1–4.3) (Taskinen et al., 1994) and Italy (high vs. low exposure during shoe manufacturing, OR = 3.85, 95% CI 1.24–11.9) (Agnesi et al., 1997). Although the latter study did not assess specific solvents, those commonly used in the local shoe industry at that time included ethylacetate, cyclohexane, methylethylketone, and hexane. Spontaneous abortion was not associated with prenatal occupational exposure to unspecified solvents in studies in Toronto (any solvent, crude OR = 1.4, 95% CI 0.4–4.9, calculated from data in paper) (Khattak et al., 1999) and Sweden (solvents other than chloroform, OR = 0.9, 95% CI 0.5–1.9) (Wennborg et al., 2000).

Paternal preconceptual exposure, glycol ethers, inadequate evidence: In a cohort study in two eastern U.S. semiconductor plants, spontaneous abortion was not associated with high paternal exposure to ethylene glycol ether exposure during the month of conception (compared to unexposed, OR = 0.7, 95% CI 0.3–1.6) (Correa et al., 1996).

Paternal preconceptual exposure, unspecified solvents, limited evidence: A recent meta-analysis of five epidemiologic studies published during 1984–1998 reported a statistically nonsignificant elevated risk of spontaneous abortion related to paternal occupational solvent exposure (overall RR = 1.30, 95% CI = 0.81–2.11) (Logman et al., 2005). Among studies not included in this meta-analysis, spontaneous abortion was associated with organic solvent exposure among men monitored for occupational solvent exposure (OR = 2.3, 95% CI 1.1–5.0) with somewhat higher risks for painters (OR = 3.3, 95% CI 1.6–6.8) and woodworkers (OR = 3.8, 95% CI 1.2–12) (Taskinen et al., 1989). In a cohort of Norwegian men in the printing industry, late spontaneous abortion (GW 20–27) was also associated with solvent exposure (with or without lead exposure, OR = 5.5, 95% CI 1.8–17.2) (Kristensen et al., 1993).

Bisphenol A Bisphenol A (BPA) is a monomer used to produce polycarbonate plastics and resins, while brominated BPA analogues are used as flame retardants.

Maternal exposure, inadequate evidence: A small case-control study reported an association between recurrent spontaneous abortion and maternal serum bisphenol A (BPA) levels (case vs. control mean maternal serum BPA (± SD), 2.59 ± 5.23 ng/ml vs. 0.77 ± 0.38 ng/ml, $p = .02$) (Sugiura-Ogasawara et al., 2005). About half or more of 1st trimester spontaneously aborted fetuses have chromosomal abnormalities, especially triploidy (Eiben et al., 1990), and BPA is a potent cause of aneuploidy in mouse oocytes in vivo (Hunt et al., 2003), possibly by interfering with spindle microtubule organization and chromosome segregation during meiosis (Can et al., 2005). In mice, prenatal exposure to high-dose BPA produced increased fetal resorption (Morrissey et al., 1987).

Summary There was limited epidemiologic evidence for the role of environmental toxicants in spontaneous abortion, including prenatal exposure to lead, arsenic, DDT/DDE, ethylene oxide, active smoking, ETS, DBPs, chlorinated solvents, glycol ethers, other and unspecified solvents, and ethylene oxide, and paternal occupational exposure to lead, chlorophenoxy herbicides other than 2,4,5-T, and other and unspecified solvents.

Stillbirths (Gestation Week ≥ 20) Stillbirths are defined here at those occurring at GW 20 or later, but some studies used other definitions (e.g., ≥28 wk). There are about 27,000 stillbirths annually in the United States (Centers for Disease Control and Prevention, 2004). Major causes of stillbirths include birth defects, infections, intrauterine growth restriction, gestational diabetes, and preeclampsia (Health Canada, 2003).

Lead Maternal exposure, inadequate evidence: The Port Pirie birth cohort study found no association between stillbirth and 2nd trimester maternal blood lead levels (only 11 cases)

(McMichael et al., 1986). In a subsequent nested case-control study within this cohort, geometric mean placental membrane lead levels were higher among pregnancies ending in stillbirth (2.73 μg/g, 95% CI 0.69–10.8, $n = 6$) than controls (0.78 μg/g, 95% CI 0.61–1.00, $n = 22$) but the difference was not statistically significant (Baghurst et al., 1991). A large population-based case-control study found a borderline association between stillbirth and self-reported prenatal occupational lead exposure (Savitz et al., 1989a). A very small cohort of female survivors of childhood lead poisoning had a nonsignificantly increased risk of fetal death (any gestation length), but biomarkers of lead body burden were not measured (Hu 1991). A small case-control study in Boston reported a nonsignificant association between stillbirth and drinking water lead levels in communities where mothers resided during the 1st trimester (drinking water lead 2.5–80 vs. <2.5 μg/L, OR = 2.1, 95% CI 0.6–7.2) (Aschengrau et al., 1993). In a Norwegian retrospective cohort study, there was a statistically nonsignificant elevated risk of late spontaneous abortion, stillbirths and neonatal deaths among women with likely high-level lead exposure based on job title (OR = 3.7, 95% CI 0.6–13) (Irgens et al., 1998).

Paternal occupational exposure, inadequate evidence: A large U.S. population-based case-control study revealed no association between stillbirth and self-reported paternal occupational lead exposure (Savitz et al., 1989a). Among a Norwegian cohort of printers, stillbirths were associated with potential lead exposure based on job title (OR = 2.0, 95% CI = 0.9–4.7) (Kristensen et al., 1993). A cohort of male lead smelter workers in British Columbia reported statistically nonsignificant associations between stillbirth and birth defects (12 stillbirths and 30 birth defect cases were combined for analysis) and blood lead levels of at least 25 μg/dl (Alexander et al., 1996). The dilution of stillbirths by birth defect cases reduces the usefulness of this study. In a large Norwegian retrospective cohort study, late spontaneous abortion, stillbirths and neonatal deaths combined were not associated with likely paternal high-level lead exposure based on job title (OR = 1.2, 95% CI 0.7–1.9) (Irgens et al., 1998).

Mercury Maternal exposure, inadequate evidence: Stillbirths were not associated with detectable inorganic mercury levels in drinking water in the community of prenatal residence in Massachusetts (OR = 0.7, $p > .05$) (Aschengrau et al., 1993) or with prenatal occupational exposure to airborne elemental mercury in North Carolina (OR = 1.42, 95% CI 0.12–37.2, calculated from data in paper) (Elghany et al., 1997).

Inorganic arsenic Maternal exposure, drinking water, inadequate evidence: A small case-control study in Massachusetts reported no association between stillbirth and detectable drinking water arsenic levels in the community of prenatal residence (drinking-water arsenic >0.8 μg/L vs. undetectable, OR = 0.7; confidence interval not stated, $p > .05$; highest arsenic level was 2.6 μg/L) (Aschengrau et al., 1993). In areas with drinking water arsenic levels above 100 μg/L, elevated stillbirth risks were reported in ecologic studies in Hungary (rate per 1000 live births, exposed vs. comparison region, 7.7 and 2.8, $p = .03$) (Borzsonyi et al., 1992) and Chile (exposed vs. comparison region, RR = 1.72, 95% CI 1.54–1.93) (Hopenhayn-Rich et al., 2000) and in a retrospective cohort study in Bangladesh (RR = 2.24, 95% CI 0.86–6.04, calculated from data in report) (Ahmad et al., 2001).

Maternal exposure, airborne, inadequate evidence: A review of epidemiologic and toxicologic literature noted limited evidence of associations between fetal deaths and arsenic exposure in humans and indicated that prenatal inorganic arsenic exposure can produce fetal death in experimental animals (Golub et al., 1998). Two original studies were not included in the latter review. There was no association between stillbirth and prenatal airborne arsenic exposure (based on self-reported work history) in a nationwide U.S. case-control study (OR = 1.0, 95% CI 0.7–1.3) (Savitz et al., 1989a). A case-control study in a Texan community with an arsenical pesticide plant reported an association between stillbirth and estimated ambient air arsenic levels above 100 $\mu g/m^3$ near the prenatal residence (OR = 4.0, 95% CI 1.2–13.7) (Ihrig et al., 1998).

Paternal occupational exposure, airborne, inadequate evidence: A U.S. case-control study found no association between stillbirth and self-reported paternal occupations with likely arsenic exposure to airborne arsenic (OR = 1.0, 95% CI 0.8–1.2) (Savitz et al., 1989a). A small case-control study revealed an inverse association between stillbirth and parental employment in a Swedish copper smelter (no data reported on maternal/paternal status but high-exposure jobs were held mainly by men) (Wulff et al., 1995).

Cadmium Maternal exposure, inadequate evidence: In a Massachusetts case-control, stillbirths were not associated with low-level drinking water cadmium levels in communities of prenatal residence (≥0.4 vs. <0.4 μg/L, OR = 1.2, $p > .05$) (Aschengrau et al., 1993). A Swedish ecologic study demonstrated no overall increased risk of stillbirths among women living in municipalities with soil cadmium levels exceeding 1.6 μg/g (OR = 0.97, 95% CI 0.72–1.29); in the municipality with the highest soil cadmium level (12 μg/g), stillbirth risk was elevated (OR = 2.17, 95% CI 1.06–4.49) (Landgren, 1996).

PCBs Maternal exposure, high-level exposure, inadequate evidence: A retrospective cohort study of women exposed to high levels of PCBs, PCDFs and related toxicants during the Yucheng incident revealed no increased risk of stillbirths (maternal serum PCB >46 vs. ≤46 ng/L, OR = 1.35, 95% CI 0.35–5.26) (Yu et al., 2000).

Maternal exposure, low-level exposure, inadequate evidence: Reviewers found insufficient evidence for an association between stillbirth and background PCB exposure (Longnecker et al., 1997). In a Swedish retrospective cohort study of fishing families, stillbirth was not associated with residence in a region with fish contaminated by relatively high PCB concentrations (OR = 1.58, 95% CI 0.50–5.04) (Axmon et al., 2000).

TCDD Paternal occupational exposure, inadequate evidence: Compared to Vietnam veterans not exposed to Agent Orange, there were statistically nonsignificant elevated risks of stillbirth (odds ratios calculated from data in paper) among exposure groups categorized as background (current and baseline TCDD ≤10 ng/L, OR = 1.89, 95% CI 0.68–5.12) or low (current TCDD ≤ 10 ng/L and baseline ≤110 ng/L, OR = 1.90, 95% CI 0.64–5.43); the odds ratio for the high TCDD category (current >10 ng/L and baseline >110 ng/L) was not calculated as there was only 1 exposed case father (Wolfe et al., 1995). Among a cohort of British Columbia sawmill workers, stillbirths were not associated with paternal occupational exposure to chlorophenate wood preservatives contaminated by TCDD and related toxicants (per 100-h increment of exposure up to 3 mo before conception, OR = 1.0, 95% CI 0.97–1.063) (Dimich-Ward et al., 1996).

Pesticides Maternal exposure, nonchlorophenoxy herbicides, inadequate evidence: In a California case-cohort study, there was an association of borderline statistical significance between stillbirths/neonatal deaths from birth defects and agricultural use of paraquat during GW 3–8 (OR = 1.8, 95% CI 0.9–3.9) in the same square mile section as the prenatal residence (Bell et al., 2001b).

Maternal exposure, DDT/DDE, limited evidence: A review of available studies found limited evidence of an association between fetal deaths and biomarkers of maternal DDT/DDE exposure (Weselak et al., 2006). Among recent studies included in their review, a retrospective cohort study based on the U.S. Collaborative Perinatal Project reported a nonmonotonic dose-response relationship between fetal deaths of any gestation length and prenatal serum DDE levels (per 60 μg/L maternal serum DDE increment, OR = 1.4, 95% CI 1.1–1.6) (Longnecker et al., 2005). The latter authors stated that the association with maternal serum DDE was similar for spontaneous abortions and stillbirths but did not include supporting data. A subsequently reported Australian retrospective cohort study observed no association between fetal death (any gestation length) and breast milk DDT or DDE levels (e.g., 3rd vs. 1st tertile DDE, OR = 0.76, 95% CI 0.41–1.39) (Khanjani & Sim, 2006).

Maternal exposure, organophosphate insecticides, inadequate evidence: A nested case-control study reported an elevated stillbirth risk among women living in regions sprayed with malathion 1–4 wk before the outcome (OR = 1.95, 95% CI 0.88–4.35) (Thomas et al., 1992). A California-wide study revealed that agricultural organophosphate application (mainly insecticides) during GW 3–8 in the same square mile section as the prenatal residence was associated with stillbirths/neonatal deaths from birth defects (OR = 2.9, 95% CI 1.3–6.4) (Bell et al., 2001b) but not with other stillbirths (1st trimester exposure, OR = 1.0, 95% CI 0.7–1.3) (Bell et al., 2001c). Although suggestive, these findings require confirmation and exploration of dose-response relationships.

Maternal exposure, pyrethroid insecticides, inadequate evidence: Stillbirths/neonatal deaths from causes other than birth defects in California were not associated with agricultural pyrethroid insecticide application in the same square mile section as the maternal residence (1st trimester use, OR = 1.0, 95% CI 0.6–1.6) (Bell et al., 2001c). However, there was an association between stillbirths/neonatal deaths from birth defects and agricultural pyrethroid insecticide application during

GW 3–8 in the same square mile section as the maternal residence (OR = 4.9, 95% CI 1.9–12.9); this analysis excluded subjects for whom other pesticide classes were also used during GW 3–8 (Bell et al., 2001a, 2001b). The California study used a highly detailed statewide pesticide use database and did not have to rely on individual pesticide exposure recall; however, it did not assess potential relationships between stillbirths/neonatal deaths and preconceptual paternal exposure.

Maternal exposure, organochlorine insecticides, inadequate evidence: An Australian retrospective cohort study found no association between fetal death (any gestation length) and breast milk dieldrin (3rd vs. 1st tertile, OR = 0.73, 95% CI 0.42–1.27), heptachlor epoxide (OR = 0.82, 95% CI 0.48–1.39) or oxychlordane levels (OR = 0.54, 95% CI 0.29–1.00) (Khanjani & Sim, 2006).

Maternal exposure, unspecified insecticides, inadequate evidence: A case-control study in California agricultural counties revealed an association of borderline statistical significance between all stillbirths/neonatal deaths and 1st trimester indoor use of insecticides at the maternal residence (OR = 1.4, 95% CI 0.9–2.3) but not insecticide use on pets (OR = 1.0, 95% CI 0.5–1.9) (Pastore et al., 1997). There was a statistically nonsignificant elevated risk of stillbirths among Sudanese women who reported prenatal spraying of pesticides (mainly insecticides) using hand pumps indoors at home (OR = 1.6, 95% CI 0.8–3.3) (Taha & Gray, 1993).

Maternal exposure, fungicides, inadequate evidence: An Australian retrospective cohort study found no association between fetal death (any gestation length) and breast HCB levels (3^{rd} vs. 1^{st} tertile, OR = 0.49, 95% CI 0.26–0.90) (Khanjani & Sim, 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: Reviewers found limited epidemiologic evidence for associations between fetal deaths and maternal exposure to unspecified pesticides (Arbuckle & Sever, 1998). Among studies of stillbirths published before these reviews, prenatal exposures linked to elevated stillbirth risks included maternal employment in agriculture or horticulture (compared to all women in cohort, RR = 5.55, 95% CI 1.51–14.2, based on 4 exposed case mothers) (McDonald et al., 1988), pesticide use at work (OR = 1.6, 95% CI 1.3–2.1) or home (OR = 1.5, 95% CI 1.3–1.7) (Savitz et al., 1989b), occupational pesticide use in China (lower 95% confidence limit = 4.48, $p < .05$; OR and upper 95% confidence limit not available as there were 7 exposed case and 0 exposed control mothers) (Zhang et al., 1992), prenatal spraying of pesticides on Sudanese farms (OR = 3.6, 95% CI 1.6–8.0) (Taha & Gray, 1993), and maternal occupational pesticide use during the 1st trimester (OR = 2.7, 95% CI 1.5–4.8) or 2nd trimester (OR = 2.2, 95% CI 1.0–4.9) (Pastore et al., 1997). In the latter study, there was a relatively strong association between the subgroup of stillbirths and neonatal deaths from complications of placenta or cord and 1st trimester maternal occupational pesticide use (OR = 4.8, 95% CI 2.0–11.4). A recent Danish pregnancy cohort study revealed a statistically nonsignificant elevated risk of fetal loss at any gestation length related to prenatal occupation as gardeners (OR = 1.7, 95% CI 0.7–4.0, 5 exposed case mothers) (Zhu et al., 2006). Studies reporting no association between stillbirths and maternal pesticide exposure indices included case-control studies in the United States (occupation in agriculture, forestry or fishing, OR = 0.8, 95% CI 0.5–1.3) (Savitz et al., 1989a), Colombia (employment in semi-enclosed horticultural greenhouses, OR = 0.99, 95% CI 0.66–1.48) (Restrepo et al., 1990b), and California (1st trimester maternal residential proximity to agricultural crops, OR = 1.0, 95% CI 0.9–1.2; 1st trimester garden pesticide use, OR = 0.7, 95% CI 0.6–3.1) (Pastore et al., 1997). Although suggestive, the heterogeneity of exposure indices precludes firm conclusions.

Paternal occupational exposure, 2,4,5-T and chlorophenate wood preservatives, inadequate evidence: See discussion of paternal occupational TCDD exposure earlier.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: A retrospective cohort study in Colombia reported no association between stillbirths and paternal employment in semi-enclosed floriculture greenhouses in which a total of 127 different types of pesticides were used (OR = 0.87, 95% CI 0.42–1.83) (Restrepo et al., 1990b). Partners of male pesticide applicators had a substantially increased risk of stillbirths in an Indian retrospective cohort study (crude OR = 4.97, 95% CI 3.85–6.42, calculated from data in paper); exposed men used backpacks to apply organochlorine and other pesticides on cotton (Rupa et al., 1991). There may have been recall bias in this study as only 2 birth defects were reported among 3016 pregnancies in the unexposed group compared to 128 among 4240 pregnancies in the exposed group. In a retrospective cohort of Norwegian farm

families, stillbirth risk (based on official records) was not elevated (compared to nonfarm families, RR = 0.88, 95% CI 0.79–0.98) (Kristensen et al., 1997a). In a Spanish retrospective cohort study of pregnancies conceived during the pesticide-use season (April–September), stillbirth (based on official records) was associated with paternal occupation in agriculture (stillbirths caused by birth defects, OR = 1.62, 95% CI 1.01–2.60; other stillbirths, OR = 1.35, 95% CI 1.11–1.65) (Regidor et al., 2004). Although suggestive, the heterogeneity of exposure indices precludes firm conclusions.

Tobacco smoke Maternal active smoking, limited evidence: The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between stillbirth and maternal active smoking (U.S. Department of Health and Human Services, 2001).

Maternal exposure, ETS, inadequate evidence: Stillbirths were not associated with ETS exposure at home (OR = 1.1, 95% CI 0.6–2.4) or at work (OR = 1.2, 95% CI 0.6–2.4) among Swedish women (Ahlborg & Bodin, 1991). A pregnancy cohort study in California reported a statistically nonsignificant association between stillbirth (defined as GW ≥20) and maternal serum cotinine levels during early pregnancy (5th vs. 1st quintile, OR = 3.36, 95% CI 0.81–14.0) (Kharrazi et al., 2004). An expert panel review found sparse data on stillbirths and inadequate evidence of an association with prenatal ETS exposure (California Environmental Protection Agency, 2005).

Outdoor air pollution Maternal exposure, inadequate evidence: Daily stillbirths were weakly associated with NO_2 levels in ecologic studies in Brazil (5-pollutant model, daily stillbirths vs. NO_2 (mg/m^3), regression coefficient = 0.0012 ± 0.0004 (Pereira et al., 1998) and the Czech Republic (per NO_2 increment of 50 $\mu g/m^3$, OR = 1.21, 95% CI 0.89–1.64) (Bobak & Leon, 1999). Stillbirths in the United Kingdom were not associated with prenatal residence proximity to coke works (major point sources of particulate air pollution) (≤2 vs. >2 km, OR = 0.94, 95% CI 0.78–1.12) (Dolk et al., 2000). A recent review concluded that the few epidemiologic studies of stillbirth provided inadequate evidence for an association with ambient air pollution (Glinianaia et al., 2004a).

Drinking water disinfection by-products Maternal exposure, limited evidence: Reviewers found limited and fairly consistent evidence for an association between stillbirth and prenatal DBP exposure (Bove et al., 2002; Graves et al., 2001; Nieuwenhuijsen et al., 2000). Studies in Nova Scotia reported nonmonotonic dose-response relationships between stillbirths and drinking water THM levels (≥100 vs. <50 μg/L, OR = 1.66, 95% CI 1.09–2.52) (Dodds et al., 1999), especially among the subset of stillbirths caused by asphyxia arising mainly from abruptio placenta (≥100 vs. <50 μg/L, OR = 4.57, 95% CI 1.93–10.8) (King et al., 2000). The association between stillbirth and THMs was mainly related to BDCM (≥20 vs. <5 μg/L, OR = 1.98, 95% CI 1.23–3.49) (King et al., 2000). An expanded study in Nova Scotia and eastern Ontario revealed that stillbirths were associated with tap water total THM levels (≥80 vs. <1 μg/L, OR = 2.2, 95% CI 1.1–4.4) and with total THM exposure from all sources including showering/bathing (5th vs. 1st quintile, OR = 2.4, 95% CI 1.2–4.6) (Dodds et al., 2004). Although this study observed nonmonotonic dose-response relationships, the authors noted that the highest exposure subgroups consistently had the highest stillbirth risks. A retrospective cohort study in England reported slightly increased stillbirth risks among women living in regions with the highest tap water THM levels (≥60 vs. <30 μg/L, OR = 1.11, 95% CI 1.00–1.23) (Toledano et al., 2005).

Drinking water nitrate Maternal exposure, inadequate evidence: A nested case-control study in Massachusetts revealed no association between stillbirths and drinking water nitrate levels in the community of maternal residence at birth (0.3–4.5 vs. <0.2 mg/L, OR = 0.8, $p > .05$) (Aschengrau et al., 1993).

Hazardous waste disposal sites Maternal exposure, inadequate evidence: A case-control study within the 1988 U.S. National Maternal and Infant Health Survey reported a weak association between stillbirth and prenatal residential proximity to U.S. EPA National Priority List[2] (NPL) hazardous waste disposal sites (maternal residence ≤1.6 km from a NPL site, OR = 1.14, 95% CI 0.95–1.36) (Sosniak et al., 1994). In record-based retrospective cohort studies in the United Kingdom, stillbirths were not associated with prenatal residential proximity to hazardous industries (per unit change in an inverse distance squared function, OR = 0.95, 95% CI 0.87–1.00) (Dummer et al., 2003b), incinerators (per unit change in an inverse distance squared function, OR = 1.04, 95% CI 0.90–1.19) (Dummer et al., 2003a), or hazardous waste landfill sites (<2 km from sites in

[2]The EPA's list of the most serious uncontrolled or abandoned hazardous waste disposal sites in the United States.

the United Kingdom, OR = 0.99, 95% CI 0.95–1.03; <2 km from landfill sites in Scotland, OR = 0.99, 95% CI 0.95–1.03 [Morris et al., 2003]).

Solvents Maternal occupational exposure, various and unspecified solvents, inadequate evidence: A large population-based U.S. case-control study reported weak associations between stillbirth and likely prenatal occupational exposure (inferred from job titles) to benzene (OR = 1.3, 95% CI 1.0–1.8) and petroleum (OR = 1.4, 95% CI 1.0–1.9) but not alcohols/glycols or chlorinated hydrocarbons (Savitz et al., 1989a). A cohort study in Montreal revealed an association between stillbirth and maternal 1st trimester occupational solvent exposure (OR = 2.76, $p < .01$) (McDonald et al., 1988). A case-control study in Brazil observed no association between stillbirth and prenatal residential proximity to a petrochemical plant (<10 vs. ≥30 km, OR = 0.71, 95% CI 0.20–2.56) (keOliveira et al., 2002).

Paternal occupational exposure, various and unspecified solvents, inadequate evidence: A large population-based U.S. case-control study observed no association between stillbirth and likely paternal occupational exposure (inferred from job titles) to benzene, petroleum, alcohols/glycols or chlorinated hydrocarbons (Savitz et al., 1989a). Fetal deaths (mainly stillbirths) were not associated with paternal occupational solvent exposure inferred from job titles recorded on birth records in Washington State (painting, OR = 0.9, 95% CI 0.8–1.1; autobody work, OR = 1.0, 95% CI 0.8–1.2; printers, OR = 1.1, 95% CI 0.8–1.3) (Daniell & Vaughan, 1988). A Norwegian cohort study of male printers showed no association between stillbirth and occupational solvent exposure (OR = 0.9, 95% CI 0.4–2.2) (Kristensen et al., 1993).

Summary There was limited epidemiologic evidence for the role of environmental toxicants in stillbirths including prenatal exposure to DDT/DDE or DBPs.

Preterm Birth Preterm birth, defined as gestation length <37 wk, accounts for 75–85% of all perinatal mortality in Canada (Public Health Agency of Canada, 2005). Affected infants have increased risks of neurodevelopmental handicaps, infections, chronic respiratory disease, and ophthalmologic problems (Health Canada, 2003). Preterm birth differs from intrauterine growth restriction (see next section) with regard to etiology and outcome.

Lead Maternal exposure, limited evidence: Reviewers found limited and somewhat inconsistent epidemiologic evidence for an association between preterm birth and prenatal lead exposure (Andrews et al., 1994). Preterm birth was generally associated with maternal but not paternal blood lead levels (Figure 1). In the Port Pirie birth cohort study, there was a monotonic dose-response relationship between preterm birth and prenatal blood lead levels with a 4.4-fold increased risk in the highest exposure category (maternal blood lead ≥14 vs. <8 μg/dl, OR = 4.4, 95% CI 1.2–17) (McMichael et al., 1986). A nested case-control study within this cohort found somewhat higher placental membrane lead levels among pregnancies ending in preterm birth (geometric mean lead concentration, cases vs. controls, 1.24 μg/g [95% CI 0.91–1.67] vs. 0.78 μg/g [95% CI 0.61–1.00]; Baghurst et al., 1991). In two other birth cohort studies, preterm birth was not associated with cord blood lead in Boston (per 1 μg/dl increment, OR = 0.98, 95% CI 0.93–1.02) (Bellinger et al., 1991) or with placental, prenatal blood, or cord blood lead levels in the former Yugoslavia (per 2nd trimester maternal blood increment (μmol/L), OR = 0.99, 95% CI 0.97–1.01) (Factor-Litvak et al., 1991). All of these studies adjusted for prenatal smoking and other potential confounders.

In a Norwegian retrospective cohort study, preterm birth was related to likely high-level occupational lead exposure based on job title (OR = 1.9, 95% CI 1.1–3.3) (Irgens et al., 1998). A case-cohort study in Mexico City reported a nonmonotonic dose-response relationship between preterm birth and cord blood lead levels but only among primiparous women (cord blood lead ≥15 vs. <5.1 μg/dl, OR = 2.6, 95% CI 1.0–6.7) (Torres-Sanchez et al., 1999). Gestation length was inversely associated with placental lead concentration in a small Spanish case control study with limited statistical analysis (Pearson's $r = -.32$, $p = .002$) (Falcon et al., 2003). A retrospective cohort study of occupationally exposed persons in Taiwan revealed a dose-response relationship between preterm birth and maternal prenatal blood lead levels (maternal blood lead 10–19 vs. <10 μg/dl, RR = 1.97, 95% CI 0.92–3.86; blood lead ≥20 vs. <10 μg/dl, RR = 1.86, 95% CI 0.68–4.28; p-trend = .06) (Chen et al., 2006). In a Californian retrospective cohort study, women with maximum pregnancy blood lead levels of at least 10 μg/dl had a substantially increased risk of preterm

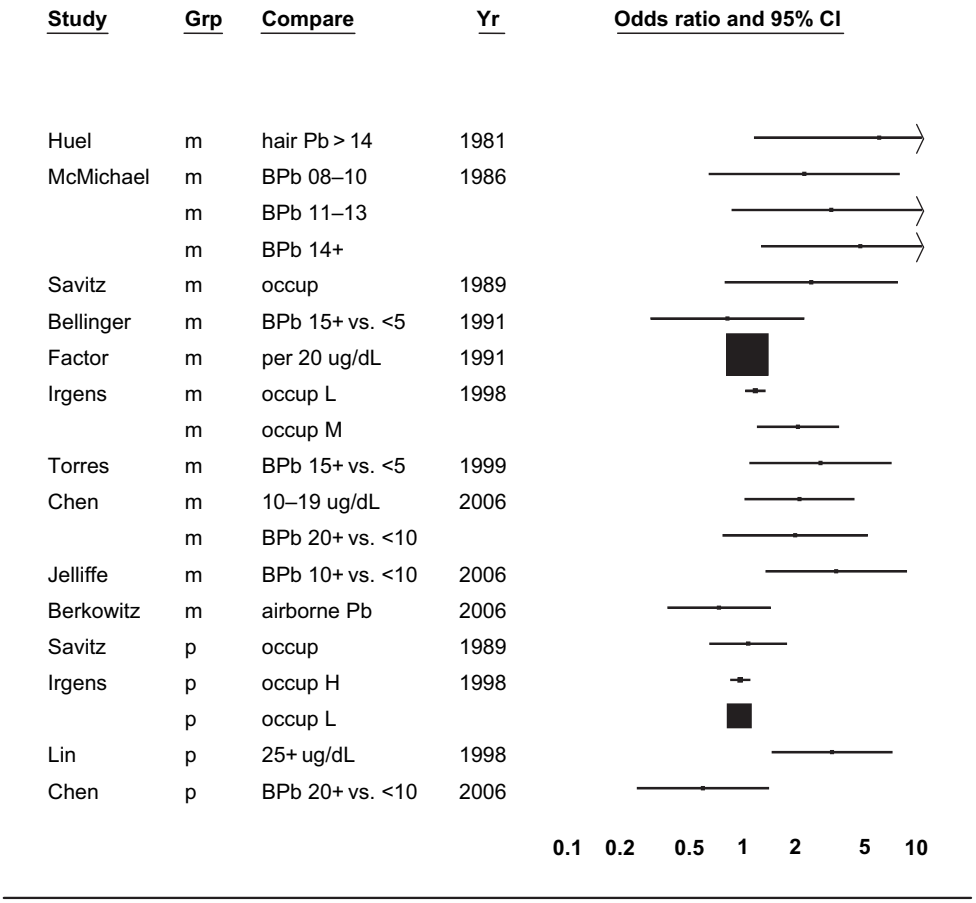

FIGURE 1. Preterm birth vs. parental lead exposure (m = prenatal, p = paternal, Pb = lead, BPb = blood lead, occup = occupational).

birth (OR = 3.2, 95% CI 1.2–7.4, compared to women with lower maximum levels); among women with blood lead levels of at least 10 μg/dl, gestation length decreased by an average of 1 day per increment of 1 μg/dl in 2nd trimester maximum maternal blood lead level (Jelliffe-Pawlowski et al., 2006). Maternal exposures to airborne lead emissions in Shoshone County, Idaho (during a 15-mo period when air emissions were high because of a damaged bag house), was not associated with increased risk of preterm birth (OR = 0.68, 90% CI 0.34–1.35) (Berkowitz et al., 2006).

Paternal occupational exposure, inadequate evidence: Three studies that inferred paternal lead exposure from job histories yielded little or no evidence of an association with preterm birth (Irgens et al., 1998; Kristensen et al., 1993; Savitz et al., 1989a). In a U.S. retrospective cohort study of occupationally exposed men, there was a moderately strong association between preterm birth and blood lead levels of at least 25 μg/dl for at least 5 yr (OR = 3.0, 95% CI 1.4–6.8) (Lin et al., 1998). A retrospective cohort study of persons occupationally exposed to lead in Taiwan reported no association between preterm birth and preconceptual blood lead levels of at least 20 μg/dl (OR = 0.6, 95% CI 0.2–1.3) (Chen et al., 2006).

Inorganic arsenic Maternal occupational exposure, airborne arsenic, inadequate evidence: A nation-wide case-control study in the United States found no association between preterm birth and prenatal occupations likely exposed to airborne arsenic (OR = 0.7, 95% CI 0.4–1.4) (Savitz et al., 1989a).

Maternal exposure, drinking water, inadequate evidence: Preterm births were associated with prenatal residence in a region with well-water arsenic levels above 100 μg/L in a retrospective cohort study in Bangladesh (RR = 2.65, 95% CI 1.10–6.58, calculated from data in report) (Ahmad et al., 2001). In an ecologic study, preterm birth was not associated with prenatal residence in regions of Taiwan with high well water arsenic levels (OR = 1.10, 95% CI 0.91–1.33) (Yang et al., 2003b).

Paternal occupational exposure, inadequate evidence: A U.S. nation-wide case-control study observed no association between preterm birth and paternal occupations likely exposed to airborne arsenic (OR = 1.1, 95% CI 0.7–1.7) (Savitz et al., 1989a).

Cadmium Maternal exposure, inadequate evidence: A small retrospective cohort study in France revealed a statistically nonsignificant elevated risk of preterm birth related to maternal hair cadmium (≥0.42 vs. <0.42 μg/g, OR = 2.69, 95% CI 0.53–15.0, calculated from data in paper) (Huel et al., 1981). A birth cohort study in a lead smelter town in the former Yugoslavia reported no association between gestation length and placental cadmium among nonsmoking women (change in gestation length per placenta cadmium increment of 1 nmol/g, 4.30 d, 95% CI –4.9 to 13.5) (Loiacono et al., 1992). A Swedish ecologic study demonstrated no association between preterm birth and maternal residence in municipalities with soil cadmium levels exceeding 1.6 μg/g (OR = 0.93, 95% CI 0.84–1.03); the risk in the municipality with the highest soil cadmium level (12 μg/g) was not elevated (OR = 0.86, 95% CI 0.61–1.21) (Landgren, 1996). A small birth cohort study in a cadmium-polluted region in Japan showed an association between preterm birth and prenatal urinary cadmium levels (≥2 vs. <2 μg/g creatinine, crude OR = 7.32, 95% CI 1.27–45.5, calculated from data in paper) (Nishijo et al., 2002). A small birth cohort study in a cadmium-polluted region of China reported no association between preterm birth among nonsmoking women and maternal or cord blood cadmium levels (cord blood cadmium >0.40 vs. ≤0.40 μg/L, OR = 1.46, 95% CI 0.23–9.56, calculated from data in paper) (Zhang et al., 2004).

PCBs Maternal occupational exposure, limited evidence: Among women prenatally exposed to airborne PCBs during capacitor production, there was an inverse dose-response relationship of borderline statistical significance between gestation length and estimated serum PCB levels (β = –1.1 d, 90% CI –2.0 to –0.1) (Taylor et al., 1989).

Maternal high-level environmental exposure, inadequate evidence: Follow-up to 1993–1994 of women exposed to high-levels of PCBs during the 1979 Yucheng incident revealed an elevated prevalence of stillbirths (exposed vs. unexposed, 4.2 vs. 1.7%, p = .07) (Yu et al., 2000). This finding is consistent with an elevated risk possibly diluted by declining body burden of PCBs, PCDFs and related toxicants over 15 yr.

Maternal low-level environmental exposure, inadequate evidence: After adjustment for the relative concentration of docosahexaenoic acid (an n–3 polyunsaturated fatty acid in seafood) in cord serum phospholipids, gestation length was not associated with prenatal serum PCB levels in a small Faroe Islands birth cohort study (Grandjean et al., 2001). A small Spanish birth cohort study revealed no association between preterm birth and mean maternal serum PCB levels (Ribas-Fito et al., 2002). Preterm birth was weakly associated with maternal residence in zip code areas of New York State with PCB-contaminated hazardous waste disposal sites (crude OR = 1.10, 95% CI 1.08–1.11); this study did not use exposure biomarkers and did not adjust for potential confounders (Baibergenova et al., 2003). In a California pregnancy cohort study conducted during the 1960s (when population serum PCB levels were substantially higher than currently) gestation length was inversely associated with prenatal serum PCB (per natural log serum PCB increment, β = –3.9 ± 2.0 d) (Hertz-Picciotto et al., 2005). However, in a similar study with mothers recruited in 12 U.S. cities during 1959–1965, preterm birth was not associated with prenatal serum PCB levels (≥4 vs. <2 μg/L, OR = 1.11, 95% CI 0.55–2.24) (Longnecker et al., 2005). There was also no association in cohort studies of Great Lakes fish eaters (change in gestation length per 2.7-fold maternal serum PCB increment, β = –0.08 wk [95% CI –0.75 to 0.59]; Weisskopf et al., 2005) or a representative sample of births in Victoria, Australia (preterm birth, breast milk PCB 10–49 vs. <10 μg/kg lipid, OR = 1.41, 95% CI 0.25–7.96; ≥50 vs. <10 μg/kg lipid, OR = 2.30, 95% CI 0.40–13.3; *p*-trend = .43) (Khanjani & Sim, 2007).

TCDD Maternal exposure, inadequate evidence: Preterm birth during an 8-year follow-up of women exposed at Seveso was not associated with maternal serum TCDD levels (per log increment, OR = 1.3, 95% CI 0.7–2.3); there was also no association between gestation length and maternal serum TCDD (per log increment, β = –1.2 d, 95% CI –2.9 to 0.5) (Eskenazi et al., 2003).

Paternal occupational exposure, inadequate evidence: Preterm birth was not associated with exposure to potentially TCDD-contaminated chlorophenate wood preservatives among male sawmill workers (per 100-h increment in cumulative exposure up to 3 mo before conception, OR = 1.00, 95% CI 0.99–1.001) (Dimich-Ward et al., 1996) or with paternal serum TCDD levels in

the study of U.S. veterans exposed to Agent Orange (serum TCDD at conception ≥79 vs. ≤10 pg/g lipid, OR = 1.36, 95% CI 0.75–2.39) (Michalek et al., 1998). Similarly, preterm birth was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (per log serum TCDD increment, OR = 0.8, 95% CI 0.6–1.1) (Lawson et al., 2004).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A large ecologic study in four U.S. Midwest states revealed no relationship between preterm birth and maternal residence in high-wheat rural counties (a proxy for chlorophenoxy herbicide exposure) (standardized incidence ratio [SIR] = 1.05, 95% CI 0.95–1.16) (Schreinemachers, 2003).

Maternal exposure, DDT/DDE, limited evidence: A large U.S. retrospective cohort study reported a monotonic dose-response relationship between preterm birth and prenatal serum DDE levels (≥60 vs. <15 μg/L, OR = 3.1, 95% CI 1.8–5.4; *p*-trend = .0001); this study exploited preserved prenatal blood samples collected during 1959–1965 when population DDT exposure was much higher than now (Longnecker et al., 2001). A small birth cohort study in Spain revealed an association between preterm birth and cord serum DDE levels (mean cord serum DDE, cases vs. controls, 2.40 vs. 0.80 μg/L, $p < 0.05$) (Ribas-Fito et al., 2002). A case-cohort study in Mexico City reported a nonmonotonic dose-response relationship between preterm birth and 1st trimester maternal serum DDE levels (3rd vs. 1st tertile, OR = 1.7, 95% CI 0.8–3.3, *p*-trend = 0.17) (Torres-Arreola et al., 2003). A retrospective cohort study of women who consumed Great Lakes fish showed no relationship between gestation length and maternal serum DDE levels (change in gestation length per natural log serum DDE increment, β = 0.03 wk, 95% CI –0.50 to 0.57) (Weisskopf et al., 2005). In an Australian retrospective cohort study, preterm birth was not associated with breast milk DDT or DDE levels (2nd vs. 1st tertile DDE, OR = 0.85, 95% CI 0.39–1.84; 3rd vs. 1st tertile, OR = 1.03, 95% CI 0.46–2.29) (Khanjani & Sim, 2006). A birth cohort study in the Salinas Valley of California revealed no association between gestation length and maternal serum DDE (per $\log_{10}$ serum DDE increment, β = –0.10 wk, 95% CI –0.40 to 0.20, $p = .51$) (Fenster et al., 2006). Although 3 recent cohort studies found no relationship, the steep decline of population serum or breast milk DDT/DDE levels over the past 40 yr may have contributed to negative findings.

Maternal exposure, other organochlorine insecticides, inadequate evidence: A case-cohort study in Mexico City found a borderline dose-response relationship between preterm birth and 1st trimester maternal serum β-hexachlorocyclohexane (β-HCH) levels (3rd vs. 1st tertile, OR = 1.9, 95% CI 0.9–3.7, *p*-trend = .08) (Torres-Arreola et al., 2003). A California study reported an inverse dose-response relationship between gestation length and maternal serum lipid-adjusted HCB levels (change in gestation length per natural log serum HCB increment, β = –0.47 wk, 95% CI –0.95 to –0.002, $p = .05$) (Fenster et al., 2006). In an Australian retrospective cohort study, preterm birth was not associated with breast milk dieldrin (3rd vs. 1st tertile, OR = 1.22, 95% CI 0.61–2.45), heptachlor epoxide (OR = 1.02, 95% CI 0.49–2.11), oxychlordane (OR = 0.93, 95% CI 0.39–2.22) or HCB (OR = 1.27, 95% CI 0.54–3.00) (Khanjani & Sim, 2006).

Maternal exposure, organophosphate insecticides, inadequate evidence: A pregnancy cohort study in New York found no association between gestation length and mean 3rd trimester maternal urinary metabolite levels of chlorpyrifos (Berkowitz et al., 2004).

Maternal exposure, other specified insecticides or repellents, inadequate evidence: Preterm birth was not associated with prenatal DEET exposure in a small Thai randomized trial (OR = 1.00, 95% CI 0.54–1.85) (McGready et al., 2001). A pregnancy cohort study in New York found no association between gestation length and mean 3rd trimester maternal urinary pyrethroid metabolite levels (Berkowitz et al., 2004).

Maternal exposure, fungicides, inadequate evidence: A case-cohort study in Mexico City found no association between preterm birth and 1st trimester maternal serum HCB levels (OR = 0.9, 95% CI 0.5–1.8, *p*-trend = .80) (Torres-Arreola et al., 2003). A birth cohort study in the Salinas Valley of California revealed an inverse association between gestation length and maternal serum HCB (per $\log_{10}$ serum HCB increment, β = –0.47 wk, 95% CI –0.95 to –0.002, p = .05) (Fenster et al., 2006). A pregnancy cohort study in New York found no association between gestation length and mean 3rd trimester maternal urinary pentachlorophenol levels (Berkowitz et al., 2004).

Maternal exposure, unspecified pesticides, inadequate evidence: Preterm birth was not associated with self-reported prenatal pesticide exposure at home (OR = 1.0, 95% CI 0.7–1.4) or work (OR = 1.1, 95% CI 0.6–2.1) in a large population-based case-control study (Savitz et al., 1989b). A nested case-control study reported an association between preterm birth and prenatal occupational pesticide exposure in Colombian greenhouses (OR = 1.86, 95% CI 1.59–2.17) (Restrepo et al., 1990b). A small cohort study of mainly Hispanic pregnant women in an intense agricultural region of California revealed a lower than expected preterm birth rate (5.6 vs. 8.9%) (Willis et al., 1993). A Danish birth cohort study showed no association between preterm birth and prenatal occupation as gardeners (OR = 1.4, 95% CI 0.8–2.4) or farmers (OR = 1.0, 95% CI 0.5–1.8) or with direct contact with pesticides at work (OR = 0.7, 95% CI 0.1–5.7) (Zhu et al., 2006). The heterogeneity of exposure indices precludes firm conclusions.

Paternal occupational exposure, 2,4,5-T or chlorophenate wood preservatives, inadequate evidence: See discussion of paternal occupational TCDD exposure earlier.

Paternal occupational exposure, other chlorophenoxy herbicides, inadequate evidence: In a retrospective cohort study of Ontario farm families, preterm birth was associated with preconceptual paternal yard use (OR = 2.5, 95% CI 0.9–7.3) but not crop use (OR = 1.4, 95% CI 0.5–3.6) of chlorophenoxy herbicides (Savitz et al., 1997a).

Paternal occupational exposure, nonchlorophenoxy herbicides, inadequate evidence: In a retrospective cohort study of Ontario farm families, preterm birth was associated with preconceptual paternal atrazine use in yards (OR = 4.9, 95% CI 1.6–15.0); there were also statistically nonsignificant elevated risks of preterm birth related to use on crops of atrazine (OR = 2.4, 95% CI 0.8–7.0) or glyphosate (OR = 2.4, 95% CI 0.8–7.9) (Savitz et al., 1997a). As in most other studies, pesticide-specific risk estimates were not adjusted for exposure to other specified pesticides.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: Preterm birth was not associated with self-reported paternal pesticide exposure in the home (OR = 1.0, 95% CI 0.7–1.4), outdoors at home (OR = 0.9, 95% CI 0.4–1.9) or at work (OR = 1.1, 95% CI 0.7–1.8) in a large U.S. population-based case-control study (Savitz et al., 1989b) or with agricultural work in a large case-control study in North Carolina (OR = 0.5, 95% CI 0.2–1.4) (Savitz et al., 1997b). In a nested case-control study, preterm birth was associated with paternal occupational pesticide use in Colombian greenhouses (OR = 2.75, 95% CI 2.01–3.76) (Restrepo et al., 1990b). A large Norwegian retrospective cohort study found no association between preterm birth and parental employment in farming (compared to nonfarm families, OR = 0.95, 95% CI 0.91–0.99) (Kristensen et al., 1997a).

Tobacco smoke Maternal active smoking, sufficient evidence: The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between maternal active smoking and preterm delivery and shortened gestation (U.S. Department of Health and Human Services, 2004).

Maternal ETS exposure, sufficient evidence: Reviewers noted limited evidence of an association between preterm birth and prenatal ETS exposure (Lindbohm et al., 2002) but an expert panel recently concluded that there is sufficient evidence (California Environmental Protection Agency, 2005). Among reviewed studies, a Finnish report indicated a dose-response relationship between preterm birth and maternal hair nicotine levels in segments corresponding to 3rd trimester exposure (≥4.0 vs. <0.75 μg/g, OR = 6.12, 95% CI 1.31–28.7; per μg/g (hair nicotine analyzed as continuous variable), OR = 1.22, 95% CI 1.07–1.39) (Jaakkola et al., 2001a), and a large cohort study of nonsmoking Californian women noted a nonmonotonic dose-response relationship with 2nd trimester maternal serum cotinine levels (5th vs. 1st quintile, OR = 1.78, 95% CI 1.01–3.13) (Kharrazi et al., 2004). In a South African cohort study, preterm birth among nonsmoking women was not associated with number of smokers in home (mean gestation lengths among unexposed women and those exposed to 1 or 2+ smokers at home, respectively, were 38.4, 38.2, and 38.2 wk) (Steyn et al., 2006). The U.S. Surgeon General reviewed eight available studies and concluded that there was suggestive evidence of a causal relationship between prenatal ETS exposure and preterm birth (U.S. Department of Health and Human Services, 2006).

Outdoor air pollution Maternal exposure, major ambient pollutants, limited evidence: Reviewers noted limited evidence from studies published up to 2001 for a weak association between preterm birth and prenatal exposure to ambient air pollutants including particulate matter

(PM) and SO_2 but no clear relationship with a critical gestational exposure period (Binkova et al., 2005; Glinianaia et al., 2004a; Maisonet et al., 2004). Several subsequently published studies revealed associations between preterm birth and 1st trimester maternal ambient air pollutant exposure with weaker or no association for exposure during later pregnancy. These included studies in Lithuania (per 10 $\mu g/m^3$ increment of NO_2, OR = 1.69, 95% CI 1.28–2.23 [in a multipollutant model]) (Maroziene & Grazuleviciene 2002), Australia (4th vs. 1st quartile ozone level during 1st trimester, OR = 1.26, 95% CI 1.10–1.45; similar results for NO_2 and SO_2) (Hansen et al., 2006) and Korea (4th vs. 1st quartile carbon monoxide (CO) level during 1st trimester, OR = 1.26, 95% CI 1.11–1.44, *p*-trend < .001) (Leem et al., 2006).

A Vancouver study observed weak associations between preterm birth and ambient air pollutant levels during the last month of pregnancy (e.g., per 1 ppm increment of CO, OR = 1.08, 95% CI 1.01–1.15) but not the first month (e.g., per 1 ppm increment of CO, OR = 0.95, 95% CI 0.89–1.01) (Liu et al., 2003). The risk of preterm birth in Taiwan was elevated among women living close to a major freeway (<0.5 vs. 0.5–1.5 km, OR = 1.30, 95% CI 1.03–1.65) (Yang et al., 2003a). In Los Angeles, there was a dose-response relationship between preterm birth and inverse-distance-weighted traffic density among women in their 3rd trimester during fall-winter (OR = 1.15, 95% CI 1.05–1.26) but not spring-summer (Wilhelm & Ritz, 2003). In further analysis of the Los Angeles study, preterm birth was associated with 1st trimester CO concentrations near the maternal residence (women <1.6 km from monitoring station, per 1 ppm CO increment during 1st trimester, OR = 1.10, 95% CI 1.01–1.20; similar results for 3rd trimester CO); preterm birth was not related to PM with a mass median aerodynamic diameter < 2.5 μm ($PM_{2.5}$) concentrations during early or late pregnancy (Wilhelm & Ritz, 2005). In a California-wide case-control study, preterm birth was associated with ambient air $PM_{2.5}$ levels near the maternal residence during early or late pregnancy (4th vs. 1st quartile $PM_{2.5}$ levels during 1st gestational month, OR = 1.21, 95% CI 1.12–1.30, adjusted for CO levels; similar results for $PM_{2.5}$ during late gestation) (Huynh et al., 2006). The latter study revealed similar associations for CO levels during early or late pregnancy, independent of $PM_{2.5}$. A time-series analysis of daily preterm birth counts in 4 Pennsylvania counties during 1997–2001 revealed associations with PM with a mass median aerodynamic diameter <10 μm (PM_{10}) (per 50 $\mu g/m^3$ increment, OR = 1.07, 95% CI 0.98–1.18) and SO_2 levels (per 15 ppb increment, OR = 1.15, 95% CI 1.00–1.32) during the 6 wk before birth (Sagiv et al., 2005). In the latter study, the associations were somewhat stronger for PM_{10} and SO_2 concentrations 2–5 d before birth, suggesting possible acute effects of such exposure.

Maternal exposure, industrial emissions, inadequate evidence: Retrospective cohort studies in Taiwan revealed weak associations between preterm birth and maternal residence within 3 km of a major oil refinery (OR = 1.41, 95% CI 1.08–1.82) (Lin et al., 2001a), within 2 km of a Portland cement plant (OR = 1.30, 95% CI 1.09–1.54) (Yang et al., 2003c), within 2 km of an industrial complex including petrochemical, petroleum, steel, and shipbuilding industries (OR = 1.11, 95% CI 1.02–1.21) (Tsai et al., 2003) or within 3 km of coal-based electricity-generating stations (OR = 1.14, 95% CI 1.01–1.30) (Tsai et al., 2004).

Drinking-water disinfection by-products Maternal exposure, inadequate evidence: Reviewers found inadequate evidence for an association between preterm birth and THMs (Bove et al., 2002; Graves et al., 2001). Among reviewed studies, there were weak associations between preterm birth and THMs in retrospective cohort studies in Sweden (hypochlorite-treated vs. unchlorinated water, OR = 1.09, 95% CI 1.01–1.17) (Kallen & Robert, 2000) and Taiwan (chlorinated vs. unchlorinated water supply, OR = 1.37, 95% CI 1.20–1.56) (Yang, 2004) but not in Denver (Gallagher et al., 1998), Nova Scotia (Dodds et al., 1999) and Norway (Jaakkola et al., 2001b). In a recent retrospective cohort study in Massachusetts, preterm birth was inversely associated with THM levels during the 3rd trimester in the municipality of maternal residence (≥90th vs. <50th percentile, OR = 0.88, 95% CI 0.81–0.94) but not with 3-chloro–4-(dichloromethyl)–5-hydroxy–2(5*H*)-furanone (MX), mutagenic activity or haloacetic acid levels (Wright et al., 2004).

Drinking water nitrate Maternal exposure, inadequate evidence: A moderately large case-control study in Prince Edward Island, Canada, revealed an association between preterm birth and median

well water nitrate level in the region of maternal residence at birth (≥3.1 vs. ≤1.3 mg/L, OR = 1.91, 95% CI 1.47–2.46, adjusted for prenatal smoking and several other potential confounders) (Bukowski et al., 2001). Although suggestive, this finding requires confirmation. Groundwater nitrate levels in rural areas may serve as proxies for pesticides and other contaminants (Ritter, 1990).

Hazardous waste sites Maternal exposure, inadequate evidence: Preterm birth was not associated with maternal residential proximity to any of 1221 NPL sites in the United States (≤1.6 vs. >1.6 km, OR = 0.99, 95% CI 0.86–1.16) (Boyle et al., 2004; Sosniak et al., 1994). In an Alaskan study, maternal residence in villages with hazardous waste dumpsites was associated with a statistically nonsignificant increased risk of preterm birth (OR = 1.24, 95% CI 0.89–1.74) (Gilbreath & Kass, 2006b). Among studies of large single landfill sites, preterm birth risk was elevated in Los Angeles (high-odor vs. unexposed region, mean difference in gestation length –1.8 d, $p = .02$) (Kharrazi et al., 1997) and New Jersey (≤1 km and downwind vs. >1 km, high exposure period, OR = 2.10, 95% CI 1.01–4.36) (Berry & Bove, 1997) but not in Montreal (<4 km vs. unexposed region, OR = 0.97, 95% CI 0.88–1.07) (Goldberg et al., 1995). An ecologic study in Nova Scotia revealed slightly increased risks of preterm birth in Sydney (RR = 1.10, 95% CI 0.98–1.26) and the rest of Cape Breton County (RR = 1.13, 95% CI 1.04–1.22) (compared to the rest of Nova Scotia) although the former is the site of a major hazardous waste site (Dodds & Seviour, 2001).

Solvents Maternal exposure, chlorinated solvents, inadequate evidence: A review of five epidemiologic studies published during 1990–2000 found inadequate evidence for an association between preterm birth and prenatal residence in regions served by drinking water contaminated by chlorinated solvents such as trichloroethylene (Bove et al., 2002). In a retrospective study at Camp Lejeune, preterm birth was not associated with exposure to tetrachloroethylene-contaminated drinking water (OR = 1.1, 95% CI 0.9–1.3) (Sonnenfeld et al., 2001).

Maternal exposure, various and unspecified solvents, inadequate evidence: In a large U.S. population-based case-control study, preterm birth was not associated with prenatal occupations with likely exposure to benzene, petroleum, or alcohols/glycols (inferred from job titles) (Savitz et al., 1989a). A small retrospective cohort study in Wisconsin observed no association between preterm birth and prenatal occupations likely exposed to solvents (OR = 1.2, 95% CI 0.4–3.1) (Hewitt & Tellier, 1998). A very small cohort study in Canada reported an elevated risk of preterm birth among women with self-reported 1st trimester occupational organic solvent exposure (crude OR = 3.26, 95% CI 0.78–15.7, calculated from data in paper) (Khattak et al., 1999).

Paternal occupational exposure, various and unspecified solvents, inadequate evidence: A retrospective cohort study based on Washington State birth certificates reported no association between preterm birth and paternal employment in occupations with likely solvent exposure (e.g., painters, OR = 1.0, 95% CI 0.8–1.3) (Daniell & Vaughan, 1988). A large U.S. population-based case-control study reported no association between preterm birth and paternal occupations likely exposed to benzene, petroleum or alcohols/glycols (inferred from job titles) (Savitz et al., 1989a).

Summary Epidemiologic evidence for the role of environmental toxicants in preterm birth includes: (a) sufficient evidence—prenatal active smoking, ETS exposure; (b) limited evidence—prenatal exposure to lead, PCBs (occupational exposure), DDT/DDE, outdoor air pollutants.

Fetal growth Deficit Intrauterine growth restriction (IUGR) is defined as a liveborn infant below the 10^{t}h percentile of birth weight for gestational age. Other indicators of intrauterine growth deficits include term low birth weight (birth weight <2500 g after at least 37 wk of gestation) and low birth weight adjusted for gestation length. Fetal growth deficit (FGD) is defined here to encompass the above indicators and is associated with increased fetal and infant morbidity and mortality. For context, prenatal smoking is the best proven preventable cause of FGD and is responsible for 30–40% of affected infants in Canada (Health Canada, 2003).

Lead Maternal exposure, limited evidence: FGD was generally associated with maternal but not paternal blood lead levels (Figure 2). Two birth cohort studies conducted in lead smelter towns revealed no association between FGD and prenatal blood, cord blood, or placental lead levels (Loiacono et al., 1992; McMichael et al., 1986). A birth cohort study in Boston reported a dose-response relationship between FGD and cord blood lead levels (relative risk increment per unit increase in cord blood lead concentrations [μg/dl], 1.06, 95% CI 1.00–1.13) (Bellinger et al., 1991).

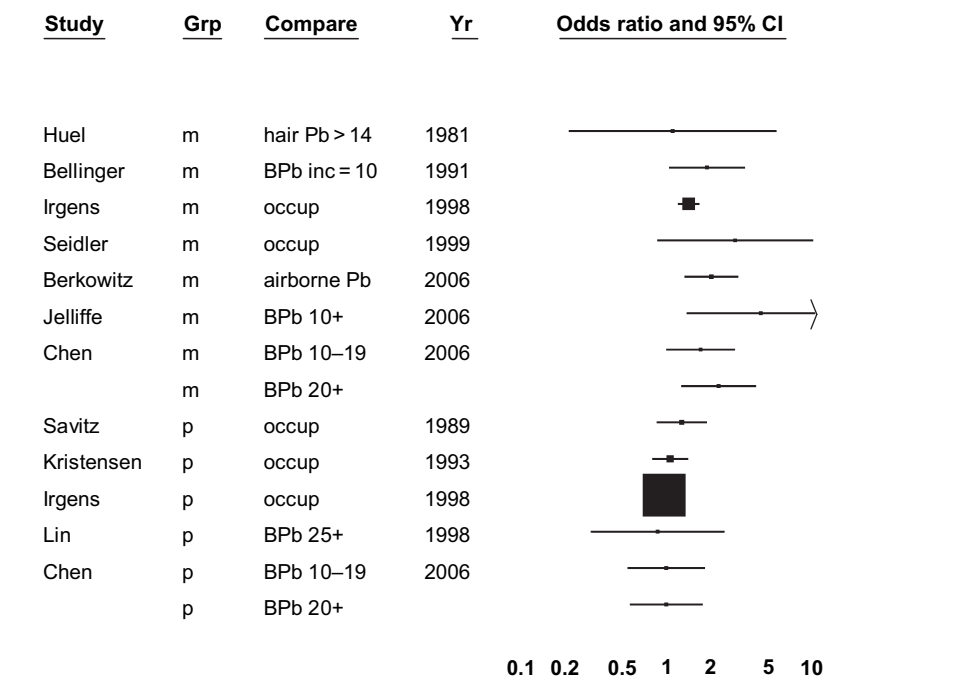

FIGURE 2. Fetal growth deficit vs. parental lead exposure (m = prenatal, p = paternal, Pb = lead, BPb = blood lead, occup = occupation).

Several recent cohort studies have consistently reported significant associations between FGD and maternal lead exposure, including: (1) tibial bone lead (change in birth weight per unit increase in bone lead level [μg/g] adjusted for gestation length, –7.29 ± 2.45 g, $p = .003$) (Gonzalez-Cossio et al., 1997), (2) maternal occupations likely exposed to lead (OR = 1.34, 95% CI 1.12–1.60) (Irgens et al., 1998), OR = 2.8, 95% CI 0.8–9.6 (Seidler et al., 1999), (3) cord blood lead (change in birth weight per unit change in cord blood lead, –9.7 g, 95% CI –16.9 to –2.5) (Osman et al., 2000), (4) placental lead concentration (change in birth weight per 0.1 μg/g placenta lead increment adjusted for gestation length, –73.6 g, 95% CI –152.7 to 5.5) (note that the range of placenta lead concentrations was 0.03–0.57 μg/g) (Odland et al., 2004) and (5) maternal blood lead level (10–19 μg/dl, OR = 1.62, 95% CI 0.91–2.75; ≥20 μg/dl, OR = 2.15, 95% CI 1.15–3.83, p-trend < .01 (Chen et al., 2006); maximum prenatal blood lead ≥10 vs. <10 μg/dl, OR = 4.2, 95% CI 1.3–13.9 (Jelliffe-Pawlowski et al., 2006). Maternal exposures to airborne lead emissions in Shoshone County, Idaho (during a 15-mo period when air emissions were high because of a damaged bag house) was associated with FGD (OR = 1.92, 90% CI 1.33–2.76) (Berkowitz et al., 2006).

Paternal occupational exposure, inadequate evidence: A case-control and two retrospective cohort studies revealed no association between FGD and paternal employment in jobs likely exposed to lead (Irgens et al., 1998; Kristensen et al., 1993; Savitz et al., 1989a). Two retrospective cohort studies in New York State and Taiwan showed no association between FGD and a history of blood lead levels above 25 μg/dl for at least 5 yr before conception (OR = 0.82, 95% CI 0.28–2.37) (Lin et al., 1998) or preconceptual blood lead level of at least 20 μg/dl (OR = 0.94, 95% CI 0.51–1.62) (Chen et al., 2006).

Inorganic arsenic Maternal exposure, airborne, inadequate evidence: A U.S. case-control study of FGD infants found no association with self-reported prenatal occupational exposure to airborne arsenic (OR = 0.8, 95% CI 0.4–1.5) (Savitz et al., 1989a).

Maternal exposure, drinking water, inadequate evidence : A birth cohort study in Chile revealed reduced birth weight among infants of women living in a city with average drinking water arsenic levels of 40 μg/L; birth weight adjusted for gestation length was 57 g less than that in a city

with drinking-water arsenic levels below 1 μg/L (95% CI–123, 9) (Hopenhayn et al., 2003). However, the association between birth weight and individual tap water arsenic levels (β = –0.26 g, 95% CI –0.85 to 0.31, per μg/L) was statistically nonsignificant.

Paternal occupational exposure, airborne, inadequate evidence: A U.S. case-control study of FGD infants found no association with self-reported paternal occupational arsenic exposure (OR = 1.2, 95% CI 0.8–1.8) (Savitz et al., 1989a).

Cadmium Maternal exposure, inadequate evidence: In a small retrospective cohort study, there was a statistically nonsignificant inverse association between FGD and maternal hair cadmium (≥0.42 vs. <0.42 μg/g, OR = 1.68, 95% CI 0.35–8.34); this study did not adjust for prenatal smoking (an important source of cadmium exposure and a known cause of FGD) (Huel et al., 1981). Two birth cohort studies of nonsmoking pregnant women found no association between birth weight adjusted for gestation length and maternal or cord blood or placental cadmium levels (Kuhnert et al., 1987; Zhang et al., 2004). A very small Italian birth cohort study with limited statistical analysis reported an inverse correlation between birth weight of term infants and maternal blood cadmium (Pearson's $r = –0.55$, $p = .0003$) (Salpietro et al., 2002). A small birth cohort study in a cadmium-polluted region of Japan observed no association between birth weight and maternal urinary cadmium levels (Nishijo et al., 2002), but there was an inverse relationship between height at birth and 3rd trimester maternal blood cadmium (β = –0.59 ± 0.277 cm, $p = .04$) (Nishijo et al., 2004). A recent Norway/Russia birth cohort study reported no association between birth weight and maternal blood cadmium level (Pearson's $r = –0.23$, $p > .05$); this study did not adjust for gestation length but only 2 of the 55 infants were preterm (Odland et al., 2004). Reviewers concluded that high-dose prenatal cadmium exposure causes fetal growth deficits in experimental animals, but there was little evidence for a relationship at the much lower exposure levels observed in humans (Agency for Toxic Substances and Disease Registry, 1999a).

PCBs Prenatal occupational exposure, inadequate evidence: Among infants of women occupationally exposed to airborne PCBs, there was an inverse association of borderline statistical significance between birth weight adjusted for gestation length and prenatal serum PCB levels estimated from those measured in a sub-sample of women (per 2.7-fold maternal serum PCB increment, β = –24 g, 90% CI –49 to 2) (Taylor et al., 1989). A German birth cohort study found no association between FGD and prenatal PCB exposure inferred from a job-exposure matrix (exposed vs. unexposed, OR = 1.2, 95% CI 0.8–1.7) (Seidler et al., 1999).

Prenatal environmental exposure, inadequate evidence: Reviewers found inadequate evidence for an inverse association between birth weight and maternal exposure to background environmental PCBs (Longnecker et al., 1997). Studies published since this review provide inconsistent evidence for an association. In a study of Swedish fishermen wives, low birth weight was associated with prenatal serum PCB-153 levels (>400 vs. ≤400 ng/g lipid, OR = 2.3, 95% CI 0.9–5.9), but there was no adjustment for gestation length (Rylander et al., 1998). Birth weight adjusted for gestation length was inversely associated with cord plasma PCB levels in Holland (per 2.7-fold plasma PCB increment, β = –119.4 ± 53.7 g, p = .03) (Patandin et al., 1998). There was an increased risk of FGD (borderline statistical significance) among Swedish fishing families in a region where fish had relatively high PCB levels (contaminated vs. less contaminated region, OR = 1.4, 95% CI 0.9–2.1) (Rylander et al., 2000). A retrospective cohort study in New York State found a weak but statistically significant association between low birth weight (adjusted for gestation length and other potential confounders) and prenatal residence in regions with PCB-contaminated hazardous waste disposal sites (OR = 1.04, 95% CI 1.02–1.07) (Baibergenova et al., 2003). In a retrospective cohort study of Lake Michigan female anglers, birth weight adjusted for gestation length was reduced among women in the highest serum PCB category (serum PCB 25–29 vs. <5 μg/L, mean birth weight 2958 ± 224.0 vs. 3520 ± 103.3 g, $p = .02$); when analyzed by gender, the association was significant among boys but not girls (Karmaus & Zhu, 2004). Similarly, in a California birth cohort, birth weight adjusted for gestation length was inversely related to maternal serum PCB levels among boys but not girls (per 2.7-fold serum PCB increment, respective birth weight Z-scores for boys and girls were –0.53 ± 0.21 and 0.01 ± 0.16) (Hertz-Picciotto et al., 2005).

A Finnish study found no association between birth weight and breast milk PCB levels (Pearson's $r = -.10$, $p = .22$); analyses did not adjust for gestation length or other potential confounders (Vartiainen et al., 1998). FGD was not associated with prenatal serum PCB levels in birth cohort studies in the Faroe Islands (per 2.7-fold maternal serum PCB increment, $\beta = -31.0 \pm 99.9$ g, $p = .76$) (Grandjean et al., 2001) and Spain (per twofold cord serum PCB increment, $\beta = -5.6 \pm 36.1$ g) (Ribas-Fito et al., 2002). A U.S. Collaborative Perinatal Project cohort study revealed elevated risks of FGD at higher maternal serum quartiles (4th vs. 1st quartile, OR = 1.64, 95% CI 0.73–3.68), but logistic regression based on PCB concentration as a continuous variable showed no association ($\beta = 0.11 \pm 0.10$) (Longnecker et al., 2005). In a Japanese birth cohort, birth weight among mostly term infants was not associated with breast milk PCB dioxin toxic equivalent (TEQ) levels ($\beta = -5.09 \pm 4.84$) (Tajimi et al., 2005). A retrospective cohort study of parents engaged in Great Lakes sport fishing observed no association between birth weight adjusted for gestation length and maternal serum PCB levels (change in birth weight per 2.7-fold serum PCB increment, $\beta = 29$ g, 95% CI –110 to 168) (Weisskopf et al., 2005). In a representative sample of births in Australia, FGD was not related to breast milk PCB levels (≤50 μg/kg lipid vs. nondetectable, OR = 0.87, 95% CI 0.34–2.22; >50 μg/kg lipid, OR = 0.61, 95% CI 0.22–1.66; p-trend = 0.41) (Khanjani & Sim, 2007).

TCDD Maternal exposure, inadequate evidence: Low birth weight at term was not associated with TCDD-contaminated soil (20–100 ng/g for 2+ yr or ≥100 ng/g for at least 6 mo) at or near the prenatal residence in Missouri (OR = 1.09, 95% CI 0.50–2.28) (Stockbauer et al., 1988). A birth cohort study of women exposed to TCDD at Seveso found a statistically nonsignificant increased risk of FGD during the first 8 yr of follow-up (per $\log_{10}$ maternal serum TCDD increment, OR = 1.8, 95 % CI 0.7–4.3) (Eskenazi et al., 2003). In a Japanese birth cohort, birth weight among mostly term infants was not associated with breast milk total TEQ from polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls ($\beta = -2.30 \pm 2.62$) (Tajimi et al., 2005).

Paternal occupational exposure, inadequate evidence: Birth weight adjusted for gestation length was not associated with paternal occupational exposure to chlorophenate wood preservatives known to be contaminated with TCDD and related toxicants (per 100-h increment in cumulative exposure up to 3 mo before conception, OR = 1.00, 95% CI 0.99–1.001) (Dimich-Ward et al., 1996). Among Vietnam veterans, FGD was not associated with paternal serum TCDD (≥79 vs. ≤10 pg/g lipid, OR = 0.9, 95% CI 0.6–1.3) (Michalek et al., 1998). Birth weight adjusted for gestation length was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (mean birth weight difference, TCDD ≥255 vs. <20 pg/g lipid, 83 ± 52 g, $p > .05$) (Lawson et al., 2004).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A large ecologic study in four U.S. Midwest states revealed no relationship between FGD and maternal residence in high-wheat rural counties (a proxy for chlorophenoxy herbicide exposure) (OR = 1.05, 95% CI 0.94–1.17) (Schreinemachers, 2003).

Maternal exposure, other and unspecified herbicides, inadequate evidence: An ecologic study in Iowa revealed associations between FGD and prenatal residence in municipalities with drinking water supplies contaminated by the herbicides atrazine (maternal age-adjusted IUGR rate (cases per 100 live births) vs. water atrazine level (μg/L), $\beta = 0.32$, $p = .001$), metolachlor ($\beta = 0.26$, $p = .006$) or cyanazine ($\beta = 0.25$, $p = .009$) (Munger et al., 1997). The ecologic design precludes strong inferences from such findings. A German pregnancy cohort study revealed no association between FGD and maternal occupational herbicide exposure (moderate vs. no exposure, OR = 0.9, 95% CI 0.3–3.0, p-trend = .82) (Seidler et al., 1999).

Maternal exposure, DDT/DDE, limited evidence: There was a dose-response relationship between FGD and prenatal serum DDE levels (≥60 vs. <15 μg/L, OR = 2.6, 95% CI 1.3–5.2, p-trend = .04); this study used preserved serum samples collected during the 1959–1966 U.S. Collaborative Perinatal Project, a time when population-wide DDT exposure was much higher than now (Longnecker et al., 2001). Term birth weight was inversely associated with maternal serum DDE levels in a retrospective cohort study of women who consumed Great Lakes fish (change in birth weight per natural log serum DDE increment, $\beta = -146$ g, 95% CI –35 to –257) (Weisskopf et al., 2005).

Negative findings all came from relatively small studies. A small birth cohort study in Spain revealed no association between birth weight adjusted for gestation length and cord serum DDE levels (change in birth weight per unit change in cord serum DDE, $\beta = -16.8 \pm 37.8$ g, $p > 0.05$) (Ribas-Fito et al., 2002). A Ukrainian pregnancy cohort study revealed increasing average birth weight z-scores (adjusted for gestation length) among infants of women in higher breast milk DDE tertiles (p-trend $< .05$) (Gladen et al., 2003). In an Australian retrospective cohort study, FGD was not associated with breast milk DDT or DDE levels (2nd vs. 1st tertile DDE, OR = 1.21, 95% CI 0.73–2.00; 3rd vs. 1st tertile, OR = 0.79, 95% CI 0.45–1.39) (Khanjani & Sim, 2006). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum DDE (per $\log_{10}$ increment, $\beta = -46$ g, 95% CI –129 to 37, $p = .28$) (Fenster et al., 2006).

Maternal exposure, other organochlorine insecticides, inadequate evidence: In an Australian retrospective cohort study, FGD was not associated with breast milk dieldrin (3rd vs. 1st tertile, OR = 0.92, 95% CI 0.56–1.51), heptachlor epoxide (3rd vs. 1st tertile, OR = 1.16, 95% CI 0.72–1.86), or oxychlordane levels (3rd vs. 1st tertile, OR = 0.93, 95% CI 0.58–1.67) (Khanjani & Sim, 2006). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum dieldrin (per $\log_{10}$ increment, $\beta = 18$ g, 95% CI –164 to 201, $p = .84$), heptachlor epoxide (per $\log_{10}$ increment, $\beta = 44$ g, 95% CI –105 to 194, $p = .56$) or oxychordane (per $\log_{10}$ increment, $\beta = 64$ g, 95% CI –39 to 168, $p = .22$) (Fenster et al., 2006).

Maternal exposure, organophosphate insecticides, inadequate evidence: FGD was not associated with maternal residence in regions of San Francisco aerially sprayed with malathion during the 1st trimester (RR = 0.90, 95% CI 0.54–1.49) (Thomas et al., 1992). In Mexican agricultural communities, FGD was associated with reduced cord blood acetylcholinesterase (AChE) levels (mean AChE activity, cases vs. controls, 3.7 vs. 4.0 U/ml, $p < .01$) (Levario-Carrillo et al., 2004). In a New York City birth cohort study, birth weight adjusted for gestation length was inversely associated with cord plasma chlorpyrifos plus diazinon expressed as chlorpyrifos equivalents (mean birth weight difference, 3rd tertile vs. nondetectable, –186 g, 95% CI –327 to –45, $p = .01$) (Whyatt et al., 2004). There was no association with maternal personal air chlorpyrifos plus diazinon levels over a 2-d period during the 3rd trimester, suggesting that dietary sources may have been important.

Maternal exposure, other insecticides and repellents, inadequate evidence: In a randomized clinical trial of prenatal DEET treatment in Thai refugee camps, the low birth weight (<2500 g) rate was not increased among exposed (14.8%) compared to unexposed women (20.2%) (McGready et al., 2001). The New York City study reported an inverse association of borderline statistical significance between birth weight adjusted for gestation length and cord plasma propoxur (a carbamate insecticide) levels (mean birth weight difference, 3rd tertile vs. nondetectable, –66 g, 95% CI –147 to 15) (Whyatt et al., 2004).

Maternal exposure, fungicides, inadequate evidence: Prenatal employment in German daycare centres with elevated indoor pentachlorophenol air concentrations was associated with reduced birth weight adjusted for gestation length and other factors but not for maternal smoking (birth weight difference, exposed vs. unexposed mothers, $\beta = -217.1 \pm 105.8$ g, $p = .04$) (Karmaus & Wolf, 1995). A small birth cohort study in Spain revealed no association between birth weight adjusted for gestation length and other covariates and cord serum HCB ($\beta = 19.8 \pm 50.9$ g, $p > .05$) or HCH levels ($\beta = 17.5 \pm 17.6$ g, $p > .05$) (Ribas-Fito et al., 2002). In an Australian retrospective cohort study, FGD was not associated with breast milk HCB levels (2nd vs. 1st tertile, OR = 0.89, 95% CI 0.54–1.48; 3rd vs. 1st tertile, OR = 0.98, 95% CI 0.58–1.67) (Khanjani & Sim, 2006). A birth cohort study in the Salinas Valley of California revealed no association between birth weight (adjusted for gestation length and other potential confounders) and maternal serum HCB (per $\log_{10}$ increment, $\beta = -23$g, 95% CI –154 to 108, $p = .73$) or β-HCH (per $\log_{10}$ increment, $\beta = 25$ g, 95% CI –154 to 108, $p = .73$) (Fenster et al., 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: A large U.S. case-control study reported an association between FGD and self-reported prenatal pesticide exposure at home (OR = 1.5, 95% CI 1.1–2.1) but not occupational exposure (OR = 1.2, 95% CI 0.6–2.3) (Savitz et al.,

1989b). In a Shanghai case-control study, FGD was associated with self-reported periconceptual maternal occupational pesticide exposure (OR = 2.9, 95% CI 1.0–8.6) (Zhang et al., 1992). In Mexican agricultural communities, FGD was associated with self-reported prenatal residential proximity to crop areas with intense pesticide use (OR = 2.3, 95% CI 1.0–5.3) (Levario-Carrillo et al., 2004). A Danish birth cohort study reported no association between FGD and prenatal occupation as gardeners (OR = 1.0, 95% CI 0.6–1.6) or farmers (OR = 0.6, 95% CI 0.3–1.0) or with use of pesticides at home or work (OR = 0.5, 95% CI 0.1–2.9) (Zhu et al., 2006). The heterogeneity of exposure indices precludes firm conclusions.

Paternal occupational exposure, 2,4,5-T and chlorophenate wood preservatives, inadequate evidence: See discussion of paternal occupational TCDD exposure earlier.

Paternal occupational exposure, other chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study of Ontario farm families found no association between FGD and preconceptual paternal crop (OR = 0.7, 95% CI 0.4–1.2) or yard (OR = 0.8, 95% CI 0.4–1.6) chlorophenoxy herbicide use; however, there was an association of borderline statistical significance for users of yard herbicides without protective equipment (OR = 1.8, 95% CI 0.9–3.4) (Savitz et al., 1997a).

Paternal occupational exposure, unspecified pesticides, inadequate evidence: A large U.S. case-control study reported an association between FGD and self-reported paternal pesticide exposure at home (OR = 1.4, 95% CI 0.9–2.3) or work (OR = 1.5, 95% CI 1.1–2.0) (Savitz et al., 1989b). A large Norwegian cohort study found a slightly reduced FGD risk among infants of farm operators compared to infants of nonfarmers in agricultural municipalities (RR = 0.90, 95% CI 0.88–0.93) (Kristensen et al., 1997a).

Tobacco smoke Maternal active smoking, sufficient evidence: The U.S. Surgeon General concluded that there is sufficient evidence of a causal relationship between prenatal active smoking and FGD (U.S. Department of Health and Human Services, 2004).

Maternal ETS exposure, limited evidence: Reviewers (Lindbohm et al., 2002) and an expert panel (California Environmental Protection Agency, 2005) noted limited evidence of an association between FGD and prenatal ETS exposure. The U.S. Surgeon General reviewed 46 available studies and concluded that there was sufficient evidence of a causal relationship between prenatal ETS exposure and a small reduction in birth weight but did not clearly distinguish between reduced birth weight from preterm birth and that from FGD (U.S. Department of Health and Human Services, 2006). Among nonsmoking pregnant women, FGD was associated with self-reported prenatal ETS exposure in studies in the Czech Republic (OR = 1.19, 95% CI 0.96–1.47) (Dejmek et al., 2002), China (mean birth weight difference, adjusted for gestation length, exposed vs. unexposed women, –37 g, 95% CI –82.6 to 8.4) (Ha et al., 2002), India (OR = 2.10, 95% CI 1.27–3.48) (Goel et al., 2004), Poland (change in birth weight per unit increase in log 2nd trimester maternal serum cotinine (over the range 0–9 ng/ml), $\beta = -100.5 \pm 60.4$ g, $p = .09$) (Hanke et al., 2004), and California (per log 2nd trimester maternal serum cotinine increment, OR = 1.41, 95% CI 0.91–2.17) (Kharrazi et al., 2004). In a Korean cohort study of nonsmoking women, birth weight at term was inversely associated with ETS exposure (confirmed by urinary cotinine measurements) among the subgroup of women with the GSTT1 null type polymorphism (mean birth weight difference, exposed vs. unexposed, –236 g, 95% CI –455 to –17) but not among those with the GSTT1 wild type or GSTM1 null or wild types (Hong et al., 2003).

Among women who smoked during part or all of pregnancy, FGD was associated with self-reported ETS exposure in the Czech Republic (≤10 cigarettes/d, OR = 2.14, 95% CI 1.67–2.73; >10 cigarettes/d, OR = 3.43, 95% CI 2.19–5.36) (Dejmek et al., 2002) and Sweden (1st trimester exposure, OR = 2.60, 95% CI 0.99–6.86) (Dejin-Karlsson & Ostergren, 2003). The latter study observed no association with ETS exposure during the 2nd and 3rd trimesters, adjusted for 1st trimester exposure (OR = 1.27, 95% CI 0.64–2.49).

In other studies, FGD was not associated with self-reported prenatal ETS exposure at home or work (Hruba and Kachlik 2000; Jedrychowski et al., 2004; Matsubara et al., 2000; Perera et al., 2004; Windham et al., 2000), maternal hair nicotine levels in segments corresponding to 3rd trimester exposure (Jaakkola et al., 2001a), or postpartum maternal plasma cotinine ($\beta = -0.02$,

$p = .42$) (Perera et al., 2004). In a South African cohort study, FGD among nonsmoking women was not associated with self-reported ETS exposure at home (Steyn et al., 2006). In a Spanish cohort study, birth weight was reduced among women with elevated hair nicotine concentrations (≥18 vs. <3 ng/mg, birth weight difference and SD = –247.1 ± 118.6 g) but this study did not adjust for maternal active smoking (Pichini et al., 2003).

Outdoor air pollution Maternal exposure, major ambient air pollutants, limited evidence: Reviewers noted limited evidence in studies published up to 2001 for an association between FGD and ambient air pollutant levels (Binkova et al., 2005; Glinianaia et al., 2004a; Maisonet et al., 2004). In recently published studies, associations were observed in Lithuania (1st trimester formaldehyde, 3rd vs. 1st tertile, OR = 2.39, 95% CI 1.07–5.32; no association with formaldehyde levels during later pregnancy) (Maroziene & Grazuleviciene, 2002), Vancouver (per 5 ppb increment of 1st trimester SO_2, OR = 1.07, 95% CI 1.00–1.14; similar results for NO_2 and CO) (Liu et al., 2003), Los Angeles County (women in 3rd trimester during fall-winter months, 5th vs. 1st quintile of distance-weighted traffic density, OR = 1.39, 95% CI 1.16–1.67, p-trend = .004) (Wilhelm & Ritz, 2003), South Korea (per interquartile SO_2 increment, OR = 1.06, 95% CI 1.02–1.11) (Lee et al., 2003), Taiwan (birth weight deficit per 1 μg/m^3 SO_2 increment during 1st trimester, 0.52 g, 95% CI 0.09–2.63; similar results for PM_{10}; no association with levels during later pregnancy) (Yang et al., 2003), Brazil (birth weight deficit per 10 μg/m^3 PM_{10} increment during 1st trimester, 14 g, 95% CI 0.4–27; per 1 ppm CO increment during 1st trimester, 23 g, 95% CI 4.9–41; no association with pollutant levels during later pregnancy) (Gouveia et al., 2004), Los Angeles (per 10 μg/m^3 PM_{10} increment during 1st trimester, multipollutant model OR = 1.36, 95% CI 1.12–1.65; per 1 ppm CO increment, OR = 1.15, 95% CI 0.98–1.35) (Wilhelm and Ritz 2005), and Nova Scotia, Canada (4th vs. 1st quartile SO2 during 1st trimester, OR = 1.36, 95% CI 1.04–1.78; similar results for PM_{10} but no association with any pollutant during later pregnancy) (Dugandzic et al., 2006). FGD was not associated with ambient air pollution in a Nevada study (3rd trimester PM_{10} >45 vs. <20 μg/m^3, OR = 1.11, 95% CI 0.71–1.71; similar findings for CO and ozone) (Chen et al., 2002a).

Maternal exposure, industrial air pollutants, inadequate evidence: A small retrospective cohort study in Taiwan reported an association between term low birth weight and prenatal residence within about 3 km of petrochemical manufacturing facilities (exposed vs. unexposed women, OR = 1.77, 95% CI 1.00–3.12) (Lin et al., 2001b), but a larger study found no association with prenatal residence in several cities with petrochemical industries (exposed vs. unexposed women, OR = 1.07, 95% CI 0.95–1.22) (Yang et al., 2002).

Drinking water disinfection by-products Maternal exposure, limited evidence: Reviewers found limited evidence for an association between FGD and indices of maternal DBP exposure (Bove et al., 2002; Graves et al., 2001). Among reviewed studies, there were dose-response relationships between FGD and prenatal community drinking water THM levels in Iowa (e.g., chloroform 1–9 μg/L vs. nondetectable, OR = 1.3, 95% CI 0.9–1.8; ≥10 μg/L, OR = 1.8, 95% CI 1.1–2.9) (Kramer et al., 1992) and New Jersey (total THM >100 vs. ≤20 μg/L, OR = 1.50, 95% CI 1.04–2.09, p-trend<0.05) (Bove et al., 1995). In a retrospective cohort study in Denver, there was a relatively strong association between term low birth weight and prenatal drinking water THM levels above 60 μg/L (relative to ≤20 μg/L, OR = 5.9, 95% CI 2.0–17) (Gallagher et al., 1998). A retrospective cohort study in Massachusetts found associations between FGD and 3rd trimester municipal drinking water DBP indices above the 90th compared to less than 50th percentile concentrations (total THM, OR = 1.13, 955 CI 1.07–1.20; MX, OR = 1.14, 95% CI 0.95–1.37; mutagenic activity, OR = 1.25, 95% CI 1.04–1.51) but not HAAs (OR = 0.97, 95% CI 0.77–1.23) (Wright et al., 2004). In a retrospective cohort study in Arizona, there were associations between FGD and 3rd trimester municipal drinking-water total THMs (3rd vs. 1st tertile total THM, OR = 1.09, 95% CI 1.00–1.18) and HAAs (3rd vs. 1st tertile total HAAs, OR = 1.25, 95% CI 0.96–1.64), especially dibromoacetic acid (OR = 1.49, 95% CI 1.09–2.04) (Hinckley et al., 2005).

Other studies reported weak or no association between FGD and measured THM levels in Nova Scotia (3rd trimester THM ≥100 vs. <50 μg/L, OR = 1.08, 95% CI 0.99–1.18) (Dodds et al., 1999), prenatal residence in communities using chlorinated versus unchlorinated water in Sweden

(OR = 1.07, 95% CI 0.96–1.19) (Kallen & Robert, 2000), Taiwan (OR = 0.90, 95% CI 0.75–1.09) (Yang et al., 2000), and Norway (OR = 1.00, 95% CI 0.91–1.10) (Jaakkola et al., 2001b) or swimming pool use in the United Kingdom (≥2 vs. 0 h/wk, birth weight difference 17 g, 95% CI –11 to 45) (Nieuwenhuijsen et al., 2002).

Drinking water nitrate Maternal exposure, limited evidence: A moderately large case-control study in Prince Edward Island, Canada, revealed an association between FGD and median well water nitrate level in the region of maternal residence at birth (≥3.1 vs. ≤1.3 mg/L, OR = 2.40, 95% CI 1.75–3.27, adjusted for prenatal smoking and several other potential confounders) (Bukowski et al., 2001).

Solvents Maternal exposure, trichloroethylene or tetrachloroethylene in drinking water, inadequate evidence: Reviewers noted that two of three studies found increased risks of FGD related to prenatal residence in regions with trichloroethylene- and tetrachloroethylene-contaminated drinking water (Bove et al., 2002). The positive studies were conducted at Camp Lejeune (main contaminant was tetrachloroethylene, OR = 1.2, 95% CI 1.0–1.3) (Sonnenfeld et al., 2001) and Woburn (main contaminants were trichloroethylene and tetrachloroethylene). A peer review panel concluded that studies in Woburn did not support an association between adverse pregnancy outcomes and drinking water contamination (Massachusetts Department of Public Health, 1998).

Prenatal exposure, other and unspecified solvents, inadequate evidence: In a large U.S. population-based case-control study, FGD was not associated with prenatal occupations likely exposed to benzene, petroleum or alcohols/glycols (inferred from job titles) (Savitz et al., 1989a). A small hospital-based case-control study in California reported no association with self-reported maternal 1st trimester occupational solvent exposure (OR = 1.4, 95% CI 0.73–2.6) (Windham et al., 1991). A retrospective cohort study in New Jersey reported an association between FGD and drinking-water carbon tetrachloride levels in water systems serving the prenatal residence (>1 vs. ≤1 μg/L, OR = 1.75, 95% CI 1.13–2.70) (Bove et al., 1995). There was a statistically nonsignificant increased risk of FGD among women with prenatal occupational solvent exposure in a retrospective cohort study in Germany (OR = 2.2, 95% CI 0.8–6.1, *p*-trend = 0.13) (Seidler et al., 1999). In a retrospective cohort study of Swedish female biomedical research laboratory employees, mean birth weight was reduced among those exposed to diethylether (compared to unexposed women, mean difference –155 g, 95% CI –356 to 46) but not acetone, chloroform or toluene (Wennborg et al., 2000). A retrospective cohort study in China reported lower birth weight among nonsmoking women occupationally exposed to aromatic solvents including benzene, toluene, styrene, and xylene (adjusted for gestation length, compared to unexposed women, birth weight difference –79.0 g, 95% CI –156.0 to –1.9) (Ha et al., 2002). In Singapore, term low birth weight was not associated with maternal employment as cleaners or related jobs with likely solvent exposure (Chia et al., 2004).

Paternal occupational exposure, unspecified solvents, inadequate evidence: A retrospective cohort study based on Washington State birth certificates reported an association between FGD and paternal employment in one of four occupations with likely solvent exposure (painters, OR = 1.9, 95% CI 1.0–3.4) (Daniell & Vaughan, 1988). In a large U.S. population-based case-control study, FGD was associated with paternal occupations likely exposed to benzene (OR = 1.5, 95% CI 1.1–2.3) but not petroleum or alcohols/glycols (inferred from job titles) (Savitz et al., 1989a). A Norwegian retrospective cohort study of male printers observed no association between FGD and paternal occupational exposure to solvents only (OR = 1.0, 95% CI 0.75–1.3) or to solvents and lead (OR = 0.9, 95% CI 0.64–1.2) (Kristensen et al., 1993). A retrospective cohort study in China reported no association between birth weight (adjusted for gestation length) among offspring of men occupationally exposed to aromatic solvents (Ha et al., 2002). In Singapore, term low birth weight was associated with paternal employment as cleaners or related jobs with likely solvent exposure (OR = 1.32, 95% CI 1.12–1.55); the crude exposure index precludes strong inferences (Chia et al., 2004).

Summary There is sufficient epidemiologic evidence that prenatal active smoking causes FGD; limited epidemiologic evidence supports associations between FGD and prenatal exposure to lead, DDT/DDE, ETS, outdoor air pollution and drinking water DBPs and nitrate.

Birth Defects Birth defects are defined as physical or biochemical defects (e.g., cleft palate, phenylketonuria) that are present at birth and may be inherited or environmentally induced. About 2–3% of liveborn infants have one or more birth defects. In addition to true differences in risk, reported birth defect prevalence rates may vary because of differences in rates of 1st trimester screening and pregnancy termination and variable diagnosis and reporting. They are the leading cause of infant deaths and can cause lifelong disability but their causes remain largely unknown (Arias & Smith, 2003). During the late 20th century, birth prevalence rates in the Atlanta birth defect monitoring system declined for several types of birth defects (especially neural tube defects [NTDs]) but increased for coarctation of the aorta, hypospadias (a urethral closure defect on the ventral surface of the penis), and cystic kidney (International Clearinghouse for Birth Defect Monitoring Systems, 2000). There are over 100 distinct types of birth defect recognized, but most registries only track the most common types. For instance, the Metropolitan Atlanta Congenital Defects Program tracks 44 distinct birth defect categories (Centers for Disease Control and Prevention, 2005a).

The following discussion of potential environmental causes of birth defects focuses on specific major birth defect types but epidemiologic studies with limited statistical power have often assessed the overall risk of birth defects in relation to environmental exposure indices. Epidemiologic studies of total birth defects are problematic because of the likely substantial etiologic heterogeneity of diverse types of birth defects; such studies may obscure true relationships with specific birth defects. The level of epidemiologic evidence for associations between major birth defects and environmental factors is summarized in Table 2.

Neural Tube Birth Defects

Lead Maternal exposure, inadequate evidence: NTDs were not associated with average municipal drinking-water lead levels in communities of maternal residence in a Canadian ecologic study (mean levels in case and control communities were 10.3 and 11.5 μg/L) (Elwood & Coldman, 1981) but were associated with the percent of homes with tap water lead levels exceeding 10 μg/L in an English ecologic study (Bound et al., 1997). A Massachusetts case-control study reported no association between NTDs and drinking water lead levels in the community of maternal residence at delivery (≥1 vs. <1 μg/L, OR = 0.8, $p > .05$); the use of such a low cutoff point greatly reduces the chance of observing an association if it exists (Aschengrau et al., 1993). In a population-based case-control study in California, NTDs were associated with periconceptual maternal residential proximity to NPL sites containing lead (OR = 2.0, 95% CI 0.9–4.1) (Croen et al., 1997). A Norwegian retrospective cohort study observed an association between NTDs and prenatal occupations likely exposed to airborne inorganic lead (inferred from job titles) (OR = 2.9, 95% CI 1.1–6.4) but this study had no information on blood lead levels (Irgens et al., 1998). A small study in Texas reported higher mean amniotic fluid lead levels among NTD cases compared to controls (12.0 ± 0.6 vs. 5.7 ± 0.1 μmol/L, $p < .0001$) (Dawson et al., 1999). There was no association between NTDs and maternal blood lead levels above 6 μg/dl (OR = 1.5, 95% CI 0.6–4.3) in a large Texan case-control study (Brender et al., 2006).

Paternal occupational exposure, inadequate evidence: A Norwegian retrospective cohort study and a Texan case-control study, respectively, found no association between NTDs and paternal occupational lead exposure (inferred from job titles) (OR = 1.0, 95% CI 0.7–1.4) (Irgens et al., 1998) or self-reported paternal occupational lead exposure (OR = 1.3, 95% CI 0.8–2.3) (Brender et al., 2002).

Arsenic, cadmium, mercury Maternal exposure, inadequate evidence: Case-control studies in Canada and Massachusetts reported no association between community drinking water cadmium levels and risk of anencephaly (mean concentration, case vs. control communities, 8.97 vs. 9.00 μg/L) (Elwood & Coldman, 1981) or the broader category of central nervous system (CNS) birth defects (>1 vs. ≤1 μg/L, OR = 1.6, $p > .05$) (Aschengrau et al., 1993). The Canadian study also revealed no association with drinking water mercury levels (mean concentration, case vs. control communities, 7.09 vs. 7.95 μg/L) (Elwood & Coldman, 1981). In a large Texan case-control study, there was no association between NTDs and biomarker levels exceeding the 95th percentile for arsenic in the third U.S. National Health and Nutrition Examination Survey (NHANES III) (1999–2000) (maternal urinary arsenic ≥38.8 μg/L, OR = 0.0, 95% CI 0.0–2.0, 0/56 exposed cases), cadmium (urinary

TABLE 2. Role of Environmental Toxicants in Birth Defects

Toxicant	Exposure	Neural tube	Cardiac	Orofacial	Musculo-skeletal	Urinary tract	Male genital
Lead	Prenatal	I	I	I			
	Paternal	I	I	I			
Arsenic	Prenatal	I	I				
	Paternal		I				
Mercury	Prenatal	I	I				
Cadmium	Prenatal	I	I		I		
Mixed metals	Prenatal		I				
	Paternal		I				
PCBs	Prenatal	I		Yucheng—**S**[g] Environ—I			I
TCDD	Prenatal	I	I	I		I	I
	Paternal	**L**	I	I	I	I	
2,4,5-T, chlorophenate wood preservatives	Paternal	I	I	I	I	I	I
Chlorophenoxy herbicides (other than 2,4,5-T)	Prenatal	I	I	I	I	I	I
	Paternal						I
Other or unspecified herbicides	Prenatal	I (amides, glyphosate)	I		I		I
DDT/DDE	Prenatal						I
Organophosphate insecticides	Prenatal			I	I		
Other or unspecified insecticides	Prenatal	I	I	I	I		I
Fungicides	Prenatal	I					
Unspecified pesticides	Prenatal	I	I	I	I		I
	Paternal	I	I	I	I	I	I
Active smoking	Prenatal			**L**			
ETS	Prenatal			I			
Outdoor air pollution[h]	Prenatal	I	**L**	I		I	I
	Paternal	I		I	I		
Drinking water DBPs	Prenatal	**L**	**L**	I	I	**L**	
Drinking water nitrate, nitrite	Prenatal	**L**	I		I		
Hazardous waste disposal sites	Prenatal	**L**	**L**	I	I		I
Incinerators	Prenatal	I	I	I	I	I	I
Chlorinated solvents	Prenatal	I		**L**			
Glycol ethers	Prenatal	**L**	I	**L**	I	I	
Unspecified solvents	Prenatal	I	**L**	I	I	I	
	Paternal	**L**	I	I	I		I
Phthalates							I[i]

Note. TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.
[g]This category refers to developmental tooth abnormalities.
[h]Major pollutants from fossil fuel combustion.
[i]Reduced anogenital index in male infants, an indicator of incomplete masculinization.

cadmium ≥1.24 μg/L, OR = 1.0, 95% CI 0.1–17.0, 1/24 exposed cases), or mercury (urinary mercury ≥5.62 μg/L, OR = 1.8, 95% CI 0.8–3.7) (Brender et al., 2006). Reviewers noted sparse and inadequate evidence for an association between NTDs and drinking-water arsenic exposure in humans, a conclusion that remains applicable almost a decade later (DeSesso et al., 1998).

PCBs Maternal exposure, inadequate evidence: In a population-based case-control study in California, NTDs were weakly associated with periconceptual maternal residential proximity to NPL sites containing PCBs (OR = 3.5, 95% CI 0.9–10.6) (Croen et al., 1997). A case-control study of Mexican-American women in Texas found no association between NTDs and individual or summed

PCB congener concentrations in maternal serum (sum of 7 PCB congeners >32 ng/g lipid vs. <LOD, OR = 0.7, 95% CI 0.3–1.6) (Suarez et al., 2005).

TCDD Maternal exposure, inadequate evidence: A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between NTDs and expert-rated hazard of incinerator emissions (high vs. low exposure, OR = 0.83, 95% CI 0.35–1.96) (Cordier et al., 2004).

Paternal occupational exposure, limited evidence: A case-control study in Atlanta reported no association between anencephaly or spina bifida and self-reported paternal exposure to Agent Orange in Vietnam (respective ORs = 0.80 and 1.19, CIs not stated) (Erickson et al., 1984). In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of CNS defects of borderline statistical significance among offspring of men with low or high TCDD categories (defined earlier) compared to offspring of unexposed men (OR = 4.18, 95% CI 0.96–21.3, calculated from data in paper, 5 exposed case fathers) (Wolfe et al., 1995). Among male sawmill workers in British Columbia, NTDs were associated with maximum preconceptual chlorophenate exposure intensity (h/yr) (75th vs. 25th percentile, OR = 2.35, 95% CI 1.1–5.3) and less strongly with cumulative exposure (h) during the 3 mo before conception (75th vs. 25th percentile, OR = 1.27, 95% CI 0.8–2.0) (Dimich-Ward et al., 1996). The latter findings are consistent with a role for cumulative exposure to PCDD and PCDF contaminants that bioaccumulate in body lipids. Reviewers noted inadequate epidemiologic evidence for an association between NTDs and paternal TCDD exposure (Longnecker et al., 1997). A subsequent review concluded that there was limited epidemiologic evidence for an association between spina bifida and paternal exposure to phenoxy herbicides potentially contaminated by TCDD (National Academy of Sciences, 2003).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study in four U.S. states reported no association between CNS birth defects and prenatal residence in high-wheat counties (a proxy for agricultural use of chlorophenoxy herbicides including 2,4-D and MCPA) (high- vs. low-wheat counties, OR = 0.81, 95% CI 0.46–1.42) (Schreinemachers, 2003). A pooled analysis of 2 case-control studies in California revealed a statistically nonsignificant elevated NTD risk related to prenatal residence less than 1 km from areas with documented agricultural use of 2,4-D or derivatives (OR = 1.5, 95% CI 0.8–2.7, in a multipesticide model) (Rull et al., 2006).

Maternal exposure, other herbicides, inadequate evidence: In the California pooled analysis, NTDs were associated with prenatal residential proximity to agricultural applications of amide herbicides (OR = 2.2, 95% CI 1.0–5.3) and a statistically nonsignificant association with glyphosate use (OR = 1.5, 95% CI 0.8–2.9) (Rull et al., 2006).

Maternal exposure, insecticides, inadequate evidence: In the California pooled analysis, NTDs were not associated with prenatal residential proximity to agricultural applications of halogenated organic insecticides (OR = 0.9, 95% CI 0.6–1.3) but elevated NTD risks were related to organophosphate (OR = 1.3, 95% CI 0.9–1.8), methyl carbamate insecticides (OR = 1.5, 95% CI 1.0–2.3) and specific carbamates including carbaryl (OR = 1.7, 95% CI 0.8–3.9) and methomyl (OR = 1.4, 95% CI 0.8–2.5) (Rull et al., 2006). This study also reported statistically nonsignificant associations between NTDs and specific organophosphate insecticides including naled (OR = 2.7, 95% CI 0.9–8.2) and oxydemeton-methyl (OR = 3.4, 95% CI 0.8–14.3) but not with malathion (OR = 1.0, 95% CI 0.4–2.7) or chlorpyrifos (OR = 1.3, 95% CI 0.7–2.3).

Maternal exposure, fungicides, inadequate evidence: In the California pooled analysis, NTDs were associated with prenatal residential proximity to agricultural applications of fungicides in the benzimadazole chemical class (OR = 2.2, 95% CI 1.1–4.7) but not with dicarboximides (OR = 1.1, 95% CI 0.6–2.1) or dithiocarbamates (OR = 0.7, 95% CI 0.3–1.5) (Rull et al., 2006). This study observed an association of borderline statistical significance with the benzimidazole fungicide benomyl (OR = 2.3, 95% CI 0.9–5.6).

Maternal exposure, unspecified pesticides, inadequate evidence: Reviewers noted limited epidemiologic evidence for an association between NTDs (anencephaly, spina bifida) and prenatal occupational pesticide exposure (Sever et al., 1997). Among Norwegian farm families, CNS birth defect risk was not elevated (compared to nonfarm families, OR = 0.94, 95% CI 0.73–1.20) but was associated with farm use of tractor pesticide spraying equipment for orchards or greenhouses

(OR = 2.30, 95% CI 1.31–4.04) (Kristensen et al., 1997b). Combined analysis of two case-control studies in California revealed an association between NTDs and maternal residential proximity to NPL sites containing pesticides (<1 vs. ≥1 mile, OR = 2.2, 95% CI 0.9–5.2) (Croen et al., 1997). A California study revealed associations between NTDs and prenatal professional pesticide use in homes (OR = 1.6, 95% CI 1.1–2.5) and maternal use of garden pesticides (OR = 2.9, 95% CI 1.3–6.7) but not with pet flea treatments (Shaw et al., 1999). Two reports of a Mexican case-control study of anencephaly revealed strong associations with self-reported periconceptual maternal occupation in agriculture; in the more recent report, the odds ratio was 4.57 (95% CI 1.05–20.0) (Blanco Munoz et al., 2005).

A Finnish case-control study found no association between NTDs and maternal 1st trimester work in agriculture (OR = 1.2, 95% CI 0.6–2.4); among the 38 exposed case mothers, half were considered lightly exposed (Nurminen et al., 1995). NTDs were associated with prenatal occupation in agriculture in a case-control study in the Netherlands (OR = 3.4, 95% CI 1.3–9.0); however, among the few women employed in agriculture, similar proportions of case (4/9) and control (5/10) mothers reported pesticide exposure (Blatter et al., 1996a). NTDs were not associated with self-reported periconceptual maternal occupational pesticide exposure in case-control studies in California (OR = 0.9, 95% CI 0.2–3.8) (Shaw et al., 1999) or Texas (OR = 1.2, 95% CI 0.3–4.8) (Brender et al., 2002). In a California case-control study, CNS defects were not associated with prenatal residence in a census tract with a NPL site containing pesticides (OR = 1.02, 95% CI 0.68–1.55) (Orr et al., 2002). The heterogeneous and nonspecific exposure indices preclude strong inferences.

Paternal occupational exposure, 2,4,5-T and chlorophenate wood preservatives, inadequate evidence: See paternal occupational TCDD exposure described earlier.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: Reviewers found limited epidemiologic evidence for an association between NTDs and paternal occupational pesticide exposure (Sever et al., 1997). Among studies published before the latter review, CNS birth defects were associated with farm use of tractor pesticide spraying equipment for orchards or greenhouses (OR = 2.30, 95% CI 1.31–4.04) (Kristensen et al., 1997b). Statistically nonsignificant elevated risks were observed in Texas (anencephaly, paternal occupations likely exposed to pesticides, OR = 1.28, 95% CI 0.77–2.13; occupation as farm or ranch workers, OR = 1.73, 95% CI 0.84–3.55) (Brender & Suarez, 1990), Minnesota (CNS defects, paternal occupation as licensed pesticide applicator, RR = 1.10, 95% CI 0.50–2.40, 6 exposed case fathers) (Garry et al., 1996), and the Netherlands (spina bifida, moderate to high vs. no periconceptual paternal occupational pesticide exposure, OR = 1.7, 95% CI 0.7–4.0) (Blatter et al., 1997). The Minnesota study also noted increased risks of NTDs among nonfarm families (neither parent was a licensed pesticide applicator) living in agricultural regions (e.g., residence in corn/soybean vs. noncrop regions, OR = 1.42, 95% CI 1.09–1.86; wheat/sugar beet/potato regions, OR = 1.49, 95% CI 0.92–2.40); the crude exposure indicator and inability to adjust for potential confounders preclude strong inferences (Garry et al., 1996).

Among recently reported studies, a country-wide Norwegian retrospective cohort study reported no association between NTDs and paternal occupation in agriculture (based on census records) (OR = 0.91, 95% CI 0.67–1.21) (Irgens et al., 2000). NTDs were not associated with self-reported paternal periconceptual occupational pesticide exposure in case-control studies in California (OR = 0.9, 95% CI 0.5–1.7) (Shaw et al., 1999) or Texas (OR = 1.2, 95% CI 0.5–2.8) (Brender et al., 2002). Anencephaly risk was elevated (but not statistically significant) among offspring of men with partner-reported periconceptual occupation in agriculture in Mexico (OR = 2.50, 95% CI 0.73–8.64) (Lacasana et al., 2006). The inconsistent findings and the heterogeneity of exposure indices precludes firm conclusions.

Outdoor air pollution Maternal exposure, inadequate evidence: A retrospective cohort study in France observed no association between NTDs and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 1.05, 95% CI 0.44–2.51) (Cordier et al., 2004).

Paternal occupational exposure, inadequate evidence: A large Norwegian retrospective cohort study reported no association between NTDs and paternal occupation as drivers (OR = 1.07, 95% CI 0.80–1.43) (Irgens et al., 2000).

Drinking-water disinfection by-products Maternal exposure, limited evidence: Reviewers found limited evidence for an association between NTDs and prenatal DBP exposure (Bove et al., 2002; Graves et al., 2001). However, a meta-analysis of four epidemiologic studies published by 1999 (Magnus et al., 1999) indicated a modest association between NTDs and THM exposure indices (OR = 1.49, 95% CI 1.08–2.05) (Hwang & Jaakkola, 2003). Among subsequently published studies, NTDs were associated with drinking water BDCM but not chloroform levels in Nova Scotia (BDCM ≥20 vs. <5 μg/L, OR = 2.5, 95% CI 1.2–5.1; chloroform ≥100 vs. <50 μg/L, OR = 1.2, 95% CI 0.7–2.3) (Dodds & King, 2001). There was no association among recent studies in Sweden (nationwide, maternal residence in hypochlorite-treated vs. nonchlorinated municipalities, OR = 1.4, 95% CI 0.7–1.4) (Kallen & Robert, 2000) and Norway (chlorinated high-color vs. unchlorinated low colour water, OR = 0.7, 95% CI 0.2–2.0) (Hwang et al., 2002). A report of two case-control studies in California noted inconsistent findings with no evidence of a dose-response relationship in either study (Shaw et al., 2003b). Halogenated acetic acids cause NTDs in experimental animals; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al., 2000).

Drinking-water nitrate Prenatal drinking water nitrate level, limited evidence: Reviewers noted limited evidence for an association between birth defects (especially neural tube) and drinking water nitrate in humans but no evidence that nitrate is teratogenic in experimental animals (Fan & Steinberg, 1996). A case-control study in Australia reported an association between CNS defects and maternal drinking water source at birth (groundwater with nitrate >15 mg/L vs. surface water with nitrate <1 mg/L, OR = 3.5, 95% CI 1.1–14.6, adjusted for maternal age and parity but not other potential confounders) (Dorsch et al., 1984). A Canadian population-based case-control study observed a statistically nonsignificant elevated risk of NTDs among women with elevated residential well water nitrate levels (≥26 vs. ≤0.1 mg/L, OR = 2.30, 95% CI 0.73–7.29) (Arbuckle et al., 1988). A large case-control study in California revealed an association between nitrate levels in drinking water from ground sources serving the periconceptual maternal residence and anencephaly (≥36 vs. <5 mg/L, OR = 6.9, 95% CI 1.9–24.9) but not spina bifida (OR = 1.1, 95% CI 0.25–4.5) (Croen et al., 2001). However, this study found no association between NTDs and maternal periconceptual dietary intake of nitrate, nitrite, or *N*-nitroso compounds, suggesting that nitrate might be a marker for other teratogenic agents in groundwater. A small case-control study in Texas reported an elevated risk of NTDs among women with elevated drinking-water nitrate levels at the maternal periconceptual residence (≥3.5 vs. <3.5 mg/L, OR = 1.9, 95% CI 0.8–4.6) (Brender et al., 2004).

Hazardous waste disposal sites Maternal exposure, limited evidence: Reviewers found limited evidence for a weak association between birth defects, especially NTDs and cardiac defects, and maternal prenatal residential proximity to hazardous waste disposal sites (Dolk & Vrijheid, 2003). They noted several important limitations of epidemiologic studies of birth defects and environmental contaminants, including the heterogeneity and relative rarity of birth defects, crude exposure indices, and inadequate assessment of potential confounders. For instance, in a population-based case-control study in New York State (excluding New York City), CNS defects were associated with prenatal residential proximity to hazardous waste disposal sites (<1.6 vs. ≥1.6 km, OR = 1.29, 95% CI 1.05–1.59) but not with an exposure index based on chemical toxicity and likelihood of exposure (high vs. no exposure, OR = 1.48, 95% CI 0.69–3.16) (Geschwind et al., 1992). Subsequently, a similar study in New York State reported no association between prenatal residential proximity to NPL sites (<1.6 vs. ≥1.6 km, OR = 0.92, 95% CI 0.79–1.08, adjusted for proximity to Toxic Release Inventory [TRI] sites) (Marshall et al., 1997) but did find a borderline association between CNS defects and prenatal residential proximity to TRI sites emitting solvents (≤0.5 vs. >0.5 km, OR = 1.39, 95% CI 0.97–2.01). In a population-based case-control study in California, NTDs were weakly associated with periconceptual maternal residential proximity to NPL sites (<1.6 vs. ≥1.6 km, OR = 1.4, 95% CI 0.8–2.4); there were stronger associations with the subsets of NPL sites containing pesticides (OR = 2.2, 95% CI 0.9–5.2), lead (OR = 2.0, 95% CI 0.9–4.1), pyrene (OR = 3.1, 95% CI 1.0–8.6), PCBs (OR = 3.5, 95% CI 0.9–10.6), or benzene (OR = 1.9, 95% CI 0.9–3.6) (Croen et al., 1997). A European case-control study revealed a nonmonotonic dose-response relationship between NTDs and hazard categories based on expert-rated potential for toxicant

exposure via air or water (high vs. low hazard, OR = 1.89, 95% CI 0.84–4.29, *p*-trend = 0.64) (Vrijheid et al., 2002b). In a large case-control study of minority-group women in California, there was no association between CNS defects and prenatal residence in a census tract with at least one NPL site containing solvents, pesticides or a category comprising PCBs, dioxins and polycyclic aromatic hydrocarbon (PAHs) (Orr et al., 2002). A United Kingdom-wide retrospective cohort study revealed no association between NTDs and prenatal residential proximity to any of 774 hazardous waste sites (≤2 vs. >2 km, OR = 1.07, 95% CI 0.95–1.20) (Elliott et al., 2001). Three studies were not included in the review by Dolk and Vrijheid (2003). A retrospective cohort study in Scotland found no association between NTDs and prenatal residential proximity to hazardous waste sites (≤2 vs. >2 km from any of 61 sites, OR = 0.71, 95% CI 0.36–1.42) (Morris et al., 2003). In an ecologic study, NTD risk was elevated among women living in Sydney, Nova Scotia, site of a major hazardous waste disposal site (SIR = 1.83, 95% CI 1.08–3.09) but not in the remainder of Cape Breton County (Dodds & Seviour, 2001). In a small Alaskan retrospective cohort study, there was a statistically nonsignificant elevated risk of CNS defects among women in Native villages with hazardous waste sites (higher vs. lower hazard dumpsite, OR = 2.36, 95% CI 0.37–14.7) (Gilbreath & Kass, 2006a).

Incinerators Maternal exposure, inadequate evidence: A UK retrospective cohort study reported a weak association between NTDs and prenatal residential proximity to incinerators (per unit change in an inverse distance function, OR = 1.13, 95% CI 1.04–1.23) but not crematoria (Dummer et al., 2003a, 2003b). In a large French retrospective cohort study, NTDs were not associated with prenatal residence in communities with solid waste incinerators or expert-rated potential for exposure to dioxin, metal or dust emissions (high vs. low hazard, OR = 0.83, 95% CI 0.35–1.96) (Cordier et al., 2004).

Solvents Recent meta-analyses reported associations between the broad category of major birth defects and periconceptual parental occupational solvent exposure (maternal, summary OR = 1.64, 95% CI 1.16–2.30; paternal, summary OR = 1.47, 95% CI = 1.18–1.83) (Logman et al., 2005).

Maternal exposure, chlorinated solvents, inadequate evidence: A retrospective cohort study in New Jersey revealed increased NTD risks for women with 1st trimester residence in communities served by drinking water with trichloroethylene levels above 10 μg/L (compared to ≤1 μg/L, OR = 2.53, 90% CI 0.91–6.37) or carbon tetrachloride levels above 1 μg/L (compared to ≤1 μg/L, OR = 5.39, 90% CI 1.12–19.0) (Bove et al., 1995).

Maternal occupational exposure, glycol ethers, limited evidence: NTDs were associated with maternal 1st trimester occupational exposure to glycol ethers in Europe (OR = 1.94, 95% CI 1.16–3.24) (Cordier et al., 1997) and Texas (OR = ∞, 95% CI 1.8–∞, 7 exposed cases and 0 exposed control mothers) (Brender et al., 2002). Reviewers concluded that NTDs were associated with maternal 1st trimester occupational exposure to glycol ethers (Shi & Chia, 2001).

Maternal exposure, unspecified solvents, inadequate evidence: In a case-control study in the Netherlands, spina bifida was not associated with 1st trimester maternal occupational solvent exposure (alcohol, yes vs. no, OR = 0.9, 95% CI 0.5–1.7; other organic solvents, OR = 1.5, 95% CI 0.6–4.0) (Blatter et al., 1996b). Combined analysis of 2 Californian case-control studies revealed no association between NTDs and periconceptual maternal residence within 1 mile of NPL sites containing volatile organic carbons (VOCs) (OR = 1.4, 95% CI 0.8–2.3) (Croen et al., 1997). A hospital-based case-control study in France found no association between CNS defects and prenatal occupational solvent exposure (OR = 1.4, 90% CI 0.6–3.2) (Cordier et al., 1992). In a population-based case-control study, CNS defects were associated with prenatal residential proximity to hazardous waste disposal sites containing solvents (<1.6 vs. ≥1.6 km, OR = 1.24, 95% CI 1.01–1.54) (Geschwind et al., 1992). In a similar New York State study, there was a borderline association between CNS defects and prenatal residential proximity to TRI sites emitting solvents (≤0.5 vs. >0.5 km, OR = 1.39, 95% CI 0.97–2.01) (Marshall et al., 1997). A case-control study in Texas reported an association between NTDs and periconceptual maternal use of solvents at home or work (OR = 2.5, 95% CI 1.3–4.7) (Brender et al., 2002).

Paternal occupational exposure, unspecified solvents, limited evidence: A recent meta-analysis of 5 epidemiologic studies published during 1976–2000 reported an association between NTDs and paternal occupational solvent exposure (summary RR = 1.86, 95% CI = 1.40–2.46) (Logman

et al., 2005). Among studies not included in the meta-analysis, CNS defects were not associated with paternal occupation as printers in Norway (compared to other occupations, SIR = 1.1, 95% CI 0.53–2.0) (Kristensen et al., 1993) or self-reported periconceptual paternal occupational solvent use in Texas (OR = 0.8, 95% CI 0.5–1.4) (Brender et al., 2002).

Summary

Epidemiologic evidence for the role of environmental toxicants in neural tube birth defects includes: limited evidence—prenatal exposure to DBPs, nitrate (drinking water), hazardous waste disposal sites (residential proximity), glycol ethers (occupational); paternal occupational exposure to TCDD, unspecified solvents.

Cardiac Birth Defects

Lead Maternal exposure, inadequate evidence: A case-control study in Massachusetts found no association between cardiac birth defects and drinking-water lead levels in communities of prenatal residence (>1 vs. ≤1 μg/L, OR = 1.13, 95% CI 0.60–2.14); 90% of lead concentrations were below 1 μg/L (Zierler et al., 1988). Further investigation with about fourfold more cases revealed a borderline association between cardiac birth defects and lead levels in the water supply serving the maternal residence during the 1st trimester (>1 vs. ≤1 μg/L, OR = 2.2, 95% CI 0.9–5.7) (Aschengrau et al., 1993). In a lead-polluted region of Italy, an ecologic study reported an elevated risk of cardiac birth defects during 1982–1986 when emission levels were higher (SIR = 2.59, 95% CI 1.68–3.82) but not during 1991–1995 (SIR = 0.97, 95% CI 0.57–1.54); annual air lead emissions in the region decreased by 93% between 1979 and 1997 (Vinceti et al., 2001). In the Baltimore–Washington Infant Study, there was a statistically nonsignificant elevated risk of pulmonary vein defects among infants of women who were likely exposed to lead at home or work during the 3-mo periods before and after conception (OR = 1.57, 95% CI 0.64–3.47) (Jackson et al., 2004).

Paternal exposure, inadequate evidence: Case-control studies within the Baltimore–Washington Infant Study found associations between pulmonary atresia and self-reported paternal frequent exposure to lead soldering (OR = 4.1, 95% CI 1.2–11) (Correa-Villasenor et al., 1993) and between total anomalous pulmonary vein return and likely paternal occupational lead exposure (based on industrial hygiene assessment, a job-exposure matrix or self-reports) during the 6 mo before conception (OR = 1.83, 95% CI 1.00–3.42) (Jackson et al., 2004).

Arsenic, cadmium, mercury, mixed metals Maternal exposure, inadequate evidence: In a Massachusetts case-control study, infants of women living in communities with detectable drinking-water inorganic mercury or arsenic, respectively, had increased risks of coarctation of the aorta (arsenic >0.8 vs. ≤0.8 μg/L, OR = 3.4, 95% CI 1.3–8.9) and patent ductus arteriosus (mercury >0.2 vs. ≤0.2 μg/L, OR = 1.6, 95% CI 0.95–2.6) (Zierler et al., 1988). A hospital-based case-control study reported no association between cardiovascular birth defects and maternal residence in communities with detectable drinking-water arsenic (>0.8 vs≤0.8 μg/L, OR = 1.3, $p > .05$) or cadmium (>0.4 vs≤0.4 μg/L, OR = 1.6, $p > .05$) (Aschengrau et al., 1993). In a Swedish retrospective cohort study, there was an elevated risk of confirmed cardiac birth defects (1.69, 95% CI 0.55–4.44) among infants of women living in parishes near a copper smelter known to produce air emissions of lead, arsenic, mercury, and cadmium (Wulff et al., 1996).

Paternal occupational exposure, inadequate evidence: A Swedish retrospective cohort study reported no association between cardiac birth defects and prenatal maternal residential proximity to a copper smelter (RR = 0.51, 95% CI 0.26–1.00) or paternal employment as a blue collar worker at the smelter (OR = 0.55, 95% CI 0.30–1.01) (Wulff et al., 1996). A small Texan case-control study found no relationship between NTDs and paternal occupations likely exposed to arsenic (OR = 1.5, 95% CI 0.7–3.0) (Brender et al., 2006).

TCDD Maternal exposure, inadequate evidence: A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between cardiac birth defects and expert-rated hazard of incinerator emissions (high vs. low exposure, conotruncal defects, OR = 0.97, 95% CI 0.58–1.60; other cardiac defects, OR = 1.05, 95% CI 0.72–1.53) (Cordier et al., 2004).

Paternal occupational exposure, inadequate evidence: In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of cardiovascular birth defects among offspring of men with low (OR = 2.39, 95% CI 1.02–5.24) but not high serum TCDD levels (OR = 0.95, 95% CI 0.28–2.65) (TCDD categories defined earlier) (Wolfe et al., 1995). Among offspring of male sawmill workers, conotruncal and septal defects were not associated with preconceptual chlorophenate exposure intensity (per 100 h exposure during peak exposure year up to 3 mo before conception, OR = 0.95, $p > .05$) or with cumulative exposure during the 3 mo before conception (per 100 hr exposure, OR = 0.94, $p > .05$) (Dimich-Ward et al., 1996).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study found no association between cardiac birth defects and prenatal residence in high-wheat counties, a proxy for agricultural use of chlorophenoxy herbicides (high- vs. low-wheat counties, OR = 1.23, 95% CI 0.70–2.17) (Schreinemachers, 2003).

Maternal exposure, unspecified herbicides, inadequate evidence: The Baltimore–Washington case-control study noted an association between transposition of great arteries and self-reported periconceptual maternal herbicide exposure at home or work (OR = 3.6, 95% CI 1.6–8.2) (Loffredo et al., 2001). Further studies are needed to assess this finding and to explore specific herbicides and dose-response relationships.

Maternal exposure, insecticides, inadequate evidence: In a California case-control study, conotruncal defects were not associated with prenatal pet flea treatments (OR = 1.2, 95% CI 0.8–1.8) or professional indoor pesticide application (OR = 1.2, 95% CI 0.7–2.0) (Shaw et al., 1999). There were statistically nonsignificant elevated risks in case-control studies in Baltimore–Washington (transposition of great arteries, self-reported maternal periconceptual insecticide exposure at home or work, OR = 1.5, 95% CI 0.9–2.6) (Loffredo et al., 2001) and California (conotruncal defects, self-reported prenatal occupational insecticide exposure, OR = 2.1, 95% CI 0.8–5.1) (Shaw et al., 2003a).

Maternal exposure, unspecified pesticides, inadequate evidence: Conotruncal defects were associated with prenatal residential proximity to crops (OR = 1.4, 95% CI 0.9–2.0) or garden pesticide application (OR = 3.1, 95% CI 1.3–7.3) in California (Shaw et al., 1999). The Baltimore–Washington case-control study reported an association between transposition of great arteries and self-reported maternal periconceptual exposure at home or work to rodenticides (OR = 5.1, 95% CI 1.7–14.9) (Loffredo et al., 2001). The Baltimore–Washington case-control study reported a statistically nonsignificant elevated risk of total anomalous pulmonary vein return defects related to self-reported periconceptual maternal pesticide exposure at home or work (OR = 2.06, 95% CI 0.82–5.15) (Correa-Villasenor et al., 1991). A retrospective cohort study revealed a statistically nonsignificant elevated congenital heart defect risk (as evidenced by heart murmurs) related to prenatal pesticide exposure in Colombian greenhouses (crude OR = 2.16, 95% CI 0.69–6.54, calculated from data in paper) (Restrepo et al., 1990a). A subsequent report of the California study revealed an association between conotruncal defects and prenatal occupational exposure to insecticides (as noted earlier) but not to pesticides other than insecticides (OR = 1.0, 95% CI 0.5–2.2) (Shaw et al., 2003a). In another California case-control study, limited to minority groups, cardiovascular birth defects were not associated with prenatal residence in a census tract with a NPL site containing pesticides (OR = 0.83, 95% CI 0.56–1.25) (Orr et al., 2002). The heterogeneity of these studies with regard to type of cardiac defect evaluated and nonspecific exposure indices precludes strong inferences.

Paternal occupational exposure, 2,4,5-T or chlorophenate wood preservatives, inadequate evidence: A case-control study of cardiovascular birth defects in Atlanta revealed no overall association with exposure to Agent Orange (based on self-reports and military records) (OR = 0.97, CI not reported) but noted elevated risks of transposition of the great vessels (OR = 1.49) and coarctation of the aorta (OR = 1.89) (Erickson et al., 1984). See also paternal occupational TCDD exposure discussed earlier.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: There was an increased risk of cardiorespiratory birth defects among offspring of male licensed pesticide applicators in Minnesota (RR = 1.69, 95% CI 1.04–2.76); this study did not present data separately for

cardiac defects (Garry et al., 1996). Among other residents of agricultural counties (after excluding licensed applicators), there were increased cardiorespiratory birth defect risks in areas with corn/soybeans (RR = 1.43, 95% CI 1.17–1.76) or wheat, sugar, and/or potatoes (RR = 1.90, 95% CI 1.37–2.63). In the Norwegian farm cohort study, cardiac birth defect risk was not elevated among offspring of farmers (compared to nonfarm families, RR = 0.83, 95% CI 0.68–1.02); 57% of fathers and 34% of mothers worked at least 500 h/yr on their farms (Kristensen et al., 1997b). A California case-control study reported no association between cardiac birth defects and periconceptual paternal occupational pesticide exposure (OR = 1.0, 95% CI 0.6–1.9) (Shaw et al., 1999).

Outdoor air pollution Maternal exposure, limited evidence: A large case-control study in southern California reported dose-response relationships between certain cardiac defects and ambient air pollutant levels near the prenatal residence during the 2nd gestational month including ozone (per 1 pphm ozone, aortic defects, OR = 1.56, 95% CI 1.16–2.09; pulmonary valve defects, OR = 1.34, 95% CI 0.96–1.87) and CO (per 1 ppm CO, VSD, OR = 1.33, 95% CI 1.00–1.78) (Ritz et al., 2002). These associations were independent of socioeconomic status (SES) and other air pollutants but this record-based study had no information on potential confounders such as prenatal smoking. A retrospective cohort study in France observed an association between conotruncal defects and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 1.88, 95% CI 1.07–3.30, *p*-trend = .02) (Cordier et al., 2004). A population-based case-control study in Texas reported associations between ambient air pollutant levels near the maternal residence during GW 3–8 and cardiac defects including ASD (4th vs. 1st quartile PM10, OR = 2.27, 95% CI 1.43–3.60, *p*-trend = .0001), VSD (4th vs. 1st quartile SO_2, OR = 2.16, 95% CI 1.51–3.09, *p*-trend < .0001) and Tetralogy of Fallot (4th vs. 1st quartile CO, OR = 2.04, 95% CI 1.26–3.29, *p*-trend = .002) (Gilboa et al., 2005).

Drinking water disinfection by-products Maternal exposure, drinking water, limited evidence: HAAs and haloacetonitriles cause cardiac defects in experimental animals (Graves et al., 2001; Nieuwenhuijsen et al., 2000). However, the five epidemiologic studies of cardiac birth defects and DBPs available to reviewers yielded inadequate evidence of an association (Bove et al., 2002). A meta-analysis of three studies published by 1999 (Bove et al., 1995; Dodds et al., 1999; Magnus et al., 1999) showed no association between major cardiac defects and DBP exposure indices (summary OR = 0.95, 0.77–1.17) (Hwang & Jaakkola, 2003). In subsequently reported studies, cardiac defects were associated with DBP indices in Sweden (total THM >10 vs. ≤10 μg/L, OR = 1.30, 95% CI 1.08–1.56) (Cedergren et al., 2002) and Norway (ventricular septal defect, chlorinated high-color vs. unchlorinated low-color water, OR = 1.81, 95% CI 1.05–3.09) but not in California (community drinking-water THM levels 50–74 vs. <1.0 μg/L, OR = 1.5, 95% CI 0.7–3.5) (Shaw et al., 2003b).

Drinking water nitrate Maternal exposure, drinking water, inadequate evidence: In a case-control study of cardiac defects in Massachusetts, there was no association with drinking water nitrate in the community of maternal residence at birth (>0.1 vs. ≤0.1 mg/L, OR = 1.08, 95% CI 0.72–1.62) (Zierler et al., 1988). A Swedish cohort study reported an association between major cardiac birth defects and water nitrate levels in the municipality of maternal residence at birth (≥4.0 vs. <1.0 mg/L, crude OR = 1.61, 95% CI 0.95–2.72, CI calculated from data in paper) (Cedergren et al., 2002).

Hazardous waste disposal sites Maternal exposure, limited evidence: In a population-based case-control study in California, there was a statistically nonsignificant elevated risk of conotruncal defects among women with periconceptual residential proximity to NPL sites (<1.6 vs. ≥1.6 km, OR = 1.8, 95% CI 0.8–4.2); there were stronger associations with the subsets of NPL sites containing lead (OR = 2.3, 95% CI 0.8–6.4), arsenic (OR = 2.3, 95% CI 0.8–6.4) or 1,1-dichloroethylene (OR = 2.0, 95% CI 0.8–5.2) (Croen et al., 1997). A European case-control study reported associations between maternal residential proximity to hazardous waste landfill sites and cardiac septal (<3 vs. 3–7 km, OR = 1.49, 95% CI 1.09–2.04) and artery/vein defects (OR = 1.81, 95% CI 1.02–3.20) (Dolk et al., 1998). Further analysis of the European study revealed a nonmonotonic dose-response relationship between hazard categories based on expert-rated potential for toxicant exposure via air or water and both cardiac defects (high vs. low hazard, OR = 1.65, 95% CI 0.86–3.16,

p-trend = 0.31) and artery/vein defects (high vs. low hazard, OR = 2.19, 95% CI 0.93–5.17, *p*-trend = 0.31) (Vrijheid et al., 2002b).

A United Kingdom-wide retrospective cohort study revealed a weak association between cardiovascular birth defects and prenatal residential proximity to any of 774 hazardous waste sites (≤2 vs. >2 km, OR = 1.11, 95% CI 1.03–1.21) (Elliott et al., 2001). In a similar study limited to Scotland, there was no association (≤2 vs. >2 km, OR = 1.03, 95% CI 0.85–1.26) (Morris et al., 2003). In a large case-control study in California, there was no association between cardiovascular defects and prenatal residence in a census tract with at least one NPL site containing solvents, pesticides or a category comprising PCBs, dioxins, and PAHs (Orr et al., 2002). A large population-based case-control study in Dallas County revealed weak associations between maternal residential proximity to any of 276 hazardous waste sites and cardiac birth defects (<1.6 vs. ≥1.6 km, OR = 1.2, 95% CI 1.1–1.4); there was a somewhat stronger association for the subgroup of endocardial cushion defects (OR = 1.8, 95% CI 1.0–3.1) (Malik et al., 2004). There was a statistically nonsignificant elevated risk of cardiovascular birth defects related to maternal residential proximity to hazardous waste disposal sites in an ecologic study in Sydney, Nova Scotia (SIR = 1.27, 95% CI 0.93–1.75) (Dodds & Seviour, 2001).

Incinerators Maternal exposure, inadequate evidence: A UK retrospective cohort study reported a weak association between cardiac defects and prenatal residential proximity to incinerators (per unit change in inverse distance function, OR = 1.12, 95% CI 1.03–1.22) but not crematoria or hazardous industries (Dummer et al., 2003a, 2003b). In a large French retrospective cohort study, conotruncal defects were not associated with prenatal residence in a communities with solid waste incinerators or expert-rated potential for exposure to dioxin, metal or dust emissions (high vs. low hazard, OR = 0.97, 95% CI 0.58–1.60) (Cordier et al., 2004).

Solvents Prenatal occupational exposure, glycol ethers, inadequate evidence: In a multicentre European case-control study, cardiac defects were associated with maternal 1st trimester occupational exposure to glycol ethers (OR = 1.45, 95% CI 0.99–2.13) (Cordier et al., 1997).

Prenatal exposure, unspecified solvents, limited evidence: The Baltimore–Washington Infant Study found an imprecise and statistically nonsignificant increased risk of total anomalous pulmonary venous return defects among women with self-reported periconceptual exposure to paint, paint strippers, solvents, or degreasing agents (OR = 3.4, 95% CI 0.7–16, 3 exposed case mothers) (Correa-Villasenor et al., 1991). In a country-wide Finnish case-control study, 1st trimester maternal occupational organic solvent exposure was associated with VSD (OR = 1.5, 95% CI 1.0–3.7) but not with total cardiovascular defects (OR = 1.3, 95% CI 0.8–2.2) (Tikkanen & Heinonen, 1991) or conal defects (OR = 0.6, 95% CI 0.2–1.4) (Tikkanen & Heinonen, 1992b). Further analyses revealed associations between 1st trimester maternal occupational exposure to dyes, lacquers or paint and VSD (crude OR = 5.4, 95% CI 1.7–17, calculated from data in paper) and conus arteriosus syndrome (crude OR = 6.7, 95% CI 1.8–24) (Tikkanen & Heinonen, 1992a). A hospital-based case-control study in France found no association between cardiac birth defects and prenatal occupational solvent exposure (OR = 1.3, 90% CI 0.3–6.2) (Cordier et al., 1992). Combined analysis of 2 Californian case-control studies revealed no association between conotruncal defects and periconceptual maternal residence within 1 mile of a NPL site containing VOCs (OR = 1.3, 95% CI 0.6–3.2) (Croen et al., 1997). The Baltimore–Washington Infant Study reported an elevated risk of isolated coarctation of the aorta among women with the highest frequency of 1st trimester occupational solvent exposure (daily vs. never, OR = 3.2, 95% CI 1.3–7.9) (Wollins et al., 2001). A large case-control study in California reported a borderline association between conotruncal defects and prenatal occupations likely exposed to aliphatic hydrocarbons (OR = 1.6, 95% CI 0.8–3.3); the association was stronger among infants with the GST M1 polymorphism (GSTM1) (OR = 4.6, 95% CI 1.0–19) (Shaw et al., 2003a).

Paternal occupational exposure, unspecified solvents, inadequate evidence: A Norwegian cohort study of offspring of male printers revealed no increased risk of cardiac defects (compared to other occupations, SIR = 0.7, 95% CI 0.33–1.2) (Kristensen et al., 1993). In the Baltimore–Washington Infant Study, there were dose-response relationships between intensity of paternal occupational exposure to paint strippers (potentially containing trichloroethylene) and coarctation of the aorta

(≥2–3 times/wk vs. unexposed, OR = 4.3, 95% CI 1.0–14.4; *p*-trend = .012) and VSD (≥2–3 times/wk vs. unexposed, OR = 7.0, 95% CI 1.6–24.6; *p*-trend = .007) (Correa-Villasenor et al., 1993).

Summary There is limited epidemiologic evidence for associations between cardiac birth defects and prenatal exposures: outdoor air pollution, DBPs in drinking water, residential proximity to hazardous waste disposal sites, unspecified solvents (occupational).

Orofacial Clefts

Lead Maternal exposure, inadequate evidence: A case-control study in Massachusetts found a statistically nonsignificant elevated risk of facial/neck birth defects among infants of women living in communities with drinking-water lead levels above 1 μg/L (OR = 1.7, $p > .05$) (Aschengrau et al., 1993). A European case-control study reported an association between isolated cleft palate and self-reported maternal 1st trimester occupational lead exposure (OR = 3.0, 95% CI 1.1–8.6) (Lorente et al., 2000). An ecologic study of a region of Italy polluted by air emissions from ceramic tile plants showed that the risk of oral cleft defects was elevated during 1982–1986 (SIR = 2.28, 95% CI 1.16–4.07) but decreased in recent years (1991–1995) after lead emissions declined substantially (SIR = 1.31, 95% CI 0.42–3.16) (Vinceti et al., 2001).

Paternal occupational exposure, inadequate evidence: Retrospective Norwegian cohort studies found borderline associations between paternal occupational lead exposure inferred from job titles and cleft lip (OR = 1.6, 95% CI 1.0–2.5) (Kristensen et al., 1993) and cleft palate (OR = 1.3, 95% CI 0.9–2.0) (Irgens et al., 1998). These studies did not measure blood lead levels and the men were likely exposed to other toxicants (e.g., solvent exposure among printers).

TCDD Maternal exposure, inadequate evidence: A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between facial clefts and expert-rated hazard of incinerator emissions (high vs. low exposure, OR = 1.01, 95% CI 0.64–1.59) (Cordier et al., 2004).

Paternal exposure, inadequate evidence: In a retrospective cohort study of Vietnam veterans and partners, there was no association between ear, face or neck defects and paternal serum TCDD categories (low or high serum TCDD vs. unexposed or serum TCDD <10 pg/g lipid, OR = 1.09, 95% CI 0.42–2.62 (calculated from data in paper)) (Wolfe et al., 1995).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study found no association between cleft lip and/or palate and prenatal residence in high-wheat counties, a proxy for chlorophenoxy herbicide exposure (high- vs. low-wheat counties, OR = 1.12, 95% CI 0.62–2.01) (Schreinemachers, 2003).

Maternal exposure, organophosphate insecticides, inadequate evidence: A small nested case-control study in San Francisco reported a statistically nonsignificant association between orofacial defects and prenatal residence ≤1 km from areas sprayed with malathion (OR = 3.35, 95% CI 0.61–18.5) (Thomas et al., 1992).

Maternal exposure, unspecified insecticides, inadequate evidence: In a California case-control study, there was no association between isolated cleft lip with or without cleft palate and 1st trimester professional indoor insecticide application (OR = 0.9, 95% CI 0.6–1.3) or pet flea treatments (OR = 0.8, 95% CI 0.6–1.2) (Shaw et al., 1999). Further analysis of this study revealed no association with maternal periconceptual occupational insecticide exposure (OR = 0.9, 95% CI 0.4–2.2) (Shaw et al., 2003a).

Maternal exposure, unspecified pesticides, inadequate evidence: In a large Finnish case-control study, orofacial clefts were associated with maternal 1st trimester employment in agriculture (compared to other work, OR = 1.9 95% CI 1.1–3.5) (Nurminen et al., 1995). In the California study, there was no association between isolated cleft lip with or without cleft palate and 1st trimester maternal occupational pesticide exposure (OR = 1.1, 95% CI 0.6–2.0), maternal application of garden pesticides (OR = 1.2, 95% CI 0.5–2.8) or residential proximity to crops treated with pesticides (OR = 0.9, 95% CI 0.6–1.4) (Shaw et al., 1999). Further analysis of this study revealed no association with maternal periconceptual occupational exposure to pesticides other than insecticides (OR = 1.0, 95% CI 0.6–1.7) (Shaw et al., 2003a). In another California case-control study, limited to minority groups, oral clefts were not associated with prenatal residence in a census tract with an

NPL site containing pesticides (OR = 0.89, 95% CI 0.45–1.74) (Orr et al., 2002). The inconsistent findings and the heterogeneous and nonspecific exposure indices preclude strong inferences.

Paternal exposure, 2,4,5-T, inadequate evidence: A case-control study in Atlanta revealed no association between exposure to Agent Orange (based on self-reports and military records) and cleft lip without cleft palate (OR = 1.07, CI not reported) or with cleft palate (OR = 0.76, CI not reported) (Erickson et al., 1984). See also paternal occupational TCDD exposure above.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: A cohort study of Norwegian farm families found no increased risks of cleft lip with or without cleft palate (compared to nonfarm families, OR = 0.94, 95% CI 0.74–1.20) (Kristensen et al., 1997b). Cleft palate was not associated with periconceptual paternal occupational pesticide exposure in a large California case-control study (OR = 1.1, 95% CI 0.8–2.1) (Shaw et al., 1999).

Tobacco smoke Maternal active smoking, limited evidence: The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between prenatal active smoking and oral clefts (U.S. Department of Health and Human Services, 2004).

Maternal ETS exposure, inadequate evidence: An expert panel concluded that there is inadequate evidence for an association between oral cleft of other specific birth defects and prenatal ETS exposure (California Environmental Protection Agency, 2005).

Outdoor air pollution Prenatal environmental exposure, inadequate evidence: A large case-control study in southern California reported a weak association between cleft lip/palate and ambient air ozone levels near the prenatal residence during the 2nd gestational month (per 1 pphm ozone, OR = 1.13, 95% CI 0.90–1.40) (Ritz et al., 2002). A retrospective cohort study in France observed no association between facial cleft defects and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 1.07, 95% CI 0.67–1.72) (Cordier et al., 2004). In a population-based case-control study in Texas, cleft lip and/or palate were marginally associated with ambient air PM_{10} levels near the maternal residence during GW 3–8 (4th vs. 1st quartile, OR = 1.37, 95% CI 0.94–2.00, *p*-trend = .09) but not with SO_2, CO, ozone, or NO_2 levels (Gilboa et al., 2005).

Paternal occupational exposure, inadequate evidence: A large Norwegian retrospective cohort study reported no association between cleft lip and/or cleft palate and paternal occupation as drivers (OR = 1.10, 95% CI 0.91–1.36) (Irgens et al., 2000).

Drinking-water disinfection by-products Prenatal drinking water DBP levels, inadequate evidence: Reviewers noted limited evidence for an association between orofacial clefts and DBP exposure indices (Bove et al., 2002), but a meta-analysis of three epidemiologic studies published by 1999 (Bove et al., 1995; Dodds et al., 1999; Magnus et al., 1999) revealed no association (summary OR = 1.09, 95% CI 0.79–1.51) (Hwang & Jaakkola, 2003). There was also no association in subsequently published studies in Sweden (hypochlorite-treated vs. nonchlorinated drinking water, OR = 1.4, 95% CI 0.7–1.4) (Kallen & Robert, 2000), Nova Scotia (chloroform ≥100 vs. <50 μg/L, OR = 1.5, 95% CI 0.8–2.8), (Dodds and King 2001) or Norway (chlorinated high color vs. nonchlorinated low color, OR = 0.90, 95% CI 0.52–1.58) (Hwang et al., 2002). A case-control study in California reported a statistically nonsignificant association between isolated cleft lip/palate and periconceptual drinking water THM levels with a nonmonotonic dose-response relationship (THM 50–74 vs. <1 μg/L, OR = 1.9, 95% CI 0.8–4.5) (Shaw et al., 2003b). Reviewers concluded that halogenated acetic acids and chloroform cause craniofacial defects in experimental animals (Graves et al., 2001; Nieuwenhuijsen et al., 2000).

Hazardous waste disposal sites Prenatal residential proximity, inadequate evidence: In a population-based case-control study, oral cleft defects were not associated with prenatal residential proximity to hazardous waste disposal sites (<1.6 vs. ≥1.6 km, OR = 1.15, 95% CI 0.87–1.51); there was a statistically nonsignificant elevated risk related to proximity to sites containing pesticides (OR = 1.27, 95% CI 0.84–1.92) (Geschwind et al., 1992).

In a population-based case-control study in California, there was no association between oral cleft defects and maternal periconceptual residential proximity to NPL sites (<1.6 vs. ≥1.6 km, OR = 1.0, 95% CI 0.5–2.3) or the subsets of sites containing lead heavy metals or solvents (Croen et al., 1997). A European case-control study reported a statistically nonsignificant elevated risk of cleft palate among women with prenatal residential proximity to hazardous waste landfill sites

(<3 vs. 3–7 km, OR = 1.63, 95% CI 0.77–3.41) (Dolk et al., 1998). In a large case-control study in California, there was no association between oral cleft defects and prenatal residence in a census tract with at least one NPL site containing solvents, pesticides or a category comprising PCBs, dioxins, and PAHs (Orr et al., 2002).

Incinerators Maternal exposure, inadequate evidence: In a large French retrospective cohort study, facial cleft defects were not associated with prenatal residence in a communities with solid waste incinerators or expert-rated potential for exposure to dioxin, metal or dust emissions (high vs. low hazard, OR = 1.01, 95% CI 0.64–1.59) (Cordier et al., 2004).

Solvents Maternal exposure, glycol ethers, limited evidence: In a multicenter European case-control study, cleft lip/palate was associated with maternal 1st trimester occupational exposure to glycol ethers (OR = 1.97, 95% CI 1.20–3.25) (Cordier et al., 1997). Further analysis of the European study, limited to subjects who worked during pregnancy, revealed associations between cleft lip/palate and 1st trimester maternal occupational exposure to glycol ethers (OR = 2.10, 95% CI 1.14–3.88) and other solvents (see later discussion) (Lorente et al., 2000). A recent large case-control study in California found a borderline association between cleft palate plus other defects and prenatal occupational exposure to glycol ethers and derivatives (OR = 2.2, 95% CI 0.8–7.0) (Shaw et al., 2003a).

Maternal exposure, chlorinated solvents, limited evidence: A retrospective cohort study in New Jersey revealed associations between oral cleft defects and 1st trimester maternal residence in communities served by drinking water with trichloroethylene levels above 10 μg/L (compared to ≤1 μg/L, OR = 2.24, 90% CI 1.16–4.20) or carbon tetrachloride levels above 1 μg/L (compared to ≤1 μg/L, OR = 3.60, 90% CI 0.75–12.5) (Bove et al., 1995). In a French case-control study, facial defects were associated with self-reported 1st trimester occupational exposure to solvents (any vs. none, OR = 1.62, 95% CI 1.04–2.52) including halogenated solvents (aliphatic, OR = 4.40, 95% CI 1.41–16.2; aromatic, OR = 1.78, 95% CI 0.89–3.54) (Laumon et al., 1996). Among subjects who worked during pregnancy, a European case-control study revealed a statistically nonsignificant elevated risk of cleft lip/palate related to 1st trimester maternal occupational trichloroethylene exposure (OR = 3.21, 95% CI 0.49–20.9, based on 4 exposed case and 2 exposed control mothers) (Lorente et al., 2000).

Maternal exposure, other and unspecified solvents, inadequate evidence: A hospital-based case-control study in France observed increased risk of oral cleft defects related to prenatal occupational solvent exposure (OR = 3.3, 90% CI 0.8–18.1) (Cordier et al., 1992). Combined analysis of 2 Californian case-control studies revealed no association between oral cleft defects and periconceptual maternal residence within 1 mile of a NPL site containing VOCs (OR = 0.8, 95% CI 0.4–1.8) (Croen et al., 1997). Among subjects who worked during pregnancy, a European case-control study revealed associations between cleft lip/palate and 1st trimester maternal occupational exposure to aliphatic alcohols (OR = 1.67, 95% CI 0.86–3.26) (Lorente et al., 2000). A recent large case-control study in California found a borderline association between isolated cleft palate and prenatal occupational exposure to aliphatic hydrocarbons (OR = 2.2, 95% CI 0.9–5.7) (Shaw et al., 2003a).

Paternal exposure, unspecified solvents, inadequate evidence: A Norwegian cohort study of offspring of male printers revealed an increased risk of cleft lip/palate (compared to other occupations, SIR = 1.6, 95% CI 0.97–2.5) (Kristensen et al., 1993).

Summary There is limited epidemiologic evidence for associations between orofacial birth defects and prenatal active smoking and occupational exposure to glycol ethers or chlorinated solvents.

Developmental Tooth Abnormalities

Natal teeth Maternal high-level PCB/PCDF exposure, sufficient evidence: Prenatal consumption of cooking oil contaminated with high levels of PCBs, PCDFs, and related toxicants in Taiwan was associated with natal teeth (prevalence, exposed vs. unexposed, 11/127 vs. 0/113, OR = ∞, 95% CI 3.0 to ∞) (Rogan et al., 1988). Further investigation revealed a dose-response relationship between a history of natal teeth and maternal serum PCB levels (0.0% among unexposed children; 5.3, 11.5, and 13.0% among those with increasing maternal serum PCB tertiles, p-trend = .003) (Wang et al., 2003a).

Maternal background PCB/PCDD/PCDF exposure, inadequate evidence: In a small Finnish cohort, natal teeth were not associated with breast milk TCDD-TEQ exposure from PCDDs/PCDFs or PCBs (cases vs. noncases, mean PCDD/PCDF-TEQ 11.9 vs. 8.6 pg/g milk lipid, $p = .11$; mean PCB-TEQ 7.2 vs. 5.3 pg/g milk lipid, $p = .31$) (Alaluusua et al., 2002).

Lactational PCB/PCDF exposure, inadequate evidence: Among Yucheng children, there was an irregular relationship between a history of natal teeth and breastfeeding duration (0.0% among unexposed children; 14.3% among forumula-fed Yucheng children and 0 and 10%, respectively, among Yucheng children breast-fed for shorter or longer periods, p-trend = .08) (Wang et al., 2003a).

Hypomineralized enamel and other developmental tooth defects Maternal high-level PCB/PCDF exposure, limited evidence: Prenatal consumption of cooking oil contaminated with high levels of PCBs, PCDFs, and related toxicants in Taiwan was associated with missing permanent tooth germ (exposed vs. unexposed, 5/18 vs. 1/44; OR = 16.5, 95% CI 1.6–411, calculated from data in paper) (Lan et al., 1989). Further investigation revealed a dose-response relationship between the prevalence at age 7–11 yr of other developmental tooth defects (fusion, microdontia, pigmentation, enamel hypoplasia, impaction) and maternal serum PCB levels (2.7% among unexposed children; 9.1, 11.5, and 24.0% among increasing maternal serum PCB tertiles, p-trend = .001) (Wang et al., 2003a).

Maternal background PCB exposure, inadequate evidence: A cross-sectional study of Slovenian children found a higher prevalence of enamel defects among residents of a PCB-contaminated region compared with those from a relatively uncontaminated region (22 vs. 13%, $p < .001$) (Jan & Vrbic, 2000). Unfortunately, this study did not assess the relationship between enamel defects and biomarkers of PCB exposure.

Maternal PCDD/PCDF/PCB-TEQ or TCDD exposure, inadequate evidence: A small Finnish cohort study (102 children) showed that hypomineralized enamel defects at age 6–7 yr were associated with total lactational TCDD-TEQ exposure from PCDDs/PCDFs and PCBs; the statistical significance was stronger for PCDD/PCDF-TEQ ($p = .004$) than for PCB-TEQ ($p = .07$); this short communication did not include other statistical data on the strength of these associations or potential confounders (Alaluusua et al., 1999). A small retrospective cohort study of persons exposed before age 10 yr to TCDD at Seveso revealed an association between developmental tooth enamel defects (opacities or hypoplasia) and serum TCDD at baseline soon after the incident (≥238 vs. <238 pg/g lipid, OR = 2.4, 95% CI 1.3–4.5) (Alaluusua et al., 2004).

Summary There is sufficient epidemiologic evidence that high-level prenatal exposure to PCBs, PCDFs, and related toxicants can produce developmental tooth abnormalities, including hypomineralized enamel defects of permanent teeth.

Musculoskeletal Birth Defects

Cadmium Maternal exposure, inadequate evidence: A Massachusetts case-control study reported no association between drinking water cadmium levels in the community of maternal residence at delivery and risk of musculoskeletal birth defects (OR = 0.9, $p > .05$) (Aschengrau et al., 1993).

TCDD Paternal occupational exposure, inadequate evidence: In a retrospective cohort study of Vietnam veterans and partners, there was no association between musculoskeletal birth defects and paternal serum TCDD levels categorized as low (current level >10 and initial level ≤110 pg/g lipid, OR = 1.08, 95% CI 0.72–1.60) or high (current level >10 and initial level >110 pg/g lipid, OR = 0.89, 95% CI 0.58–1.32, calculated from data in paper) (Wolfe et al., 1995).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study found an association between musculoskeletal birth defects and maternal residence in high-wheat counties, a proxy for agricultural chlorophenoxy herbicide use (high- vs. low-wheat counties, OR = 1.50, 95% CI 1.06–2.12) (Schreinemachers, 2003). There was also an association between such exposure and polydactyly/syndactyly (OR = 2.43, 95% CI 1.26–4.71) but not clubfoot (OR = 0.84, 95% CI 0.39–1.80).

Maternal exposure, unspecified herbicides, inadequate evidence: A case-control study in New York State reported no association between limb reduction defects and maternal residence in

counties with high agricultural herbicide use (high vs. low acres treated (1987 census), OR = 0.82, 95% CI 0.41–1.64 (Lin et al., 1994).

Maternal exposure, organophosphate insecticides, inadequate evidence: The San Francisco study observed a statistically nonsignificant association between limb defects and 1st trimester maternal residence in areas sprayed with malathion (OR = 1.73, 95% CI 0.87–3.46) (Thomas et al., 1992).

Maternal exposure, unspecified insecticides, inadequate evidence: A case-control study in New York State reported no association between limb reduction defects and maternal residence in counties with high agricultural insecticide use (high vs. low acres treated (1987 census), OR = 0.68, 95% CI 0.34–1.36 (Lin et al., 1994). In a California case-control study, limb reduction defects were associated with self-reported 1st trimester professional indoor insecticide application at the maternal residence (OR = 1.6, 95% CI 1.0–2.7) but not with pet flea insecticide use (OR = 0.9, 95% CI 0.6–1.4) (Shaw et al., 1999). Further analysis of this study revealed no association with periconceptual maternal occupational insecticide exposure (OR = 0.7, 95% CI 0.2–3.4, only 2 exposed case mothers) (Shaw et al., 2003a).

Maternal exposure, unspecified pesticides, inadequate evidence: Among women prenatally exposed to pesticides in Colombian semi-enclosed greenhouses, there was an elevated risk of congenital dislocated hip (crude OR = 2.90, 95% CI 1.19–6.99, calculated from data in paper) (Restrepo et al., 1990a). A retrospective cohort study in Minnesota observed increased risks of musculoskeletal defects in families (neither parent was a licensed pesticide applicator) living in regions with corn/soybean (compare to noncrop regions, OR = 1.36, 95% CI 1.18–1.58) or wheat/sugar beet/potato crops (OR = 1.75, 95% CI 1.37–2.22) (Garry et al., 1996). In a California case-control study, limb reduction defects were associated with self-reported 1st trimester professional (OR = 3.5, 95% CI 1.2–9.9) but not maternal application of garden pesticides (OR = 1.5, 95% CI 0.5–4.6, 5 exposed case mothers) (Shaw et al., 1999). Further analysis of this study revealed no association with prenatal residential proximity to crops treated with pesticides (OR = 1.0, 95% CI 0.6–1.8) or occupational exposure to insecticides or noninsecticide pesticides (OR = 0.7, 95% CI 0.3–1.9, only 5 exposed case mothers) (Shaw et al., 2003a). In a cohort study of women employed in agriculture in Washington State, limb reduction defect risk was elevated (compared to neither parent in agriculture, OR = 2.8, 95% CI 1.2–6.3) (Engel et al., 2000).

In a California case-control study, limb reduction defects were not associated with parental employment in agriculture (either parent vs. neither, OR = 0.9, 95% CI 0.4–1.7) but were related to intensity of restricted agricultural pesticide use in counties of maternal residence (high vs. minimal use, OR = 1.9, 95% CI 1.2–3.1, p-trend = 0.02) (Schwartz & LoGerfo, 1988). A case-control study in New York State reported no association between limb reduction defects and maternal occupations likely exposed to pesticides (OR = 0.7, 95% CI 0.4–1.5) or with maternal residence in counties with high per capita acreage in farms (high vs. low acreage, OR = 1.49, 95% CI 0.53–4.23, calculated from data in paper) (Lin et al., 1994). A Finnish case-control study revealed no association between skeletal defects and 1st trimester maternal employment in agriculture (OR = 0.8, 95% CI 0.4–1.7, only 3 exposed case mothers) (Nurminen et al., 1995). In New York State, musculoskeletal defects were not associated with maternal residence within 1.6 km of a hazardous waste disposal site known to contain pesticides (OR = 0.80, 95% CI 0.51–1.26) or a TRI industrial site known to emit pesticides into air (OR = 1.12, 95% CI 0.93–1.35) (Marshall et al., 1997). Another California case-control study, limited to racial or ethnic minority populations, revealed no association between musculoskeletal defects and prenatal residence in a census tract with a NPL site containing pesticides (OR = 1.19, 95% CI 0.92–1.54) (Orr et al., 2002). The inconsistent findings and the heterogeneous and nonspecific exposure indices and the variable scope and great heterogeneity of musculoskeletal defects preclude strong inferences.

Paternal occupational exposure, 2,4,5-T, inadequate evidence: A case-control study of musculoskeletal birth defects in Atlanta revealed no association with exposure to Agent Orange (based on self-reports and military records) (OR = 1.06, CI not reported) (Erickson et al., 1984). See also paternal occupational TCDD exposure discussed earlier.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: Among infants of women age 30 or older, musculoskeletal defects were associated with paternal occupation as licensed pesticide applicators in Minnesota (OR = 2.52, 95% CI 1.58–4.01); there was no association among offspring of younger mothers (OR = 0.94, 95% CI 0.52–1.71) (Garry et al., 1996). A case-control study in New York State found no association between limb reduction defects and paternal occupations likely exposed to pesticides (OR = 0.9, 95% CI 0.5–1.6) or the subgroup employed as farmers (OR = 1.1, 95% CI 0.5–2.7) (Lin et al., 1994). Limb reduction defect risk was not elevated among all infants in Norwegian farm families (OR = 0.84, 95% CI 0.51–1.37) but was elevated on all farms reporting pesticide expenditures during agricultural censuses (OR = 1.79, 95% CI 0.98–3.26) and the subgroup of grain farms with such expenditures (OR = 2.50, 95% CI 1.06–5.90) (Kristensen et al., 1997b). A retrospective cohort study of the general Norwegian population reported no association between limb reduction defects and paternal occupation in agriculture, based on birth certificates (OR = 0.89, 95% CI 0.56–1.33) (Irgens et al., 2000). A case-control study in California found no association between limb reduction defects and self-reported periconceptual paternal occupational pesticide exposure (OR = 1.2, 95% CI 0.6–2.2) (Shaw et al., 1999).

Outdoor air pollution Paternal occupational exposure, inadequate evidence: A large Norwegian retrospective cohort study reported no association between club foot and paternal occupation as drivers (OR = 0.94, 95% CI 0.79–1.10) (Irgens et al., 2000).

Drinking-water disinfection by-products Prenatal drinking-water DBP level, inadequate evidence: A large population-based case-control study in New York State found no association between musculoskeletal birth defects and drinking water THM levels (≥100 vs. <100 μg/L, OR = 0.76, 95% CI 0.61–0.95) (Marshall et al., 1997).

Drinking-water nitrate/nitrite Prenatal drinking-water DBP level, inadequate evidence: A case-control study in Australia reported an association between musculoskeletal defects and maternal drinking water source at birth (groundwater with nitrate generally >15 mg/L vs. surface water with nitrate <1 mg/L, OR = 2.9, 95% CI 1.2–8.0, adjusted for maternal age and parity but not other potential confounders) (Dorsch et al., 1984).

Hazardous waste disposal sites Maternal exposure, inadequate evidence: In a population-based case-control study in New York State, musculoskeletal defects were weakly associated with prenatal residential proximity to any hazardous waste disposal site (<1.6 vs. ≥1.6 km, OR = 1.16, 95% CI 1.06–1.26); the association was somewhat stronger for the subgroup of sites with a high exposure index, based on chemical toxicity and likelihood of exposure (high vs. no exposure, OR = 1.75, 95% CI 1.31–2.34) and for sites containing pesticides (OR = 1.20, 95% CI 1.05–1.38) (Geschwind et al., 1992). Subsequently, a similar study in New York State reported no association between musculoskeletal defects and prenatal residential proximity to NPL sites (<1.6 vs. ≥1.6 km, OR = 1.00, 95% CI 0.94–1.07, adjusted for proximity to TRI sites) (Marshall et al., 1997). A European case-control study reported an association between gastroschisis and maternal residential proximity to hazardous waste landfill sites (<3 vs. 3–7 km, OR = 3.19, 95% CI 0.95–10.8) (Dolk et al., 1998). A United Kingdom-wide retrospective cohort study revealed no association between abdominal wall defects and prenatal residential proximity to any of 774 hazardous waste sites (≤2 vs. >2 km, OR = 1.03, 95% CI 0.86–1.25) (Elliott et al., 2001). In a large case-control study in California, there were statistically nonsignificant elevated risks of musculoskeletal defects among women living in a census tract with at least 1 NPL site containing solvents, pesticides, or a category comprising PCBs, dioxins and PAHs (e.g., pesticides, OR = 1.19, 95% CI 0.92–1.54) (Orr et al., 2002). In a small Alaskan retrospective cohort study, musculoskeletal defects were associated with maternal residence in Native villages with hazardous waste sites (higher vs. lower hazard dumpsite, OR = 4.27, 95% CI 1.76–10.4) (Gilbreath & Kass, 2006a). Given the heterogeneity of musculoskeletal birth defects and exposure indices, it is difficult to draw firm conclusions from the few available epidemiologic studies.

Incinerators Maternal exposure, inadequate evidence: In a large French retrospective cohort study, limb reduction defects were not associated with prenatal residence in a communities with solid waste incinerators (OR = 0.78, 95% CI 0.51–1.20) (Cordier et al., 2004).

Solvents Prenatal occupational exposure, glycol ethers, inadequate evidence: In a multicentre European case-control study, musculoskeletal birth defects were weakly related to maternal 1st trimester occupational exposure to glycol ethers (OR = 1.32, 95% CI 0.85–2.05) (Cordier et al., 1997).

Maternal exposure, unspecified solvents, inadequate evidence: In a similar New York State study, there was no association between musculoskeletal defects and prenatal residential proximity to hazardous waste disposal sites containing solvents (<1.6 vs. ≥1.6 km, OR = 1.03, 95% CI 0.81–1.31) or TRI sites emitting solvents (<1.6 vs. ≥1.6 km, OR = 1.02, 95% CI 0.93–1.12) (Marshall et al., 1997).

Paternal occupational exposure, unspecified solvents, inadequate evidence: A hospital-based case-control study in France found no association between musculoskeletal defects and prenatal occupational solvent exposure (OR = 1.7, 90% CI 0.7–4.2) (Cordier et al., 1992). A Norwegian cohort study of offspring of male printers revealed no increased risk of clubfoot (compared to other occupations, SIR = 0.9, 95% CI 0.70–1.1) or other limb reduction defects (Kristensen et al., 1993).

Summary There inadequate epidemiologic evidence for associations between musculoskeletal birth defects and any of the environmental contaminants examined.

Urinary-Tract Birth Defects

TCDD Maternal exposure, inadequate evidence: A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities revealed that expert-rated hazard of incinerator emissions was associated with obstructive urinary tract defects (high vs. low exposure, OR = 1.93, 95% CI 0.94–3.93, *p*-trend = 0.07) but not with renal dysplasia (OR = 1.30, 95% CI 0.57–2.97) (Cordier et al., 2004).

Paternal occupational exposure, inadequate evidence: In a retrospective cohort study of Vietnam veterans and partners, urinary tract birth defects were associated with paternal serum TCDD levels categorized as low (OR = 1.97, 95% CI 0.70–4.97) or high (OR = 2.12, 95% CI 0.81–5.12) (calculated from data in paper)) (Wolfe et al., 1995). These findings preclude firm inferences as the odds ratios were not statistically significant (there were only 17 cases among the 3 exposure categories) and there was no testing or adjustment for potential confounders. A review concluded that early gestational exposure to relatively low doses of TCDD and dioxin-like chemicals can cause ureteral hyperplasia and hydronephrosis in experimental animals (Birnbaum, 1995).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: A retrospective cohort study of Minnesota and 3 adjacent states found no association between genitourinary defects and maternal residence in high-wheat regions, a proxy for chlorophenoxy herbicide exposure (high- vs. low-wheat rural counties, OR = 1.01, 95% CI 0.65–1.55) (Schreinemachers, 2003).

Paternal occupational exposure, 2,4,5-T, inadequate evidence: See also paternal occupational TCDD exposure discussed earlier.

Paternal occupational exposure, unspecified pesticides, limited evidence: Among offspring of male licensed pesticide applicators in Minnesota, there was an increased risk of urogenital birth defects compared to the general population (OR = 1.69, 95% CI 1.06–2.64) (Garry et al., 1996). This study also found increased risks of these defects among offspring of women living in high-crop regions of Minnesota (high corn/soybean vs. noncrop regions, OR = 1.56, 95% CI 1.29–1.89; high wheat/sugar beet/potato regions, OR = 2.25, 95% CI 1.67–3.03). A cohort study of Norwegian farm families reported an association between kidney and other urinary tract birth defects and pesticide expenditures on farms with orchards and/or greenhouses (OR = 2.94, 95% CI 1.19–7.29); there was no increased risk of such defects among all farm families (OR = 0.82, 95% CI 0.53–1.27) (Kristensen et al., 1997b). The heterogeneity of exposure indices precludes firm conclusions.

Outdoor air pollution Maternal exposure, inadequate evidence: A retrospective cohort study in France reported an association between obstructive urinary tract defects and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 2.10, 95% CI 0.94–4.70, *p*-trend = .07) and an elevated risk of renal dysplasia (OR = 1.75, 95% CI 0.73–4.20) (Cordier et al., 2004).

Drinking-water disinfection by-products Prenatal drinking-water DBP level, limited evidence: Reviewers noted limited epidemiologic evidence for an association between urinary tract birth defects and THM levels (Bove et al., 2002). Combined analysis of studies in Massachusetts and Norway (Aschengrau et al., 1993; Magnus et al., 1999) indicated an association (summary

OR = 2.27, 95% CI 1.34–3.85) (Hwang & Jaakkola, 2003). In a Swedish retrospective cohort study, maternal residence in communities using chlorinated drinking water was not associated with hypospadias (hypochlorite-treated vs. unchlorinated water, OR = 1.1, 95% CI 0.6–2.0) or major kidney malformations (OR = 1.4, 95% CI 0.7–3.0) (Kallen & Robert, 2000). Haloacetonitriles produce urogenital defects in experimental animals (Graves et al., 2001).

Incinerators Maternal exposure, inadequate evidence: In a large French retrospective cohort study, renal dysplasia was associated with prenatal residence in communities with solid waste incinerators (OR = 1.55, 95% CI 1.10–2.20) but not with expert-rated potential for exposure to dioxin, metal, or dust emissions (high vs. low hazard, OR = 1.30, 95% CI 0.57–2.97) (Cordier et al., 2004). This study also found borderline associations between obstructive urinary tract birth defects and prenatal residence in communities with solid waste incinerators (OR = 1.22, 95% CI 0.90–1.65) and expert-rated potential for exposure to dioxin, metal, or dust emissions (high vs. low hazard, OR = 1.93, 95% CI 0.94–3.93) (Cordier et al., 2004).

Solvents Maternal exposure, glycol ethers, inadequate evidence: In a multicenter European case-control study, urinary tract defects were not associated with maternal 1st trimester occupational exposure to glycol ethers (OR = 1.25, 95% CI 0.59–2.63) (Cordier et al., 1997).

Maternal exposure, unspecified solvents, inadequate evidence: A hospital-based case-control study in France found no association between urinary tract defects and prenatal occupational solvent exposure (OR = 1.1, 90% CI 0.2–5.2) (Cordier et al., 1992).

Summary There is limited epidemiologic evidence for an association between male urinary-tract birth defects and prenatal exposure to drinking water DBPs.

Male Genital Birth Defects A recent systematic review of epidemiological studies for evidence linking indicators of prenatal serum levels of maternal estrogen with hypospadias and cryptorchidism found no strong evidence to indicate that prenatal exposure to estrogens (including some environmental exposures) was linked to disturbed development of the male reproductive organs (Storgaard et al., 2006).

PCBs Maternal exposure, inadequate evidence: A small German case-control study observed no association between cryptorchidism and infant adipose tissue PCB levels (median concentrations, cases vs. controls, 558 vs. 561 μg/kg lipid, $p > 0.05$) (Hosie et al., 2000).

TCDD Maternal exposure, inadequate evidence: A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between hypospadias and expert-rated hazard of incinerator emissions (high vs. low exposure, OR = 1.12, 95% CI 0.53–2.35, *p*-trend > .05) (Cordier et al., 2004).

Paternal exposure, 2,4,5-T or chlorophenate wood preservatives, inadequate evidence: In a retrospective cohort study of Vietnam veterans, genital tract birth defects were not associated with paternal serum TCDD levels categorized as low or high (OR = 1.66, 95% CI 0.41–6.10) calculated from data in paper) (Wolfe et al., 1995). Among British Columbia sawmill workers exposed to chlorophenate wood preservatives known to be contaminated with TCDD and related toxicants, genital-tract defects were weakly associated with hours of exposure during the 3 preconceptual months (75^{th} vs. 25^{th} percentile, OR = 1.29, 95% CI 0.9–1.5) (Dimich-Ward et al., 1996).

Pesticides Maternal exposure, chlorophenoxy herbicides, inadequate evidence: In a population-based case-control study in Arkansas, hypospadias (cases identified from statewide registry) was associated with agricultural use of the herbicide diclofop-methyl within 0.5 km of the maternal residence during GW 6–16, the window of genital-tract development (≥0.3 vs. 0 lb active ingredient, OR = 2.33, 95% CI 1.02–5.31) (Meyer et al., 2006).

Maternal exposure, other herbicides, inadequate evidence: The Arkansas study found no association between hypospadias and use within 0.5 km of the maternal residence during GW 6–16 of alachlor (>0 vs. 0 lb, OR = 0.56, 95% CI 0.35–0.89), atrazine (≥3.6 vs. 0 lb, OR = 1.02, 95% CI 0.58–1.79), dicamba (≥0.04 vs. 0 lb, OR = 0.91, 95% CI 0.38–2.14), trifluralin (>8.5 vs. 0 lb, OR = 0.60, 95% CI 0.23–1.56), or diuron (>0 vs. 0 lb, OR = 0.78, 95% CI 0.37–1.62) (Meyer et al., 2006).

Maternal exposure, DDT/DDE, inadequate evidence: In a case-control study nested within the U.S. Collaborative Perinatal Project pregnancy cohort, 3rd trimester maternal serum DDE levels

were not associated with cryptorchidism (per natural log serum DDE (μg/g lipid) increment, OR = 1.07, 95% CI 0.97–1.18) or hypospadias (OR = 1.01, 95% CI 0.90–1.16) (Longnecker et al., 2002). There was no association in a Mexico City case-control study between cryptorchidism and maternal plasma DDE (>840 vs. ≤840 μg/g lipid, OR = 0.48, 95% CI 0.15–1.60) or DDT levels (≥50 vs. <50 μg/g lipid, OR = 1.13, 95% CI 0.24–5.29 (Flores-Luevano et al., 2003). A case-control study nested within a California pregnancy cohort enrolled during 1959–1967 (when population serum DDT/DDE levels were much higher than recently) revealed no association between cryptorchidism and prenatal serum DDE (4th vs. 1st quartile, OR = 1.34, 95% CI 0.51–3.48, *p*-trend = .75) or DDT (OR = 1.01, 95% CI 0.44–2.28, *p*-trend = .38) (Bhatia et al., 2005). This study also found no association between hypospadias and maternal serum DDE (OR = 1.18, 95% CI 0.46–3.02, *p*-trend = .82) or DDT (OR = 0.79, 95% CI 0.33–1.89, *p*-trend = .30). A Finnish/Danish case-control study of cryptorchidism reported higher median breast milk DDT plus DDE concentrations in case compared to control mothers (140.4 vs. 116.3 ng/g lipid, p = .27) (Damgaard et al., 2006). A small German case-control study reported a statistically nonsignificant relationship between cryptorchidism and infant adipose tissue *p,p'*-DDE levels (median concentrations, cases vs. controls, 265 vs. 170 μg/kg lipid, $p > .05$) (Hosie et al., 2000). DDE and other androgen receptor antagonists (vinclozolin, procymidone, linuron) produce feminization of prenatally exposed male rats with reduced anogenital distance and induced areolas at low doses and hypospadias, retained nipples, undescended testes, and epididymal agenesis at higher doses (Gray et al., 2001).

Maternal exposure, other organochlorine insecticides, inadequate evidence: A small German case-control study observed associations between cryptorchidism and infant adipose tissue heptachlor (median concentrations, cases vs. controls, 5.2 vs. 2.4 μg/kg lipid, $p = .01$) and HCB levels (61 vs. 20 μg/kg lipid, p = .01) (Hosie et al., 2000). The Finnish/Danish case-control study revealed higher median breast milk levels for 17 of 21 organochlorine pesticides in case compared to control mothers with differences being statistically significant for *trans*-chlordane (but not oxychlordane) and of borderline significance for HCB and α-endosulfan (Damgaard et al., 2006).

Maternal exposure, other insecticides, inadequate evidence: The Arkansas study found no association between hypospadias and use within 0.5 km of the maternal residence during GW 6–16 of carbaryl (>0 vs. 0 lb, OR = 0.80, 95% CI 0.20–3.18) or permethrin (>0 vs. 0 lb, OR = 0.37, 95% CI 0.16–0.86) (Meyer et al., 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: Infants of women occupationally exposed to pesticides in Colombian semi-enclosed greenhouses had an elevated risk of cryptorchidism (OR = 5.08, 95% CI 1.67–15.7) (Restrepo et al., 1990a). In a hospital-based case-control study in Spain, there was a dose-response relationship between cryptorchidism and expert-rated agricultural pesticide use intensity near the maternal residence (low vs. no use, OR = 0.93, 95% CI 0.43–2.01; medium use, OR = 1.56, 95% CI 0.72–3.38; high use, OR = 2.32, 95% CI 1.26–4.29) (Garcia-Rodriguez et al., 1996). In a very large Danish case-control study, maternal occupation in farming or gardening was associated with cryptorchidism (OR = 1.36, 95% CI 1.05–1.77) but not hypospadias (OR = 0.90, 95% CI 0.42–1.92) (Weidner et al., 1998). In a small Sicilian case-control study, self-reported prenatal occupational or domestic pesticide exposure was related to a statistically nonsignificant elevated risk of cryptorchidism (OR = 2.74, 95% CI 0.72–10.4) but not hypospadias (OR = 0.42, 95% CI 0.05–3.56) (Carbone et al., 2007). Although suggestive, the heterogeneity of exposure indices and inconsistent findings precludes firm conclusions.

A proportional birth prevalence study in the United Kingdom revealed no association between hypospadias and maternal occupations likely exposed to pesticides (OR = 0.84, 95% CI 0.50–1.41) (Vrijheid et al., 2003). A retrospective cohort study in four Midwest states found no association between male genital tract defects and prenatal residence in high-wheat counties, a proxy for chlorophenoxy herbicide exposure (high- vs. low-wheat counties, OR = 1.03, 95% CI 0.51–2.09) (Schreinemachers, 2003). In the Arkansas case-control study noted above, hypospadias was not associated with total agricultural pesticide use within 0.5 km of the maternal residence during GW 6–16 (per 0.5 lb pesticide active ingredient, OR = 0.82, 95% CI 0.70–0.96) (Meyer et al., 2006).

Paternal exposure, 2,4,5-T or chlorophenate wood preservatives, inadequate evidence: See also paternal occupational TCDD exposure discussed earlier.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: As noted earlier, a study of male licensed pesticide applicators in Minnesota reported an increased risk of urogenital birth defects compared to the general population but did not include data for urological and genital defects separately (Garry et al., 1996). Among Norwegian farm families, cryptorchidism was associated with pesticide expenditure (yes/no, OR = 1.70, 95% CI 1.16–2.50); the association was somewhat stronger for pesticide purchases on the subset of farms with field vegetables (OR = 2.32, 95% CI 1.34–4.01) (Kristensen et al., 1997b). The latter study also reported associations between hypospadias and tractor spray equipment (OR = 1.38, 95% CI 0.95–1.99) and the use of such equipment on farms with grain crops (OR = 1.51, 95% CI 1.00–2.26). In a case-control study in the Netherlands, paternal employment in occupations with likely pesticide exposure was associated with cryptorchidism (OR = 3.8, 95% CI 1.1–13.4) (Pierik et al., 2004).

In a very large Danish case-control study, paternal occupation in farming or gardening was not associated with cryptorchidism (OR = 1.08, 95% CI 0.94–1.23) or hypospadias (OR = 1.15, 95% CI 0.83–1.58) (Weidner et al., 1998). A record-based retrospective cohort study in Norway revealed no association between hypospadias and paternal occupation in agriculture (OR = 0.68, 95% CI 0.34–1.23) (Irgens et al., 2000). A Sicilian case-control study revealed a statistically nonsignificant association between cryptorchidism and self-reported preconceptual paternal employment in agriculture (OR = 2.45, 95% CI 0.63–9.59) but not with probable preconceptual pesticide exposure based on job title (OR = 0.60, 95% CI 0.21–1.74) (Carbone et al., 2007). This study also revealed no association between hypospadias and paternal employment in agriculture (OR = 1.61, 95% CI 0.29–9.01) or likely pesticide exposure (OR = 1.07, 95% CI 0.42–2.73).

Outdoor air pollution Maternal exposure, inadequate evidence: A retrospective cohort study in France observed no association between hypospadias and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 1.33, 95% CI 0.59–3.01) (Cordier et al., 2004).

Hazardous waste disposal sites Maternal exposure, inadequate evidence: A European case-control study reported an association between hypospadias and maternal residential proximity to hazardous waste landfill sites (<3 vs. 3–7 km, OR = 1.96, 95% CI 0.98–3.92) (Dolk et al., 1998). A United Kingdom-wide retrospective cohort study revealed a weak association between NTDs and prenatal residential proximity to any of 774 hazardous waste sites (≤2 vs. >2 km, OR = 1.11, 95% CI 1.03–1.21) (Elliott et al., 2001). A similar study limited to Scotland also found no association (≤2 vs. >2 km from any of 61 sites, OR = 0.84, 95% CI 0.58–1.22) (Morris et al., 2003).

Incinerators Maternal exposure, inadequate evidence: In a French retrospective cohort study, hypospadias was not associated with prenatal residence in communities with solid waste incinerators (OR = 0.88, 95% CI 0.66–1.19) or expert-rated potential for exposure to dioxin, metal or dust emissions (high vs. low hazard, OR = 1.12, 95% CI 0.53–2.35) (Cordier et al., 2004).

Solvents Paternal occupational exposure, inadequate evidence: A Norwegian cohort study of offspring of male printers revealed no increased risk of cryptorchidism (compared to other occupations, SIR = 0.6, 95% CI 0.36–1.0) or hypospadias (OR = 1.0, 95% CI 0.48–1.7) (Kristensen et al., 1993).

Phthalates Maternal exposure, inadequate evidence: In a pregnancy cohort study, there was a dose-response relationship between reduced anogenital index (anogenital distance divided by weight at examination, an indicator of incomplete masculinization) among male infants age 2–36 mo and prenatal urinary phthalate metabolite levels (e.g., mono-*n*-butyl phthalate ≥75th vs. <25th percentile, OR = 10.2, 95% CI 2.54–42.2) (Swan et al., 2005). Other associations included monobenzyl phthalate (OR = 3.8, 95% CI 1.03–13.9), monoethyl phthalate (OR = 4.7, 95% CI 1.2–17.4), and monoisobutyl phthalate (OR = 9.1, 95% CI 2.3–35.7). The median maternal urinary concentrations of phthalate metabolite concentrations associated with reduced anogenital index were below the U.S. 25th percentile for women. Although this was a well-designed study, the findings require confirmation before a higher level of evidence can be assigned. Several phthalates disrupt male genital-tract development in offspring of experimental animals exposed during pregnancy (Foster, 2006).

Summary There was inadequate epidemiologic evidence for associations between male genital birth defects and exposure to the environmental contaminants examined here.

Neuropsychological Deficits

Although population-based statistics for neuropsychological deficits are not routinely available, surveys indicate that several hundred thousand U.S. children have disabling childhood mental health conditions including mental retardation, learning disabilities, autism, and attention deficit hyperactivity disorder (ADHD) (Halfon & Newacheck, 1999). An expert panel estimated that 10% of neurobehavioral disorders (dyslexia, ADHD, autism, cognitive deficits, and mental retardation) are attributable to environmental contaminants (National Academy of Sciences, 2000b). The complex changes underlying brain growth and development during pregnancy and childhood confer unique susceptibility to neurotoxins such as lead and methylmercury (MeHg) (Clarkson 2002; Mendola et al., 2002; National Academy of Sciences, 2000c; Newland, 2002). The level of epidemiologic evidence for associations between developmental milestones, cognitive function and problem behaviors and environmental factors is summarized in Table 3.

Developmental Milestones

Lead Prenatal or childhood exposure, inadequate evidence: A large cross-sectional study (based on NHANES II) reported an association between delayed onset of sitting, speaking and walking and ranked order of current blood lead levels (Schwartz & Otto, 1987). The authors stated that childhood blood lead levels reflect both prenatal and postnatal exposure.

Methylmercury In the following discussion, high-level MeHg exposure refers to doses sufficient to cause clinical symptoms of poisoning in mothers and/or infants (as during Minamata and Iraq episodes). Low-level exposure refers to background sources not linked to overt signs of poisoning and does not imply low risk or safety.

High-level maternal exposure, sufficient evidence: Follow-up of 16 infants with congenital MeHg poisoning at Minamata revealed that most could not understand maternal speech or walk at age 3 yr; only half could walk alone and all had speech impairment at age 9–14 yr (Harada 1977). Among children prenatally exposed to high doses of MeHg in Iraq, maternal hair mercury levels were associated with delayed motor development and speech (Amin-Zaki et al., 1981). A WHO expert panel (Marsh et al., 1981, 1987) concluded that extrapolation of the Iraqi data suggested the

TABLE 3. Role of Environmental Toxicants in Developmental Milestones, Cognitive Function, and Problem Behaviors

Toxicant	Exposure	Developmental milestones	Cognitive function age 0–2 yr	Cognitive function age ≥3 yr	Problem behaviors
Lead	Prenatal	I	**L**	**L**	
	Childhood	I	**L**	High-level—S Low-level—**S**	**L**
Methylmercury	Prenatal	High-level—**S** Low-level—I	High-level—**S** Low-level—I	High-level—**S** Low-level—**L**	I
	Childhood	High-level—**L**		I	I
Arsenic	Childhood			I	
Manganese	Prenatal			I	
	Childhood			I	
PCBs	Prenatal	High-level—**L**	High-level—**S** Low-level—**L**	High-level—**S** Low-level—**L**	High-level—**L**
	Lactational		I	**L**	
DDT/DDE	Prenatal		I	I	
	Lactational		I	I	
Organophosphate insecticides	Childhood			I	
Other herbicides	Paternal				I
Environmental tobacco smoke	Prenatal				I
	Childhood			**L**	**L**
Unspecified solvents	Prenatal			I	

Note. TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

potential for increased risk of delayed developmental milestones at prenatal hair mercury levels as low as 10–20 μg/g (World Health Organization 1990), a view shared by subsequent reviewers (Clarkson, 2002; Newland, 2002).

Low-level maternal exposure, inadequate evidence: Extrapolation of dose-response data from the Iraqi MeHg poisoning incidents indicates that neurodevelopmental milestone delay during infancy may occur at prenatal hair mercury levels as low as 10 μg/g (Cox et al., 1989). However, direct observation of populations with maternal hair mercury levels in the range of about 1–40 μg/g have yielded generally negative results. A birth cohort study in the Faroe Islands observed no association between age at milestone development and prenatal hair (geometric mean 4.5 μg/g; 85th percentile 10 μg/g) or cord blood mercury levels (finding stated without supporting data), although early milestone development was associated with infant hair mercury level at age 12 mo (e.g., age at sitting, Spearman $r = -.10$, $p = .01$) (Grandjean et al., 1995). Infant hair mercury at age 1 yr was associated with breast-feeding duration, a predictor of early milestone attainment in this study. The Faroe Islands study did not adjust for potential confounders such as maternal smoking. A small birth cohort study in Peru reported no association between age at milestone development and prenatal hair mercury levels (geometric mean 7.1 μg/g, range 0.9–29) (Marsh et al., 1995). In the Seychelles Islands birth cohort study, age at walking was associated with maternal hair mercury levels (range 0.5–27 μg/g) in boys but not girls; age at talking was not associated with maternal hair mercury (Axtell et al., 1998; Myers et al., 1997). The Peruvian and Seychelles studies only reported data on *p*-values, not strength of associations.

High-level childhood exposure, limited evidence: Follow-up of 12 Iraqi infants postnatally exposed to MeHg mainly through breast-feeding revealed that 4 had delayed motor milestones (ages at sitting, standing, walking) and 8 had delayed language development (i.e., they did not respond to simple verbal communication by age 2 yr even though hearing was not impaired) (Amin-Zaki et al., 1981). The range of prenatal hair mercury concentrations was 2–384 μg/g and 40% of infants had blood mercury ≥400 μg/L.

PCBs High-level maternal exposure, limited evidence: Compared to unexposed children, prenatally exposed Yucheng children were delayed on many of 32 developmental milestones and experienced psychomotor and cognitive deficits at older ages (Guo et al., 2004).

Summary Epidemiologic evidence for the role of environmental toxicants in delayed developmental milestones includes: (a) sufficient—high-level prenatal MeHg exposure; (b) limited—high-level childhood MeHg exposure, high-level prenatal exposure to PCBs, PCDFs, and related toxicants.

Cognitive Function: Children Age 0–2

Lead Maternal exposure, limited evidence: Several birth cohort studies found inverse dose-response relationships between Bayley's Mental Development Index (Bayley MDI) scores during infancy and prenatal or cord blood lead levels adjusted for potential confounders (Bellinger et al., 1984, 1988; Gomaa et al., 2002; Shen et al., 1998; Wasserman et al., 1992). The Sydney and Port Pirie birth cohort studies reported no association between Bayley MDI at age 2 and prenatal or cord blood lead (Cooney et al., 1989a; Wigg et al., 1988). In the Cincinnati birth cohort study, prenatal blood lead was inversely associated with Bayley MDI at age 6 mo per log maternal blood lead increment, ($\beta = -5.91 \pm 2.68$) but not at age 2 ($\beta = 3.30 \pm 1.71$) (Dietrich et al., 1990). In the Oswego birth cohort study (consumers of Lake Ontario sports-caught fish), Fagan intelligence test scores at ages 6 and 12 mo were not associated with cord blood lead levels (Darvill et al., 2000; Stewart et al., 2000). However, a recent small birth cohort study in Atlanta reported an apparent inverse association between Fagan intelligence scores at age 7 mo and very low prenatal blood lead levels (all were below 5 μg/dl) (difference in mean maternal blood lead, 15th vs. 85th percentile Fagan Scores, 0.94 ± 0.26 (SD) vs. 0.44 ± 0.15 μg/dl, $t = 5.77$, $p < .001$) (Emory et al., 2003). After adjustment for other prenatal and postnatal lead concentrations, the strongest lead exposure predictor of Bayley MDI at age 2 yr in a Mexico City birth cohort was 1st trimester maternal blood lead (change in Bayley MDI per 1 SD of $\log_e$ lead concentration, $\beta = -3.5$, $p = 0.03$, there was also a statistically non-significant inverse relationship with 1st trimester maternal plasma lead concentration ($\beta = -2.4$, $p = 0.19$).

Postnatal exposure, limited evidence: Three of 4 major birth cohort studies reported associations between Bayley MDI scores before age 3 yr and postnatal blood lead levels. The Boston birth cohort study reported an inverse association between Bayley MDI scores at age 2 yr and blood lead levels at ages 6–24 mo (Bellinger et al., 1988). In the Port Pirie birth cohort study, Bayley MDI scores at age 2 yr were inversely associated with blood lead levels (μg/dl) at age 6 mo ($\beta = -0.16$, $p = .07$) but not with levels at birth or ages 15 or 24 mo (Wigg et al., 1988). Bayley MDI scores at age 2 yr were inversely associated with current blood lead levels in the Yugoslavia birth cohort study (MDI vs. log current blood lead, $\beta = -5.31 \pm 2.44$) (Factor-Litvak et al., 1999; Wasserman et al., 1992). In a Mexico City birth cohort study, Bayley MDI scores at age 2 yr were inversely associated with natural log current blood lead ($\beta = -1.04$, $p < .01$) (Tellez-Rojo et al., 2006) (see also maternal exposure discussed earlier). In the Cincinnati birth cohort study, Bayley MDI scores at age 24 mo were favourably associated with both prenatal and postnatal blood lead (change in MDI per log current blood lead increment, $\beta = 3.20 \pm 1.70$) (Dietrich et al., 1990). A small cross-sectional study in New York City found Bayley scale deficits among children age 12–36 mo with current blood lead levels at least 10 μg/dL (compared to <10 μg/dL, $\beta = -6.2$, 95% CI –10.8, –1.7) (Mendelsohn et al., 1998).

Methylmercury High-level prenatal exposure, sufficient evidence: Among 15 mother–infant pairs with high prenatal exposures during the 1972 Iraq MeHg poisoning episode, 40% (6 mothers, 6 infants) had clinically obvious neurotoxicity when examined less than 1 mo after exposure ended (Amin-Zaki et al., 1974a). Severe manifestations included less than 3rd percentile head circumference (3 infants), total blindness (4), and severe hearing deficit (4). Most infant blood mercury levels exceeded 200 μg/L; the blood mercury range among the 6 infants with severe neurotoxicity was 564–4220 μg/L. Repeat measurements indicated that infant blood mercury levels were about twice those of their mothers at delivery and during follow-up to age 6 mo. When reexamined at age 1–7 yr, 22 Japanese children with high prenatal MeHg exposure (neonatal Minamata disease) all had abnormal chewing, swallowing, speech, gait, and coordination, and most had abnormal tendon reflexes and involuntary movements (Harada, 1977). Among 9 Minamata cases examined at age 3 yr, 6 children were unable to walk alone and 3 had no head control or ability to sit without support. Several literature reviews concluded that high-level prenatal MeHg exposure causes severe neurotoxic effects in infants, including mental retardation (Clarkson, 2002; Harada, 1978, 1995; Harada et al., 1999; Myers & Davidson, 2000; Myers et al., 1998, 2000; National Academy of Sciences, 2000c; United Nations Environment Programme, 2002).

Low-level maternal exposure, inadequate evidence: Three of 5 birth cohort studies reported no association between neuropsychological test scores before age 3 yr and prenatal mercury exposure indices in populations potentially exposed through consumption of marine or fresh water fish. Among infants of Seychellois women with hair mercury levels greater than 12 μg/g compared to 3 μg/g or lower, mean Fagan visual recognition memory scores at age 6 mo were virtually identical (60.5 ± 7.8 vs. 60.8 ± 7.6) (Myers et al., 1995). Similarly, there was no association between maternal hair mercury and Bayley MDI scores at 19 or 29 mo (Davidson et al., 1995). Among infants of women who consumed Great Lakes fish, Fagan test scores of infant IQ at ages 6 and 12 mo were not associated with maternal hair mercury levels (e.g., at age 12 mo, $r = 0.05$, $p = .42$) (Darvill et al., 2000). In the Avon Longitudinal Study of Parents and Children birth cohort study, MacArthur Communicative Development Inventory and Denver Developmental Screening Test subscale scores at age 15 mo were not associated with umbilical cord tissue mercury levels (e.g., change in vocabulary comprehension score per quartile change in umbilical cord tissue mercury, $\beta = 6.1 \pm 24.1$[SE], $p = .80$) (Daniels et al., 2004). In a pregnancy cohort study in Massachusetts, there was an inverse dose-response relationship between visual recognition memory novelty preference scores at age 6 mo and 3rd trimester maternal hair mercury levels, independent of prenatal fish consumption and several other potential confounders (change in score per unit change in maternal hair mercury [μg/g], $\beta = -7.5$, 95% CI –13.7 to –1.2) (Oken et al., 2005). A pregnancy cohort study of nonsmoking women in Poland reported inverse associations between Bayley MDI or psychomotor development index (PDI) scores below 85 at age 1 yr and cord blood mercury (≥ median vs. < median, OR = 3.58, 95% CI 1.40–9.14) and maternal blood mercury

levels (OR = 2.82, 95% CI 1.17–6.79); note—this study did not report data for Bayley MDI and PDI separately (Jedrychowski et al., 2006).

PCBs High-level maternal exposure, sufficient evidence: Compared to unexposed children, Yucheng children had a statistically nonsignificant Bayley MDI score deficit at ages 6–30 mo (difference in mean Bayley MDI 6.0 points, $t = 1.67$, $p = .10$; t and p calculated from data in paper) (Rogan et al., 1988). A WHO expert group concluded that high-level prenatal exposure to PCBs, PCDFs, and related compounds caused childhood cognitive deficits and persistent global developmental delays, mild behavior disorders, and hearing deficits (Brouwer et al., 1998; World Health Organization, 2000).

Low-level maternal exposure, limited evidence: In the Michigan cohort, the Fagan test of visual recognition memory at 7 mo was inversely associated with cord serum PCB levels (change in MDI score per unit change in cord serum PCB, $\beta = -0.35$ points, $F(1,76) = 10.2$, $p < .005$) (Jacobson et al., 1985). The authors stated that, unlike the Bayley MDI, the Fagan test during infancy is predictive of childhood cognitive function, likely because it measures visual discrimination and short-term memory, which are essential for information processing (Jacobson & Jacobson, 1996a). In the North Carolina birth cohort, Bayley MDI scores at ages 6 and 12 mo were not associated with breast milk PCB levels (change in MDI score at age 12 mo per unit change in breast milk PCB at birth [μg/g lipid], $\beta = -0.54 \pm 0.54$(SD), $p = .32$) (Gladen et al., 1988). A birth cohort study in the Netherlands revealed a favourable but statistically nonsignificant relationship between Bayley MDI scores at age 7 mo and maternal plasma PCB (sum of 4 noncoplanar congeners) (change in MDI per natural log increment of maternal plasma PCB, $\beta = 2.3 \pm 1.7$, $p = .18$) (Koopman-Esseboom et al., 1996). In a German birth cohort, Bayley MDI at age 7 mo was inversely associated with breast milk PCB concentrations at 2 and 4 wk after delivery (change in MDI per unit change in breast milk PCB, $\beta = -0.69 \pm 0.41$(SE), $p = .05$) but not with cord plasma PCB (change in MDI per unit change in cord plasma PCB, $\beta = 0.06 \pm 0.38$(SE), $p = .43$) (Winneke et al., 1998). In the Oswego birth cohort, Fagan Test of Infant Intelligence scores at ages 6 and 12 mo were not associated with breast milk total PCBs (change in Fagan test score at age 12 mo per unit change in breast milk PCB, $\beta = -0.075$ points, $t = -0.51$, $p = .30$); this study did not assess cumulative lactational PCB exposure (Darvill et al., 2000). However, the latter study observed inverse relationships between Fagan scores and cord blood total PCBs (change in Fagan test score at age 12 mo per unit change in cord blood PCB, $F(1,207) = 2.04$, $p = .08$) and cord blood highly chlorinated PCBs (change in Fagan test score at age 12 mo per unit change in cord blood highly chlorinated PCB, $F(1,207) = 4.08$, $p = .02$); the study did not report β values for the latter analyses). In a German birth cohort, breast milk PCB concentrations about 2 wk postpartum were inversely associated with Bayley MDI scores at 7, 18, or 30 mo (change in MDI scores at age 7, 18, or 30 mo per $\log_2$ breast milk PCB increment, $\beta = -4.19$, $t = -1.99$, $p = .025$) (Walkowiak et al., 2001). Further analysis showed that compared to infants of mothers in the 5th percentile of breast milk PCBs (≤173 ng/g lipid), infants of mothers in the 95th percentile (≥679 ng/g lipid) had an average MDI score deficit of 8.3 points (95% CI 0.0 to 16.5). In the U.S. Collaborative Perinatal Project birth cohort, Bayley MDI scores at age 7–10 mo were not associated with 3rd trimester maternal serum PCB levels (change in MDI score at age 8 mo per unit increase in maternal serum PCB (μg/L), $\beta = 0.10 \pm 0.26$(SE), $p = .71$) (Daniels et al., 2003).

Low-level lactational exposure, inadequate evidence: In the Michigan cohort, the Fagan test of visual recognition memory at 7 mo was not associated with lactational PCB exposure (β not stated, $F(3,80) = 1.18$, $p > .05$) (Jacobson et al., 1985). In the North Carolina cohort, Bayley MDI scores at 6 and 12 mo were not associated with cumulative lactational PCB exposure from birth to age at test (change in MDI score at age 12 mo per 1 mg cumulative breast milk PCB intake, $\beta = -0.06 \pm 0.16$(SE), $p = .70$; this study did not include the Fagan test (Gladen et al., 1988). In the Dutch cohort, Bayley MDI at age 18 mo was not associated with lactational PCB exposure (result stated without supporting data) (Koopman-Esseboom et al., 1996). The Oswego birth cohort study reported no association between Fagan Test of Infant Intelligence scores at ages 6 and 12 mo and PCB levels in breast milk samples collected at 1–3 mo postpartum, an index of postnatal exposure (Darvill et al., 2000). In the German birth cohort, cumulative lactational PCB dose was not associated with Bayley MDI scores at 7, 18 or 30 mo (result stated without supporting data) (Walkowiak et al., 2001).

Pesticides Maternal exposure, DDT/DDE, inadequate evidence: In a North Carolina birth cohort study, there was a favorable relationship between Bayley MDI scores at age 6 mo and breast milk DDE levels ($\beta = 0.65 \pm 0.22$, $p = .004$); Bayley MDI scores at age 12 mo were not associated with breast milk DDE levels (Gladen et al., 1988). A birth cohort study in New York State (offspring of women who consumed Lake Ontario fish) reported an inverse association between cord serum DDE and Bayley MDI scores at age 12 mo ($r = -.14$, $p = .3$) but not at age 6 mo ($r = -.09$, $p = .18$); there was no adjustment for potential confounders (Darvill et al., 2000). In a small Spanish birth cohort study in the region of an organochlorine production plant, Bayley MDI scores at age 13 mo were inversely associated with cord serum DDE levels ($\beta = -3.44 \pm 1.39$, $p < .05$) (Ribas-Fito et al., 2003). A birth cohort study of Mexican farm workers in California revealed no association between prenatal serum DDE and Bayley MDI scores at ages 6 or 12 mo and an inverse association of borderline statistical significance at age 24 mo ($\beta = -2.44$, 95% CI –4.92 to 0.05) (Eskenazi et al., 2006).

Lactational exposure, DDT/DDE, inadequate evidence: The North Carolina birth cohort study reported no association between Bayley MDI scores at ages 6 or 12 mo and cumulative lactational DDE exposure (Gladen et al., 1988).

Summary Epidemiologic evidence for the role of environmental toxicants in cognitive deficits among children age 0–2 includes: (a) sufficient evidence—high-level prenatal exposure to MeHg or PCBs, PCDFs and related toxicants; (b) limited evidence—low-level prenatal exposure to lead or PCBs, low-level childhood lead exposure.

Cognitive Function: Children Age 3 or Older

Lead It has been known for over 60 yr that high-level childhood lead exposure causes severe neurotoxicity including persistent cognitive deficits (Byers & Lord, 1943). This section focuses on the relationship between cognitive function and relatively low-level childhood lead exposure that does not produce clinically obvious signs or symptoms.

Low-level prenatal exposure, limited evidence: Several birth cohort studies found that cognitive scores among children age 3 yr or older were inversely associated with prenatal or cord blood lead levels (Dietrich et al., 1990; Schnaas et al., 2006; Wasserman et al., 2000a). In the Mexico City birth cohort study, IQ at age 6–10 yr was inversely associated with 3rd trimester maternal blood lead (per natural log blood lead increment, $\beta = -3.90$, –6.45 to –1.36) but not with childhood blood lead at age 1–5 yr ($\beta = 0.10$, –3.88 to 4.06) or 6–10 yr ($\beta = 0.17$, –1.41 to 1.76), in analyses that adjusted for blood lead levels at other time periods (Schnaas et al., 2006). Other studies reported no association between childhood cognitive function scores and prenatal or cord blood lead levels (Tong et al., 1996).

Low-level childhood exposure, sufficient evidence: Several meta-analyses and literature reviews covering studies published before 1996 found suggestive but inconclusive evidence for cognitive deficits in children at relatively low childhood blood or tooth dentin lead levels (Agency for Toxic Substances and Disease Registry, 1999b; Banks et al., 1997; Needleman & Gatsonis, 1990; Pocock et al., 1994; Schwartz, 1994; Thacker et al., 1992). The estimated average full-scale IQ deficit for a blood lead increment of 10 μg/dl was 2–3 points (Pocock et al., 1994; Schwartz, 1994). In a reanalysis of two birth cohort studies (Bellinger et al., 1991; Needleman et al., 1979), there were inverse dose-response relationships in nonparametric smoothing models between Bayley MDI scores and blood lead levels and between WISC full-scale IQ scores and dentin lead levels cross the observed ranges with no apparent thresholds (Schwartz, 1993).

Subsequent to the reviews noted above, longitudinal cohort studies in Port Pirie (Baghurst et al., 1992; Tong et al., 1996, 1998), Yugoslavia/Kosovo (Factor-Litvak et al., 1999; Wasserman et al., 1997, 2000a, 2003), Cincinnati (Ris et al., 2004), Mexico City (Schnaas et al., 2000), Rochester, NY (Canfield et al., 2003), Boston (Bellinger & Needleman, 2003; Bellinger et al., 1992), Detroit (Chiodo et al., 2004), and 4 U.S. cities (Chen et al., 2005) found significant inverse associations between full-scale IQ among children age 3 yr or older and relatively low-level childhood blood lead levels (current, previous or lifetime average). Findings included dose-response relationships and independence from several potential confounders.

The Rochester cohort study found relatively strong inverse associations between full-scale IQ at ages 3 and 5 yr and blood lead at levels below 10 μg/dl, independent of several potential confounders (Canfield et al., 2003). The IQ deficit per unit current blood lead increment (μg/dl) was greater among the subgroup whose peak lifetime blood lead level was less than 10 μg/dl ($\beta = -1.37 \pm 0.60$, $p = .03$) compared to the whole group ($\beta = -0.46 \pm 0.15$, $p = .004$). In a pooled analysis of 7 longitudinal cohort studies (involving 1333 children), there were inverse dose-response relationships between IQ and early-childhood, peak, lifetime average, and current blood lead levels (Lanphear et al., 2005). Over the blood lead range 2.4–30 μg/dl, the average adjusted IQ decrement estimated using a log-linear model was 6.9 points (95% CI 4.2–9.4).

An important exception was the Mexico City birth cohort study in which IQ at age 6–10 yr was inversely associated with 3rd trimester maternal blood lead (see earlier discussion) but not with blood lead at age 1–5 yr (per natural log blood lead increment, $\beta = 0.10$, –3.88 to 4.06) or 6–10 yr ($\beta = 0.17$, –1.41 to 1.76), in analyses that adjusted for blood lead levels at other time periods (Schnaas et al., 2006). Recent reviews concluded that: (1) lead impairs behavioral and cognitive development of children at blood lead levels below 10 μg/dl, (2) no blood lead threshold for such effects has been demonstrated, (3) there appears to be a steeper slope for the inverse association between IQ and blood lead below 10 μg/dl compared to higher levels, (4) lead accounts for 1–4% of variance in cognitive ability whereas social and parenting factors account for at least 40% (Bellinger, 2004; Koller et al., 2004; Lidsky & Schneider, 2003), and (5) the best fit for the relationship between childhood cognitive scores and blood lead concentrations is inverse log-linear (using the natural log of blood lead concentration) (Rothenberg & Rothenberg, 2005).

A large cross-sectional study, based on almost 5000 children in NHANES III, found inverse associations between scores on 4 cognitive test subscales (Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised and the Block Design and Digit Span subtests of WISC-R) and current blood lead level, independent of several potential confounders (Lanphear et al., 2000). Further analysis of children enrolled in NHANES III revealed inverse dose-response relationships between current blood lead and Wide Range Achievement Test-Revised subtest scores for math ($\beta = -0.57 \pm 0.17$) and reading ($\beta = -0.80 \pm 0.21$) and WISC-III block design subtest scores ($\beta = -0.08 \pm 0.03$) after adjustment for several potential confounders including serum cotinine (Yolton et al., 2005). In the Kosovo birth cohort study, IQ at age 3–7 yr was inversely associated with both prenatal blood lead ($\beta = -6.05 \pm 1.35$) and postnatal increases of at least 50% in blood lead (Wasserman et al., 2000a). In a subsequent report of this study, there were inverse dose-response relationships between full-scale IQ at age 10–12 yr and current blood and tibial bone lead levels and lifetime average blood lead levels when modeled separately (Wasserman et al., 2003). In models that included both bone and blood lead levels, full-scale IQ at age 10–12 yr was inversely associated with bone but not blood lead levels.

Methylmercury Low-level prenatal MeHg exposure, limited evidence: Major birth cohort studies have found inconsistent evidence of low-dose effects of MeHg on cognitive function among children age 3 yr or older. Maternal hair mercury levels in Iraq ranged up to 674 μg/g but were much lower among populations exposed mainly via consumption of fish with background MeHg levels including the Faroe Islands (0.6–39.1 μg/g), the Seychelles (0.5–27 μg/g), Madeira (1.1–54 μg/g), Massachusetts (0.02–2.38 μg/g), and Poland (0.1–3.40 μg/g). In the Seychelles Islands birth cohort study, full-scale IQ at age 5 yr was not associated with prenatal or current child hair mercury levels (range 0.9–26 μg/g) (Davidson et al., 1998). Also, there were no unfavorable associations between mercury exposure indices and language, visual-spatial function or applied problem solving scores. A re-analysis of the Seychelles Islands cohort data suggested a nonlinear dose-response relationship; McCarthy GCI scores at age 5–6 yr increased with prenatal hair mercury concentrations up to 10 μg/g and then decreased (Axtell et al., 2000). Among 46 neuropsychological outcomes measured in the Seychelles Islands study, only one (a test of fine motor function among boys using their nonpreferred hand) was unfavorably associated with prenatal MeHg exposure; there were favorable associations between maternal hair mercury levels and 2 outcomes (language function at age 5 yr, attention deficit index at age 9 yr) (Davidson et al., 2004). Based on reanalyses of the relationships between maternal hair mercury and scores on 26 neuropsychological tests in the

Seychelles Islands cohort at age 9 yr, the estimated average benchmark dose 95% lower confidence limit for maternal hair mercury was 20.1 μg/g (range 17.2–22.5) (van Wijngaarden et al., 2006).

In the Faroe Islands birth cohort study, cord blood mercury levels were unfavorably associated with test scores at age 7 yr for digit spans (average change in score per log cord blood mercury increment, $\beta = -0.27$, $p = .05$), language ($\beta = -2.03$, $p = .007$), long-term memory ($\beta = -0.99$, $p = .03$), and attention ($\beta = 39.3$ ms, $p < .001$) (Grandjean et al., 1997). Further analyses of maternal hair, cord blood, and current child hair mercury levels revealed that associations with attention, language, and memory deficits were virtually limited to the prenatal exposure indices (see also childhood exposure discussion later). After adjustment for cord tissue PCB levels, associations persisted between cord blood mercury and scores for memory (average change in long-term memory score per unit change in cord blood mercury (μg/L), $\beta = -0.94$, $p = .04$), attention (average change in CPT reaction time (ms) per unit change in cord blood mercury, $\beta = 40.3$, $p = .0002$) and language (Boston Naming Test, $\beta = -1.94$, $p = .009$) (Grandjean et al., 2001). A reanalysis of the Faroe Islands birth cohort study, excluding children with vision deficits and adjusting for visual contrast sensitivity, found that there was still no association between WISC subscale scores at age 7yr and cord blood mercury levels (e.g., average change in WISC block design score per unit change in cord blood mercury, $\beta = -0.12$, $p = .25$) (Grandjean et al., 2001). Among the subgroup of children for whom mercury levels in 2 prenatal hair segments were available and consistent, there were inverse associations between cord blood mercury levels and test scores at age 7 yr for WISC block design (average change in WISC block design score per unit change in cord blood mercury, $\beta = -0.28$, $p = .06$), CPT reaction time (ms) ($\beta = 47.0$, $p = .01$), long-term memory ($\beta = -0.81$, $p < .04$), Bender Gestalt copying errors ($\beta = 1.53$, $p < .03$), and language ($\beta = -1.59$, $p < .02$) (Grandjean et al., 2003). When Faroese children were examined at age 14 yr, there were inverse associations between maternal hair mercury and verbal (change per doubling of mercury level, $\beta = -6.87$, $p = .05$) and attention ($\beta = -9.54$, $p = .017$) but not memory scores ($\beta = -3.05$, $p = .38$) (Debes et al., 2006).

In the New Zealand birth cohort study, there were inverse associations (of borderline statistical significance) between average prenatal hair mercury levels and test scores at age 6–7 yr including WISC full-scale IQ ($\beta = -0.42$, 95% CI –1.1 to 0.18), McCarthy perceptual scale ($\beta = -0.50$, 95% CI –0.92 to –0.077) and spoken language ($\beta = -0.42$, 95% CI –0.98 to 0.13) (Crump et al., 1998). These authors estimated the benchmark doses and its 95% lower limit for average prenatal hair mercury versus abnormal WISC full-scale IQ scores to be, respectively, 15 and 10 μg/g. Bench mark dose was defined as the average prenatal hair concentration expected to cause a 10% increase in abnormal (≤95th percentile) test scores. The Oswego birth cohort study reported an inverse association between McCarthy CGI scores at ages 38 and 54 mo and an interaction term modeled as maternal hair mercury during the first half of pregnancy times cord blood PCB concentration (change in CGI per unit change in mercury/PCB term, $\beta = -0.50$, $p = .008$); there was a weaker nonsignificant inverse association with maternal hair mercury during the second half of pregnancy times cord blood PCB ($\beta = -0.31$, $p = .16$) (Stewart et al., 2003).

Expert panels concluded that the associations between language, verbal memory, and other subtle neuropsychological deficits and low-level prenatal MeHg exposure from fish consumption observed in epidemiologic studies are consistent with neuropsychological deficits in experimental animals after low-dose prenatal MeHg exposure (National Academy of Sciences, 2000c; United Nations Environment Programme, 2002).

Childhood exposure, inadequate evidence: A cross-sectional study in Germany revealed no association between vocabulary, block design or CPT reaction times and current urinary mercury excretion rates (range 0.02–2.83 μg/d) (Walkowiak et al., 1998). In the Faroe Islands cohort, attention scores (but not language or memory scores) were inversely associated with child hair mercury levels at age 1 yr (Grandjean et al., 1999). In a cross-sectional study of children age 7–12 yr in the Amazon basin, there were inverse associations between current hair mercury and Stanford–Binet subscales scores for visuospatial function (change in score per unit change in log hair mercury, $\beta = -6.2$, $p < .001$), memory ($\beta = -2.9$, $p < .001$) and attention functions ($\beta = -0.9$, $p < .001$) (Grandjean et al., 1999).

Arsenic Childhood exposure, inadequate evidence: A small cross-sectional study of children age 6–9 yr in Mexico found an inverse association between full-scale IQ and urinary arsenic levels among the subgroup of children living in a smelter town (partial correlation coefficient $r = -0.33$, $p = .04$) but not in the whole group including children from an unexposed comparison town ($r = -0.15$, $p = .22$) (Calderon et al., 2001).

Manganese Prenatal exposure, inadequate evidence: A birth cohort study in France observed no association between cognitive function scores at ages 9 mo to 6 yr and prenatal manganese levels in maternal blood or hair, cord blood, or placenta; attention, nonverbal memory, and hand skill scores at age 3 yr were inversely associated with cord blood manganese levels (geometric mean 38.6 μg/L, range 22.0–67.7) (Takser et al., 2003). The geometric mean newborn hair manganese concentration was 0.77 μg/g (range 0.22–4.25).

Childhood exposure, inadequate evidence: A small cross-sectional study of Chinese children including some from a region with elevated drinking-water manganese levels reported that most neuropsychological scores (manual dexterity, digit span, digit symbol, Benton visual retention, and pursuit aiming tests) were inversely associated with current hair manganese levels (mean 1.25 μg/g) (He et al., 1994).

PCBs High-level maternal exposure, sufficient evidence: Compared to unexposed children, Yucheng children age 6–7 yr had lower WISC full-scale IQ scores at age 6–7 yr (mean IQ, exposed vs. unexposed, 84 vs. 88, $t = 1.06$, $df = 40$, $p = .29$) (Rogan et al., 1988). Yucheng children also had increased auditory event-related P300 potential latencies and reduced P300 amplitudes; such neurophysiological changes have been linked to cognitive deficits, attention deficit disorder and reading disability (Chen & Hsu, 1994). Reviewers concluded that prenatal high-level maternal exposure to PCBs, PCDFs, and related toxicants were associated with persistent cognitive function deficits (Longnecker et al., 1997) and a WHO expert group concluded that this is a causal relationship (Brouwer et al., 1998).

Background maternal exposure, limited evidence: Reviewers noted that there were inverse associations between cognitive function scores and prenatal PCB exposure indices in four of the five studies that were published by 1999 and assessed this relationship (Ribas-Fito et al., 2001). Other reviewers concluded that the growing weight of evidence from epidemiologic studies supports an inverse association between childhood cognitive scores and prenatal PCB exposure levels but noted that there have been few attempts to assess the role of specific PCB congeners or classes of congeners (Schantz et al., 2003). In the Michigan birth cohort, McCarthy GCI scores at age 4 were not associated with cord serum PCB (change in GCI per unit change in cord serum PCB, $\beta = -0.11$, $p = .22$) (Jacobson et al., 1990a). Follow-up of the Michigan cohort at age 11 yr revealed an inverse dose-response relationship between WISC-R full-scale IQ and breast milk PCB levels at birth (IQ vs. 5 categories of increasing breast milk PCBs, $\beta = -0.17$, $p = .02$) (Jacobson & Jacobson, 1996b). This study also reported an inverse association of borderline statistical significance between executive function scores at age 11 yr and prenatal PCB exposure (change in Stroop Color-Word test score per unit change in prenatal PCB, $\beta = -0.15$, $p < .10$) (Jacobson & Jacobson, 2003). The latter study observed no association between another test of executive function at age 11yr and prenatal PCB exposure (change in Wisconsin card sort categories completed per unit change in prenatal PCB, $\beta = -0.04$, $p > .05$). In the Dutch cohort, Kaufman ABC scores at age 42 mo were inversely associated with maternal 3rd trimester plasma PCBs (per natural log PCB increment, $\beta = -4.56 \pm 1.62$, $p = .005$); this association was stronger among the subgroup of formula-fed infants ($\beta = -8.69 \pm 2.49$, $p = .0006$) than the breastfed group ($\beta = -2.20 \pm 2.14$, $p = .30$ (Patandin et al., 1999). McCarthy GCI scores at age 7 yr in the Dutch cohort were not associated with 3rd trimester maternal plasma PCBs (per natural log PCB increment, $\beta = -0.14 \pm 1.58$) (Vreugdenhil et al., 2002). This study reported inverse associations between Tower of London test scores at age 9 yr and maternal plasma PCBs (change in score, 4th vs. 1st quartile maternal plasma PCB, $\beta = -1.85 \pm 0.67$(SE), $p = .007$) (Vreugdenhil et al., 2004a). In the German birth cohort, breast milk PCB concentrations about 2 wk postpartum were inversely associated with Kaufman ABC scores at age 42 mo (per $\log_2$ breast milk PCB increment, $\beta = -4.30$, $t = -1.93$, $p = .03$) (Walkowiak et al., 2001). In the Oswego Newborn and Infant Development cohort, cord blood highly chlorinated PCB concentrations were inversely

associated with McCarthy GCI scores at 38 mo (linear trend test, $F(1,165) = 7.33$, $p = .008$) but not at 54 mo (linear trend test, $F(1,166) = 1.25$, $p > .05$) (Stewart et al., 2003). In the U.S. Collaborative Perinatal Project cohort, WISC full-scale IQ at age 7 yr was not associated with 3rd trimester maternal serum PCB in a fully adjusted model (change in IQ per unit change in maternal serum PCB (μg/g lipid), $\beta = 1.90 \pm 1.92$(SE), $p > .05$) (Gray et al., 2005).

Lactational exposure, limited evidence: In the Michigan birth cohort, McCarthy GCI scores at age 4 yr were not associated with current serum PCB (stated without supporting data) (Jacobson et al., 1990a). This study reported no association between executive function scores at age 11 yr and postnatal PCB exposure (e.g., change in Wisconsin card sort categories completed per unit change in serum PCB at age 4 yr, $\beta = 0.01$, $p > .05$) (Jacobson & Jacobson, 2003). In the German birth cohort, lactational PCB exposure was inversely associated with Kaufman ABC scores at age 42 mo (change in Kaufman-ABC index per unit change in current serum PCB, $t = -2.01$, $p = .03$; β-coefficient not reported) (Walkowiak et al., 2001).

General findings Reviewers concluded that prenatal and lactational exposure to PCBs, PCDDs, and PCDFs can cause neuropsychological and neuromotor deficits in humans and in experimental animal with LOAELs in the range of background general population dioxin-TEQ body burdens (Brouwer et al., 1995). Cord plasma and breast milk noncoplanar PCB congener levels have also been associated with cognitive deficits in children age 6–7 yr (Vreugdenhil et al., 2002). Such congeners were the most potent in reducing dopamine content and disrupting calcium metabolism in neurons in vitro (Tilson & Kodavanti, 1997). Inconsistent findings in epidemiologic studies may arise from PCB exposure intensity differences; for instance, average prenatal serum PCB-153 levels in 10 epidemiologic studies of neurodevelopment varied from 30 to 450 ng/g lipid, being highest in the Faroe Islands birth cohort study and lowest in two U.S. studies (Longnecker et al., 2003).

Pesticides Maternal exposure, DDT/DDE, inadequate evidence: In the North Carolina birth cohort, McCarthy CGI scores at ages 3, 4, and 5 yr were not obviously associated with breast milk DDE levels (results were displayed in graphs without statistical analysis) (Gladen & Rogan, 1991).

Lactational exposure, DDT/DDE, inadequate evidence: The North Carolina study also reported no association between McCarthy CGI scores and cumulative lactational DDE exposure (Gladen & Rogan, 1991).

Childhood exposure, organophosphate pesticides, inadequate evidence: In a small cross-sectional study of children age 2–11 yr living in homes where methyl parathion had been illegally used for pest control in Mississippi and Ohio, cognitive function scores were similar to those in a comparison group of unexposed children (result stated without supporting data); methyl parathion exposure status (yes/no) was based on urinary *p*-nitrophenol and environmental wipe methyl parathion levels above defined limits (Ruckart et al., 2004).

Environmental tobacco smoke Childhood exposure, limited evidence: Expert panels found limited evidence of an inverse association between childhood cognitive function and postnatal ETS exposure (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006). The panel noted that this relationship has been much less studied than prenatal active smoking and that smoking mothers tend to smoke both during and after pregnancy—thus associations with childhood maternal smoking may partially reflect the impact of prenatal smoking. Among children age 6–16 yr enrolled in NHANES III, there were inverse dose-response relationships between log serum cotinine and math ($\beta = -1.93 \pm 0.70$), reading ($\beta = -2.69 \pm 0.75$) and visual construction scores ($\beta = -0.55 \pm 0.12$) (Yolton et al., 2005). In a pregnancy cohort study, Bayley MDI scores at age 3 yr were inversely associated with 3rd trimester maternal personal air PAH exposure (>4.16 vs. ≤4.16 ng/m^3, $\beta = -5.69$, $p < .01$) (Perera et al., 2006). However, ETS is only one source of PAH exposure (e.g., other sources include outdoor air pollution and diet).

Solvents Maternal exposure, unspecified solvents, inadequate evidence: A small retrospective cohort study in Canada found no association between full-scale, verbal or performance IQ scores at ages 6–8 yr and maternal 1st trimester occupational organic solvent exposure (Laslo-Baker et al., 2004).

Summary Epidemiologic evidence for the role of environmental toxicants in cognitive deficits among children age 3 yr or older includes: (a) sufficient evidence—high- or low-level childhood lead exposure; high-level prenatal exposure to MeHg or to PCBs, PCDFs, and related toxicants; (b) limited evidence—prenatal low-level exposure to lead, MeHg, or PCBs; low-level lactational exposure to PCBs; childhood ETS exposure.

Problem Behaviors Problem behaviors include hyperactivity, distractibility, impulsivity, and impersistent and aggressive behaviors.

Lead Childhood exposure, limited evidence: Several birth cohort studies found fairly consistent associations between teacher- and/or mother-reported problem behaviors (e.g., inattention, easily distracted, aggressiveness) among school-age children and current or lifetime average blood lead or tooth dentin lead levels, independent of potential confounders (Bellinger et al., 1994; Burns et al., 1999; Chiodo et al., 2004; Dietrich et al., 2001; Factor-Litvak et al., 1999; Leviton et al., 1993; Needleman et al., 1996; Silva et al., 1988; Wasserman et al., 1998). Two large U.S. cross-sectional studies reported associations between problem behaviors and current blood lead levels (Needleman et al., 1979; Schwartz & Otto, 1987). A large European cross-sectional study in which the blood lead range was 5–60 μg/dl observed no association with problem behaviors (Winneke et al., 1990). Two small cross-sectional studies reported associations between problem behaviors and dentin or current blood lead levels (Hansen et al., 1989; Mendelsohn et al., 1998) but several others did not (Harvey et al., 1988; Landrigan et al., 1975; Lansdown et al., 1986; Winneke et al., 1983). A case-control study in Boston observed an association between court-adjudicated delinquency and current tibial bone lead levels, independent of race and other potential confounders (OR = 3.7, 95% CI 1.3–10.5) (Needleman et al., 2002). In sum, these studies provide moderately strong evidence of an association between problem behaviors and childhood lead exposure.

Methylmercury Maternal exposure, inadequate evidence: The Seychelles Islands study appears to be the only cohort to have assessed the relationship between aggressive and other problem behaviors and MeHg exposure indices. Inattentive, aggressive, and other problem behaviors at age 5–6 yr (identified by parents using a checklist) were not associated with prenatal hair mercury levels (Myers et al., 2000). When reassessed at age 9 yr, prenatal hair mercury levels were inversely associated with the Connor's teacher rating scale hyperactivity index ($\beta = -0.0067 \pm 0.0023$, $p = .004$) and were not related to attention scores (Myers et al., 2003).

Childhood exposure, inadequate evidence: In the Seychelles Islands study, inattentive, aggressive and other problem behaviors at age 5–6 yr were not associated with current child hair mercury levels (e.g., for Myers et al., 2000).

PCBs High-level maternal PCB/PCDF exposure, limited evidence: Four reviews of epidemiologic studies noted that high-level maternal exposure to PCBs, PCDFs, and related toxicants during the Yusho and Yucheng incidents was associated with persistent problem behaviors including hyperactivity (Brouwer et al., 1998; Guo et al., 2004; Longnecker et al., 1997; Schantz, 1996). There appears, however, to have been no association between problem behaviors and prenatal or postnatal PCB exposure indices (stated without supporting data) (Chen et al., 1994).

Background maternal PCB exposure, inadequate evidence: A Michigan birth cohort study found an inverse association between freedom from distractibility at age 11 yr and prenatal but not postnatal PCB exposure levels (change in WISC-R subscale for freedom from distractibility per unit change in cord or maternal serum PCB level (5 categories), $\beta = -0.17$, $p = .02$) (Jacobson & Jacobson, 1996b). Further follow-up of this cohort revealed no association between reaction time and prenatal or postnatal PCB levels in the whole group; however, there was an inverse association between mother-reported attentiveness and prenatal PCB levels among the subgroup of infants who were breastfed less than 6 wk (change in score per unit change in prenatal PCB level, $\beta = -0.39$, $p < .05$) (Jacobson & Jacobson, 2003). The Faroe Islands birth cohort study found an inverse association between attention scores (measured using the continous performance test) at age 7 yr and umbilical cord tissue PCB levels (change in reaction time per log increment of cord tissue levels of 3 noncoplanar PCBs, $\beta = -7.2$, $p = .45$, adjusted for cord blood mercury) (Grandjean et al., 2001). In the Rotterdam component of the Dutch birth cohort, sustained attention scores at age 9 yr were inversely associated with maternal plasma PCB levels (change in reaction time, 4th vs. 1st quartile

maternal plasma levels of 4 noncoplanar PCBs, β = 20.4 ± 14.0 ms, $p = .15$) (Vreugdenhil et al., 2004a).

Lactational PCB exposure, inadequate evidence: The Michigan birth cohort study found no association between freedom from distractibility at age 11 yr and serum PCB at age 4 yr (an index of lactational exposure) when adjusted for prenatal serum PCB levels; the report does not give data for β related to freedom from distractibility at age 11 yr vs. serum PCB at age 4 yr (Jacobson & Jacobson, 1996b). In the Rotterdam component of the Dutch birth cohort, sustained attention scores at age 9 yr were not associated with breast-feeding duration (change in reaction time, breast-fed long vs. short, β = 1.53 ± 15.7 ms, $p = .92$) (Vreugdenhil et al., 2004a).

Pesticides Paternal occupational exposure, other herbicides, inadequate evidence: A cross-sectional study of offspring of licensed pesticide applicators reported an association between parent-reported attention deficit hyperactivity disorder and paternal use of the herbicide glyphosate (OR = 3.6, 95% CI 1.35–9.65) (Garry, 2002).

Environmental tobacco smoke Maternal exposure, inadequate evidence: A WHO expert group found inadequate evidence for an association between childhood behavioral problems and prenatal ETS exposure (World Health Organization, 1999).

Childhood exposure, limited evidence: A WHO expert group found inadequate evidence for an association between childhood behavioral problems and childhood ETS exposure (World Health Organization, 1999). A more recent expert panel review concluded that there is limited evidence of an association between childhood problem behaviors and childhood ETS exposure but noted that this may partially reflect the impact of prenatal active smoking (California Environmental Protection Agency, 2005).

Summary Epidemiologic evidence for the role of environmental toxicants in problem behaviors includes limited evidence for high-level prenatal exposure to PCBs, PCDFs, and related toxicants and childhood exposure to lead or ETS.

Motor Function: Children Age 0–2 The level of epidemiologic evidence for associations between motor and sensory function and environmental factors is summarized in Table 4.

Lead Prenatal or early childhood exposure, inadequate evidence: Several birth cohort studies found no association between PDI scores at ages 6 mo to 2 yr and cord blood or childhood blood lead levels (Bellinger et al., 1984; Cooney et al., 1989a, 1989b; Ernhart et al., 1988; Wigg et al., 1988). In a Mexico City birth cohort, PDI scores were inversely associated with current blood lead (β = –1.18, $p < .01$) at age 2 yr but not at age 1 yr (Tellez-Rojo et al., 2006).

TABLE 4. Role of Environmental Toxicants in Motor and Sensory Function

Toxicant	Exposure	Motor function, age 0–2	Motor function, age ≥3	Auditory function	Visual function
Lead	Prenatal	I	I	**L**	
	Childhood	I	**L**	**L**	I
Methylmercury	Prenatal	High-level—**S** Low-level—**L**	**L**	High-level—**S** Low-level—**L**	High-level—**S** Low-level—I
	Childhood	High-level—**L**	I	I	High-level—**S** Low-level—I
Cadmium	Childhood		I		
PCBs	Prenatal	High-level—**S**[j] Low-level—**L**	I	High-level—**L** Low-level—**L**	High-level—I
	Lactational	I		I	
DDT/DDE	Prenatal	I			
	Lactational	I			
Organophosphate insecticides	Childhood	I	I		
HCB	Prenatal	I			
	Childhood		I		

[j]Neonatal hypotonia, delayed psychomotor development during infancy.

Methylmercury High-level prenatal exposure, sufficient evidence: A review of congenital MeHg poisoning at Minamata noted that most infants age 1–2 yr had abnormal reflexes, increased muscle tone, and displayed involuntary movements (Harada, 1977). Delayed motor development of Iraqi infants was associated with high prenatal hair and childhood blood mercury levels (Amin-Zaki et al., 1981; Marsh et al., 1980, 1981). Extrapolation of Iraqi data suggested increased risk of delayed motor development at prenatal hair mercury levels as low as 10–20 μg/g (World Health Organization, 1990), a view shared by recent reviewers (Clarkson, 2002; Newland, 2002).

Low-level prenatal exposure, limited evidence: Among Seychellois infants age 6 mo, there was a statistically nonsignificant elevated risk of abnormal or questionable neurologic signs (deep tendon reflexes, limb tone) among infants of women with hair mercury exceeding 9 μg/g (compared to ≤6 μg/g, crude OR = 1.67, 95% CI 0.49–5.63, calculated from data in paper) (Myers et al., 1995). Among infants of women who consumed Great Lakes fish, abnormal reflex scores on postnatal day 2 were not associated with maternal hair mercury levels during early or later pregnancy (e.g., change in score per unit change in hair mercury during gestation month 5–9, $\beta = -0.019$, $p = .76$) (Stewart et al., 2000). A pregnancy cohort study of nonsmoking women in Poland found inverse associations between Bayley MDI or PDI scores below 85 at age 1 and cord blood mercury (≥median vs. <median, OR = 3.58, 95% CI 1.40–9.14) and maternal blood mercury levels (OR = 2.82, 95% CI 1.17–6.79); this study did not report data for Bayley MDI and PDI separately (Jedrychowski et al., 2006).

Childhood high-level exposure, limited evidence: Among children exposed at age 0–14 yr during the Iraq MeHg poisoning episodes and followed for 2 yr, the severity and persistence of ataxia and muscle weakness were associated with baseline blood mercury levels (Amin-Zaki et al., 1978). Children with mild/moderate poisoning improved slowly but all had persistent hyperreflexia; 7 of 18 children with severe poisoning had persistent physical disability.

PCBs Neonatal hypotonia High-level exposure, sufficient evidence: A WHO working group concluded that high-level prenatal exposure to PCBs, PCDFs, and related compounds caused neonatal hypotonia (Brouwer et al., 1998).

Background exposure: A recent review concluded that the evidence from birth cohort studies suggests an association between neonatal hypotonia and hyporeflexia and background PCB exposure levels (Longnecker et al., 1997). A review of seven cohort studies noted that abnormal neonatal reflexes were associated with PCB exposure in all four studies that assessed it (Ribas-Fito et al., 2001).

Motor function, age 0–2 High-level maternal PCB/PCDF exposure, limited evidence: Compared to unexposed children, Yucheng children age 6–30 mo had lower Bayley Scale psychomotor development index (PDI) scores (mean PDI score, exposed vs. unexposed children, 101 ± 2.7(SE) vs. 108 ± 2.1, mean difference $t = 2.05$, df = 88, $p = .04$ (t and p calculated from data in paper) (Rogan et al., 1988). Further investigation showed that Yucheng children age 7 yr had small and statistically nonsignificant gross (exposed vs. unexposed, Chinese Child Developmental Inventory (CCDI) scores, 27.4 ± 0.6(SE) vs. 28.2 ± 0.6, $t = -1.5$, $p = .14$) and fine motor function deficits (exposed vs. unexposed, CCDI scores, 31.5 ± 1.0(SE) vs. 32.6 ± 0.9, $t = -1.3$, $p = .20$) (Guo et al., 1994; Lai et al., 1994, 2001)

Low-level maternal PCB exposure, limited evidenc: A WHO working group concluded that childhood psychomotor function was inversely associated with low-level prenatal exposure to PCBs and related compounds but noted that most of the individual neuropsychological test results were within normal limits (Brouwer et al., 1998). Among reviewed studies, a North Carolina birth cohort study revealed inverse associations between Bayley PDI scores at ages 6 and 12 mo and breast milk PCBs soon after birth (an index of prenatal PCB exposure) (change in PDI score at age 6 mo per unit change in breast milk PCB (μg/g lipid), $\beta = -0.96 \pm 0.46$, $p = .04$; at age 12 mo, $\beta = -1.34 \pm 0.61$, $p = .03$) (Gladen et al., 1988; Rogan & Gladen, 1991). The PDI deficits at ages 18 and 24 mo of infants of women with the highest breast milk PCB levels, compared to those with the lowest levels, were not statistically significant (18 mo, deficit = –4.0 ± 3.9(SE); 24 mo,deficit –7.9 ± 4.5) (Rogan & Gladen, 1991). In a Dutch birth cohort, suboptimal neonatal neurologic scores at 10–21 d after birth (based in part on reflexes and postural tone) were associated with breast milk PCB-TEQ and

PCDD/PCDF-TEQ levels (per doubling of breast milk PCB-TEQ levels (pg/g lipid), OR = 3.21, 95% CI 1.37–7.48; per doubling of breast milk PCDD/PCDF-TEQ, OR = 3.12, 95% CI 1.36–7.18) but not with maternal or cord serum individual or aggregate levels of 4 noncoplanar PCB congeners (per doubling of maternal or cord serum noncoplanar PCBs, OR = 1.11, 95% CI 0.74–1.65) (Huisman et al., 1995a). At this age, maternal and cord serum and breast milk PCB levels all reflect prenatal exposure. Continued follow-up of the whole Dutch birth cohort revealed a persistent inverse association between neurologic optimality scores at age 18 mo and cord plasma levels of 4 noncoplanar congeners (change in score per log increment of cord serum PCBs, $\beta = -0.149 \pm 0.049$, $p = .003$) (Huisman et al., 1995b). Within the Rotterdam component of the Dutch cohort, there was an inverse association between Bayley PDI scores at age 3 mo and maternal plasma levels of 4 noncoplanar PCBs (per natural log PCB increment, $\beta = -4.8 \pm 2.0$, $p = .02$) but not at age 7 mo ($\beta = 2.3 \pm 1.7$, $p = .18$) (Koopman-Esseboom et al., 1996). A small German birth cohort study observed no association between Bayley PDI scores at age 7 mo and cord plasma levels of 3 noncoplanar PCBs (change in PDI per log increment of cord plasma PCBs, $\beta = 0.009 \pm 0.63$, $p > .9$) (Winneke et al., 1998). A small Faroe Islands birth cohort study found no association between neonatal optimality scores at age 2 wk and maternal serum or breast milk PCB levels (Spearman's rank correlation coefficients, scores vs. maternal serum or breast milk PCBs, $R = 0.03$ and -0.03, respectively, $p > .05$) (Steuerwald et al., 2000). The Oswego birth cohort study observed an association between abnormal reflexes on postnatal day 2 and cord blood levels of highly chlorinated PCB congeners ($F(1,262$ df) = 2.81, $p = .095$) (Stewart et al., 2000). In a German birth cohort, Bayley PDI scores at ages 7–30 mo were inversely associated with breast milk PCBs, an index of prenatal exposure (per $\log_2$ increment, $\beta = -4.61$, $t = -2.22$, $p = .015$) (Walkowiak et al., 2001). There was no association between 3rd trimester maternal serum PCBs (11 congeners) and Bayley PDI at age 8 mo in the U.S. Collaborative Perinatal Project (change in Bayley PDI per unit change in maternal serum PCBs (μg/L), $\beta = 0.47 \pm 0.32$, $p = .14$) (Daniels et al., 2003). In a small Spanish birth cohort, there was a statistically nonsignificant inverse association between Bayley PDI at age 13 mo and cord serum PCBs (7 congeners) (change in Bayley PDI per doubling of cord serum PCB (μg/L, $\beta = -2.84 \pm 1.72$, $p < .10$) (Ribas-Fito et al., 2003). The U.S. study was much larger than the Spanish cohort and included women recruited during 1959–1966 when population serum PCB levels were substantially higher than recently (median and 95th percentiles were 2.7 and 6.3 μg/L).

Low-level lactational exposure, inadequate evidence: A North Carolina birth cohort study revealed no association between Bayley PDI scores at ages 6 and 12 mo and cumlulative lactational PCB exposure (change in PDI score at age 6 mo per mg PCB ingested, $\beta = -0.27 \pm 0.20$, $p = .17$; at age 12 mo, $\beta = -0.27 \pm 0.18$, $p = .13$) (Gladen et al., 1988; Rogan & Gladen, 1991). In a Dutch birth cohort, suboptimal neonatal neurologic scores at 10–21 d after birth (based in part on reflexes and postural tone) were associated with breast milk PCB-TEQ and PCDD/PCDF-TEQ levels (per doubling of breast milk PCB-TEQ levels (pg/g lipid), OR = 3.21, 95% CI 1.37–7.48; per doubling of breast milk PCDD/PCDF-TEQ, OR = 3.12, 95% CI 1.36–7.18) (Huisman et al., 1995a). Within the Rotterdam component of the Dutch cohort, there was an inverse association of borderline statistical significance between Bayley PDI scores at age 3 mo and breast milk PCB-TEQ (per natural log increment, $\beta = -7.4 \pm 4.0$, $p = .07$), adjusted for breastfeeding duration (Koopman-Esseboom et al., 1996). At age 7 mo, PDI scores were inversely and significantly associated with breast milk PCB-TEQ levels, adjusted for breastfeeding duration (medium vs. lowest category, $\beta = -9.5 \pm 3.9$, $p = .01$; highest vs. lowest category, $\beta = -7.7 \pm 4.9$, $p = .12$) (Koopman-Esseboom et al., 1996). A small German birth cohort study observed an statistically nonsignificant inverse relationship between Bayley PDI scores at age 7 mo and breast milk levels of 3 noncoplanar PCBs (change in PDI per log increment of breast milk PCBs, $\beta = -0.71 \pm 0.63$, $p = .13$, adjusted for breastfeeding duration) (Winneke et al., 1998). In the German birth cohort, Bayley PDI scores at age 7–30 mo were not associated cumulative lactational PCB dose (stated without supporting data) (Walkowiak et al., 2001).

Pesticides Maternal exposure, DDT/DDE, inadequate evidence: In the North Carolina cohort study, neonatal hyporeflexia was associated with breast milk DDE levels (≥5 vs. <2 μg/g lipid, OR = 2.13, 95% CI 0.85–5.22) (Rogan et al., 1986). However, Bayley PDI scores at ages 6, 12, and 18 mo were not associated with breast milk DDE levels and there was a favourable association at

age 24 mo (≥6 vs. <1 μg/g lipid, mean PDI difference = 8.0 ± 3.9 points) (Rogan & Gladen, 1991; Rogan et al., 1986). A New York State birth cohort study involving mothers who consumed Lake Ontario fish revealed no association between abnormal reflexes on postnatal day 2 and cord blood DDE levels (Stewart et al., 2000). In a Faroe Islands birth cohort study, neurologic optimality test scores at age 2 weeks were not associated with maternal serum (Spearman $R = 0.02$) or breast milk DDE levels ($R = -0.01$) (Steuerwald et al., 2000). There was an inverse association between cord serum DDE and Bayley PDI scores among Spanish children age 13 mo (per doubling of cord serum DDE, $\beta = -3.83 \pm 1.46$, $p < .05$), independent of several covariates including breast-feeding duration and cord serum PCB and HCB levels (Ribas-Fito et al., 2003). In a California birth cohort study, PDI scores at ages 6 and 12 but not 24 mo were inversely associated with prenatal serum DDE levels (change in PDI per 10-fold DDE increment: age 6 mos, $\beta = -2.14$, 95% CI –4.20 to –0.08; 12 mos, $\beta = -2.14$, 95% CI –4.83 to 0.56; 24 mos, $\beta = 0.59$, 95% CI –1.58 to 2.77) (Eskenazi et al., 2006).

Lactational exposure, DDT/DDE, inadequate evidence: The North Carolina cohort found no association between cumulative lactational DDE exposure and PDI scores at ages 6, 12, 18, or 24 mo (Gladen et al., 1988; Rogan & Gladen, 1991).

Maternal exposure, HCB, inadequate evidence: The New York State birth cohort study reported no association between abnormal reflexes on postnatal day 2 and cord blood HCB levels (Stewart et al., 2000).

Maternal exposure, organophosphate insecticides, inadequate evidence: A birth cohort study in California reported an association between abnormal reflexes among infants age less than 2 mo and maternal urinary organophosphate insecticide metabolites (total dialkyl phosphates, $\beta = 0.53$, 95% CI 0.23–0.82); the association was stronger for infants with 4 or more versus 3 or fewer abnormal reflexes (per 10-fold urinary dialkyl phosphate increment, OR = 4.9, 95% CI 1.5–16.1) (Young et al., 2005).

Summary Epidemiologic evidence for the role of environmental toxicants in motor deficits among children age 0–2 includes: (a) sufficient evidence—high-level prenatal exposure to MeHg or PCBs, PCDFs and related toxicants; (b) limited evidence—low-level prenatal or high-level childhood MeHg exposure; low-level prenatal PCB exposure.

Motor Function: Children Age 3 or Older

Lead Maternal exposure, inadequate evidence: In the Cincinnati birth cohort study, fine motor function scores at age 15–17 yr were inversely associated with blood lead at age 6 but not with prenatal or average childhood levels (Ris et al., 2004).

Childhood exposure, limited evidence: Fine motor function scores were inversely associated with childhood blood lead levels in several birth cohorts (Needleman et al., 1990; Ris et al., 2004; Stiles & Bellinger 1993; Stokes et al., 1998; Wasserman et al., 2000b) and cross-sectional studies (Landrigan et al., 1975). A small cross-sectional study of children age 7–12 yr revealed no association between fine motor function and dentin lead levels (Winneke et al., 1983). In sum, there is fairly consistent evidence for an association between childhood fine motor function deficits and low to moderate lead exposure levels.

Methylmercury Low-level prenatal exposure, limited evidence: An expert panel review noted that low-level prenatal MeHg exposure from prenatal fish consumption was associated with fine-motor function deficits in two of the three large birth cohort studies and that evidence from experimental animal studies showed motor deficits at low-dose prenatal MeHg exposure (National Academy of Sciences, 2000c). In the Faroe Islands birth cohort study, fine motor function scores (finger tapping speed and hand-eye coordination errors) at age 7 yr were unfavorably associated with prenatal hair and/or cord blood mercury levels (change in score per doubling of maternal hair mercury, finger tapping speed (nonpreferred hand), $\beta = -0.32$, $p < .05$; hand-eye coordination errors, $\beta = 0.018$, $p < .05$) (Dahl et al., 1996). Further analysis of this study revealed an inverse association between finger tapping speed using the preferred hand (change per log cord blood mercury, $\beta = -1.10$, $p = .05$) but not the other (Grandjean et al., 1997). In analyses limited to children of women with prenatal hair mercury below 10 μg/g, the associations just described persisted with similar regression

coefficients and *p*-values. Reanalysis of the Faroe Islands birth cohort study, excluding children with strabismus or needing eye glasses and adjusting for visual contrast sensitivity, revealed inverse associations between finger tapping speed but not hand–eye coordination errors at age 7 yr and cord blood mercury levels (Grandjean et al., 2001). Data from the Faroe Islands birth cohort study on finger tapping speeds at age 7 yielded a benchmark dose lower limit of 4.3 μg/g for prenatal hair mercury (using a log dose-response model and a 5% probability of an adverse response) (Budtz-Jorgensen et al., 2000). An analysis limited to Faroese children for whom two prenatal hair segment mercury levels were available and consistent, revealed persistent unfavourable associations between cord blood mercury levels and finger tapping speed and hand–eye coordination errors (Grandjean et al., 2003). In the Faroe Islands cohort, there were inverse dose-response relationships between maternal prenatal hair mercury levels and motor function test scores at age 14 ($\beta = -9.37$, $p = .009$) (Debes et al., 2006).

In the Seychelles Islands study, prenatal hair mercury was inversely associated with grooved pegboard time at age 9 (preferred hand, $\beta = -1.07 \pm 0.52$, $p = .045$; nonpreferred hand, $\beta = -1.39 \pm 0.63$, $p = .03$) (Davidson et al., 2000) but not with finger tapping speed (either hand) at age 9 yr (Myers et al., 2003). In the New Zealand birth cohort study, there was an inverse association of borderline statistical significance between McCarthy motor scale scores at age 6–7 and average prenatal hair mercury levels (Crump et al., 1998). These authors estimated the bench mark dose and its lower limit for average prenatal hair mercury versus abnormal McCarthy motor scale scores to be, respectively, 21 and 9.8 μg/g. A cross-sectional study of children age 0–6 in French Guiana reported no association between maternal hair mercury and finger tapping speed ($\beta = 1.27$, $p = .64$) or McCarthy leg coordination scores ($\beta = -0.15$, $p = .62$) (Cordier et al., 2002).

Low-level childhood MeHg exposure, inadequate evidence: After adjustment for cord blood mercury, finger tapping scores at age 7 yr in the Faroe Islands birth cohort study were not associated with current hair mercury (Grandjean et al., 1997, 1999). In a cross-sectional study of German children age 5–7, finger tapping speed was not associated with current urinary mercury excretion rates (μg/d) ($\beta = 0.32$, $p > .05$) (Walkowiak et al., 1998). A larger cross-sectional study of children age 7–12 in the Amazon Basin reported inverse associations between log current hair mercury levels and finger tapping speed (preferred hand, $\beta = -6.53$, $p < .001$) and motor coordination and dexterity score ($\beta = -2.23$, $p = .005$) (Grandjean et al., 1999).

Cadmium Low-level childhood exposure, inadequate evidence: A small cross-sectional study of children age 5–16 in Maryland reported an inverse association between current hair cadmium levels and fine motor function (finger tapping score vs. hair cadmium, partial $R = -0.20$, $p = .05$) (Thatcher et al., 1982).

Manganese High-level childhood manganese exposure, sufficient evidence: Case reports indicate that children exposed to high levels of manganese from chronic parenteral nutrition developed neurologic abnormalities including mild psychomotor retardation, frequent static and intention tremor and magnetic resonance imaging (MRI) abnormalities (Fell et al., 1996; Komaki et al., 1999). The latter report indicated that symptoms and MRI abnormalities disappeared after manganese administration ceased (Komaki et al., 1999). Reviewers concluded that children exposed to high manganese levels because of liver disease with impaired excretion or dependency on parenteral nutrition developed neurotoxicity including loss of motor control of limbs and tremor (Agency for Toxic Substances and Disease Registry, 2000b).

PCBs Background maternal PCB exposure, inadequate evidence: A Dutch birth cohort study found no associations between neurologic optimality scores at age 42 mo and cord or maternal levels of 4 noncoplanar PCBs (results stated without supporting data) (Lanting et al., 1998b). Further follow-up of this cohort revealed a statistically nonsignificant association between McCarthy motor subscale scores at age 6–7 and 3rd trimester maternal plasma levels of 4 noncoplanar PCBs (per natural log PCB increment, all children, $\beta = -2.45 \pm 1.45$, $p = .09$, adjusted for breastfeeding duration); this association was somewhat stronger among the formula-fed subgroup ($\beta = -3.92 \pm 2.04$, $p = .06$) (Vreugdenhil et al., 2002). In the Faroe Islands birth cohort, fine motor function test scores at age 7 were not associated with log cord tissue levels of 3 noncoplanar PCBs, adjusted for cord blood mercury levels and other potential confounders

(finger tapping score, preferred hand, $\beta = -0.76$, $p = .30$; hand-eye coordination errors, $\beta = 0.04$, $p = .26$) (Grandjean et al., 2001).

Background lactational PCB exposure, inadequate evidence: A Dutch birth cohort study found no associations between neurologic optimality scores at age 42 mo and breast milk PCB-TEQ levels (results stated without supporting data) (Lanting et al., 1998b). Further follow-up of this cohort revealed an association of borderline statistical significance between McCarthy motor subscale scores at age 6–7 and 3rd trimester maternal plasma levels of 4 noncoplanar PCBs among formula-fed but not among breastfed children (per natural log PCB increment, formula-fed, $\beta = -3.92 \pm 2.04$, $p = .06$; breastfed, $\beta = -1.28 \pm 1.84$, $p = .49$, adjusted for breastfeeding duration) (Vreugdenhil et al., 2002).

Pesticides Childhood exposure, organophosphate pesticides, inadequate evidence: A small cross-sectional study of children age 2–11 living in homes where methyl parathion had been illegally used for pest control in Mississippi and Ohio reported no association between lowest decile motor function scores and exposure status (exposed vs. unexposed, Mississippi, OR = 1.39, 95% CI 0.66–2.94; Ohio, OR = 1.20, 95% CI 0.42–3.49) (Ruckart et al., 2004).

Childhood exposure, hexachlorobenzene, inadequate evidence: Follow-up of adults exposed to hexachlorobenzene as children (after eating treated seed grain) revealed that about half had weakness, myotonia and other neurological symptoms (Gocmen et al., 1989). There were no analyses of these traits in relation to exposure intensity.

Summary There was limited epidemiologic evidence for the role of environmental toxicants in motor deficits among children age 3 yr or older including low-level childhood lead exposure and low-level prenatal MeHg exposure.

Sensory Function

Maternal exposure, limited evidence: In the Cincinnati birth cohort, central auditory processing ability at age 5 yr was inversely associated with neonatal and childhood blood lead levels (Dietrich et al., 1992). Among neonates in Mexico City, wave III latencies (the time intervals between auditory stimuli and brainstem responses as detected on electroencephalographs, EEGs) were inversely associated with prenatal and cord blood lead levels; wave III–V interpeak intervals were associated with prenatal blood lead levels over the range 6–25 μg/dl (Rothenberg et al., 1994). Follow-up of this cohort found a dose-response relationship between I-V and III-V conduction intervals at age 5 yr and maternal 2nd trimester blood lead levels over the range 8–31 μg/dl (Rothenberg et al., 2000).

Auditory function Lead Childhood exposure, limited evidence: Evidence from two large well-designed cross-sectional studies based on NHANES II and a similar survey of the U.S. Hispanic population (Schwartz & Otto, 1987, 1991) and a Polish cohort study (Osman et al., 1999) suggests that childhood lead exposure produces increased hearing thresholds. Findings included monotonic dose-response relationships extending to blood lead levels below 10 μg/dl with no evidence of a threshold (Schwartz, 1993). Reviewers concluded that epidemiologic and toxicologic evidence support a relationship between increased hearing thresholds and low or moderate lead exposure (Otto & Fox, 1993). Cross-sectional studies in Massachusetts and Denmark but not in Ecuador observed unfavourable associations between central auditory processing indices and dentin or current blood lead levels (Counter et al., 1997; Hansen et al., 1989; Needleman et al., 1979). A review concluded that epidemiologic and toxicologic evidence indicate increased brainstem auditory evoked potential latencies at low to moderate lead exposure levels (Otto & Fox, 1993). The Mexico City cohort found inverse (i.e., apparently favorable) associations between I-V interpeak latencies at age 5 years and blood lead levels at ages 1 and 4 years; there were similar associations for III-V latencies (Rothenberg et al., 2000). The authors speculated that these results might be explained by reduced auditory brainstem pathway length caused by lead exposure (similar to the known inverse association between head circumference and lead exposure). Among Chinese children age 1–6 yr, auditory evoked potential latencies were associated with blood lead over the range 3–38 μg/dl and were significantly increased at levels above 10 μg/dl (Zou et al., 2003).

Methylmercury High-level prenatal exposure, sufficient evidence: During the 1972 Iraq MeHg poisoning episode, many of the most affected infants had severely impaired hearing (Amin-Zaki

et al., 1974b, 1979), a finding supported by several reviewers (Clarkson, 2002; National Academy of Sciences, 2000c; United Nations Environment Programme, 2002).

Low-level prenatal exposure, limited evidence: In the Faroe Islands birth cohort, hearing thresholds at age 14 yr were not associated with cord blood mercury except for an inverse association for right ear threshold at 4 kHz (p-trend$<.01$) (Murata et al., 2004). However, brain stem auditory-evoked potential latencies and interpeak intervals at age 7 and 14 were associated with prenatal hair and cord blood mercury levels (e.g., age 7, change in potential III latency at 40 Hz per log cord blood mercury increment, $\beta = 0.108$, $p = .02$) (Murata et al., 1999, 2004). Combined analysis of the Faroe Islands and Madeira studies yielded a benchmark dose for prenatal hair mercury of 9.5 μg/g for a doubling of a 5% prevalence of abnormal auditory-evoked potential latencies at 40 Hz, with similar results at 20 Hz (Murata et al., 2002). A reviewer concluded that prenatal or childhood MeHg exposure affects auditory systems at the cortical level (Newland 2002).

Childhood (United Nations Environment Programme, 2002) exposure, inadequate evidence: A small cross-sectional study of Ecuadorian children age 3–15 yr reported an inverse (i.e., favourable) association between current blood mercury levels and hearing threshold at 3 kHz in the right ear (Pearson $r = .55$, $p = .01$) but not the left ear (Counter et al., 1998). This study also found associations between brainstem auditory-evoked potential wave V latencies and I-V interpeak intervals at age 3–15 and current child blood mercury levels (e.g., wave V latency vs. current blood mercury, Spearman $R = 0.38$, $p = .03$) but there was no adjustment for potential confounders (Counter, 2003). In the Faroe Islands birth cohort study, brain stem auditory-evoked potential latencies and interpeak intervals at age 7 and 14 were not associated with current child hair mercury levels (e.g., age 7, change in potential III latency at 40 Hz per log child hair mercury increment, $\beta = 0.002$, $p = .96$) (Murata et al., 1999, 2004).

PCBs High-level maternal PCB/PCDF exposure, limited evidence: Yucheng children age 7–12 prenatally exposed to high levels of PCBs, PCDFs and related toxicants had increased auditory-evoked potential latencies compared to those of unexposed children (mean auditory-evoked potential latencies, 356.0 ± 36.9 ms vs. 329.3 ± 25.5 ms, $t = 3.09$, $p = .003$) (Chen & Hsu, 1994).

Background maternal PCB exposure, limited evidence: In the Faroe Islands birth cohort, there was no association between auditory-evoked potential latencies at age 7 yr and umbilical cord tissue levels of 3 noncoplanar PCBs (change in latency per log increment cord tissue levels of 3 noncoplanar PCBs, 20 Hz III $\beta = 0.02$ ms, $p = .68$; 20 Hz V $\beta = 0.07$ ms, $p = .08$; 40 Hz III $\beta = 0.05$ ms, $p = .34$; 40 Hz V $\beta = 0.03$ ms, $p = .54$) (Grandjean et al., 2001). Among children age 9 in the Rotterdam component of the Dutch birth cohort study with 4th quartile maternal plasma levels of 4 noncoplanar PCBs, mean auditory-evoked potential latencies were greater than those of children with 1st quartile maternal plasma levels (adjusted mean latency difference, P300Fz 14.3 ± 9.5 ms, $p = .14$; P300Cz 25.6 ± 9.6 ms, $p = .01$; P300Pz 22.0 ± 9.4 ms, $p = .02$) (Vreugdenhil et al., 2004b). In the U.S. Collaborative Perinatal Project cohort, sensorineural hearing loss at age 8 was not associated with maternal serum PCB levels over the range <1.25 to ≥ 5 μg/L (p-trend $= .76$) (Longnecker et al., 2004).

Lactational PCB exposure, inadequate evidence: Among children age 9 in the Rotterdam component of the Dutch birth cohort study, those who were breast-fed for at least 17 wk had reduced auditory-evoked potential latencies compared to those who were formula-fed (adjusted mean latency difference, P300Fz –19.8 ± 10.8 ms, $p = .07$; P300Cz–20.2 ± 10.9 ms, $p = .07$; P300Pz –22.5 ± 10.6 ms, $p = .04$) (Vreugdenhil et al., 2004b).

Summary There is sufficient epidemiologic evidence that high-level prenatal or childhood MeHg exposure produces auditory and visual function deficits. Limited evidence supports associations between auditory function deficits and low-level prenatal or childhood lead exposure, low-level prenatal MeHg exposure or prenatal exposure to PCBs, PCDFs, and related toxicants can impair auditory function in children.

Visual function *Lead* Childhood exposure, inadequate evidence: A German cross-sectional study of children age 6 reported no association between visual evoked potential (VEP) latencies and current blood lead levels over the range 1.3–19.0 μg/dl; among 6 relationships explored, only one was related to tooth lead concentrations (F2/N2 was inversely associated with tooth lead, $p = .06$) (Winneke et al., 1994).

Methylmercury Maternal exposure, inadequate evidence: VEP latencies at age 7 were not associated with cord blood mercury in the Faroe Islands birth cohort study (Grandjean et al., 1997). In a cross-sectional study of children age 6–7 in Madeira, N145, N75-N145 and P100-N145 VEP latencies were associated with maternal hair mercury levels (Murata et al., 1999). A pooled study of children age 7–12 in Greenland, Madeira and the Faroes observed no association between VEP latencies and prenatal hair mercury levels (Weihe et al., 2002). A Quebec birth cohort study revealed associations between P100 VEP latencies and cord blood mercury levels (Saint-Amour et al., 2006). It should be noted, however, that high-level prenatal or early childhood MeHg exposure in Iraq caused blindness in several children (Amin-Zaki et al., 1974a, 1974b).

Childhood exposure, inadequate evidence: A German cross-sectional study revealed no association between VEP latencies at age 7 and current urinary mercury levels (Altmann et al., 1998). However, 4 of 10 contrast sensitivity values tested, indicators of visual cortical function, were inversely associated with current urinary mercury levels. In the Madeira cross-sectional study, only P100-N145 VEP latencies were associated with current child hair mercury levels (Murata et al., 1999). The Quebec birth cohort study reported inverse associations between N75 and P100 VEP latencies and current child blood mercury levels, independent of potential confounders including maternal alcohol or marijuana use and current child blood PCB levels (Saint-Amour et al., 2006). Although inverse associations between VEP latencies and child blood mercury levels might be attributed to a favorable effect of a high-fish diet, both increased and reduced latencies might reflect disruption of visual processing (Saint-Amour et al., 2006).

PCBs High-level maternal PCB/PCDF exposure, limited evidence: Yucheng children age 7–12 yr prenatally exposed to high levels of PCBs, PCDFs, and related toxicants had visual-evoked potential latencies similar to those of unexposed children (mean visual-evoked potential latencies, 148.7 ± 15.0 ms vs. 153.1 ± 19.2 ms, $t = 0.94$, $p = .35$) (Chen & Hsu, 1994).

Background maternal PCB exposure, limited evidence: In the Faroe Islands birth cohort, there was no association between visual-evoked potential latencies at age 7 yr and umbilical cord tissue levels of 3 noncoplanar PCBs (change in latency per log increment cord tissue levels of 3 noncoplanar PCBs, N75 $\beta = 0.74$ ms, $p = .26$; P100 $\beta = 1.44$ ms, $p = .22$; N145 $\beta = 3.35$ ms, $p = .11$) (Grandjean et al., 2001). A Quebec birth cohort study reported no association between VEP latencies and cord plasma PCB-153 levels (result stated without supporting data) (Saint-Amour et al., 2006).

Lactational PCB exposure, inadequate evidence: The Quebec birth cohort study observed associations between P100 and N150 VEP latencies and current child blood PCB levels, independent of potential confounders including maternal alcohol or marijuana use and current child blood mercury levels (change in latency per natural log increment of cord plasma PCB-153, 12% contrast, N75 $\beta = -0.44$ ms, $p > .05$; P100 $\beta = 3.22$ ms, $p < .05$; N150 $\beta = 5.58$ ms, $p < .05$) (Saint-Amour et al., 2006). Current plasma PCB levels in young children with a history of breastfeeding mainly reflect lactational exposure.

Respiratory Diseases

Lower respiratory tract diseases (including asthma, bronchiolitis/bronchitis and pneumonia) are the leading cause of hospitalization among U.S. children age 1–9 yr (U.S. Department of Health and Human Services, 2003). Over 4 million U.S. children have asthma and asthma prevalence, and morbidity and mortality rates increased substantially among children and young adults during recent decades in Canada and other developed countries (Commission for Environmental Cooperation, 2006; Millar & Hill, 1998). Upper respiratory tract infections are major causes of illness leading to physician visits. There were about 8 million physician visits for middle ear infections among children age 0–12 yr in United States during 2004 (Hing et al., 2006).

The level of epidemiologic evidence for associations between major childhood respiratory diseases and environmental chemical contaminants is summarized in Table 5. Sufficient evidence was found for associations between: (1) new onset asthma and ETS, (2) asthma severity and ETS and outdoor air pollution, and (3) lung and middle ear infections and ETS. Children in household with relatively low socioeconomic status are at increased risk of exposure to the above environmental

TABLE 5. Role of Environmental Toxicants in Common Childhood Respiratory Diseases

Toxicant	Exposure	New-onset childhood asthma	Childhood asthma severity	Childhood lung infections	Childhood middle ear Infections
PCBs	Prenatal			High-level—**L** Low-level—I	High-level—I Low-level—I
	Lactational			I	**L**
DDT/DDE	Prenatal			I	
	Lactational or childhood	I		I	**L**
Other organochlorine pesticides	Lactational or childhood	I		I	I
Unspecified pesticides	Prenatal			I	
	Childhood	I			
Environmental tobacco smoke	Childhood	**S**	**S**	**S**	**S**
Indoor air NO_2	Childhood	I			
Indoor chlorinated swimming pools	Childhood	**L**			
Indoor house dust, di(2-ethylhexyl) phthalate	Childhood	**L**			
Indoor air, VOCs	Childhood	I			
Indoor air, formaldehyde	Childhood	**L**			
Indoor biomass smoke	Childhood		**L**	**S**	**L**
Outdoor air pollution	Childhood	**L**	**S**	**L**	**L**

risk factors for respiratory diseases (Almqvist et al., 2005; Perera et al., 2002; Shapiro & Stout, 2002). Relatively little is known about critical exposure time windows for the influence of environmental agents on the risk of childhood respiratory diseases. However, prenatal and early-life exposures may be especially important as lung development continues from the prenatal period through adolescence (Dietert et al., 2000; Pinkerton & Joad, 2000).

New-Onset Asthma

Pesticides Maternal exposure, organochlorine pesticides, inadequate evidence: A prospective study of Spanish children revealed an association between wheezing at age 4 yr and cord serum DDE levels (4th vs. 1st quartile serum DDE, RR = 2.63,95% CI 1.19–4.69) (Sunyer et al., 2005). There were also associations between cord serum DDE and persistent wheezing (wheezing at age 4 yr and during previous year) (RR = 1.26, 95% CI 1.04–1.54) and for physician-diagnosed asthma (RR = 1.46, 95% CI 0.92–2.32). No associations were observed between wheezing and cord serum HCB quartiles.

Maternal exposure, unspecified pesticides, inadequate evidence: The Ontario Farm Family Study found no association between physician-diagnosed childhood asthma and prenatal farm pesticide use (any vs. none, OR = 1.00, 95% CI 0.71–1.40) or any specific pesticide (Weselak et al., 2007).

Paternal exposure, chlorophenoxy herbicides, inadequate evidence: Among U.S. Vietnam veterans, the prevalence of parent-reported asthma up to age 5 yr was higher than that among children of non-Vietnam veterans (crude OR = 1.1, 95% CI 1.0–1.4) (Centers for Disease Control, 1989). Potential limitations include differential recall bias as well as a lack of data on maternal and other environmental exposures.

Childhood exposure, DDT/DDE or HCB, inadequate evidence: In a retrospective cohort study of German children age 7–10, physician-diagnosed asthma was associated with blood DDE (≥0.3 vs. <0.3 μg/L, OR = 3.71, 95% CI 1.10–12.6) but not with HCB levels (Karmaus et al., 2001). Further investigation showed that an inverse association between asthma and a history of breast feeding was strongest among children with blood DDE levels below 0.29 μg/L (Karmaus et al., 2003).

Childhood exposure, unspecified pesticides, inadequate evidence: A retrospective cohort study of Lebanese children age 5–16 yr indicated associations between physician-diagnosed asthma and

parent-reported residential proximity to agricultural pesticide use (OR = 2.10, 95% CI 1.01–4.42), residential pesticide use (home or garden use, yes vs. no, OR = 1.99, 95% CI 1.00–3.99) or parental occupational pesticide exposure (OR = 4.61, 95% CI 2.06–10.3) (all ORs adjusted for ETS and other risk factors) (Salameh et al., 2003). The questionnaire used in this study did not permit assessment of age at diagnosis of asthma or pesticide exposure before the onset of asthma. Also, there was potential for recall bias in parental completion of the questionnaire.

A case-control study nested within the Children's Health Study revealed that onset of asthma by age 3 and persistent to at least age 5 was associated with exposure beginning before age 1 to residential or agricultural use of any pesticide (OR = 3.58, 95% CI 1.59–8.06) and herbicides in particular (OR = 10.1, 95% CI 2.46–41.3) (Salam et al., 2004). The latter study found no link with pesticide exposure beginning after age 1 yr.

Environmental tobacco smoke Early childhood exposure, sufficient evidence: Several recent reviews concluded that incident childhood asthma is associated with childhood ETS exposure (California Environmental Protection Agency, 2005; DiFranza et al., 2004; Jaakkola & Jaakkola, 2002; World Health Organization 1999). The California expert panel noted that the evidence is particularly strong for young children and those whose mothers smoked during pregnancy (California Environmental Protection Agency, 2005). A meta-analysis of 4 cohort studies indicated an association between incident asthma before age 8 yr and maternal smoking (summary OR = 1.31, 95% CI 1.22–1.41) (Strachan & Cook, 1998b). A UK birth cohort study reported that incident asthma/wheeze by age 3 yr was associated with postnatal maternal smoking, independent of prenatal smoking and other potential confounders (OR = 1.93, 95% CI 1.10–3.38) (Murray et al., 2004). A recent case-control study nested in the Children's Health Study in California reported a statistically nonsignificant increased risk of asthma before age 5 among children in homes with 2 or more smokers (OR = 1.3, 95% CI 0.8–2.1, not adjusted for prenatal smoking) (Li et al., 2005).

Indoor gases Childhood exposure, inadequate evidence: At relatively high levels, nitrogen dioxide (NO_2) can precipitate asthma episodes but there is inadequate evidence to assess its role in asthma development (National Academy of Sciences, 2000a). See also later discussion of outdoor air pollution, since NO_2 is a major ambient air pollutant and respiratory toxicant.

Other indoor contaminants Childhood exposure, indoor chlorinated swimming pools, limited evidence: Ecologic studies in Belgium and Europe revealed associations between the prevalence of exercise-induced asthma among children in 15 schools and cumulated frequency of indoor swimming pool attendance (Bernard et al., 2003) and between the prevalence of self-reported childhood asthma in 66 European cities and the per capita prevalence of indoor chlorinated swimming pools (Nickmilder & Bernard, 2007). Further investigation in Belgium showed a dose-response relationship between childhood asthma and cumulated indoor chlorinated pool attendance among the subset with elevated serum immunoglobulin (Ig) E levels, especially among those exposed before age 7, and independent of other risk factors including ETS (physician-diagnosed asthma, serum IgE >100 kIU/L, per 100 h cumulative exposure, OR = 1.57, 95% CI 1.07–2.30) (Bernard et al., 2006). Chlorinated swimming pools contain DBPs including volatile compounds that are inhaled by swimmers; nitrogen trichloride is the most volatile and concentrated DBP in the air of indoor pools and is a powerful respiratory tract irritant (Hery et al., 1995).

Childhood exposure, various VOCs, inadequate evidence: In an Australian case-control study, asthma among preschool children was associated with residential indoor air concentrations of several VOCs, particularly benzene (per 10 mg/m^3 increment, OR = 2.92, 95% CI 2.25–3.80), ethylbenzene (OR = 2.54, 95% CI 1.16–5.57) and toluene (OR = 1.84, 95% CI 1.41–2.41) (Rumchev et al., 2004).

Childhood exposure, formaldehyde, limited evidence: A recent review found limited evidence for an association between childhood asthma and indoor levels of formaldehyde or the presence of formaldehyde-emitting materials (Mendell, 2007). Because such materials also emit other VOCs including aldehydes, it is uncertain that formaldehyde per se explains the latter association.

Childhood exposure, house dust di(2-ethylhexyl) phthalate (DEHP), limited evidence: A nested case-control study in Sweden revealed a dose-response relationship between childhood asthma and house dust DEHP concentrations (ORs for increasing quartiles relative to 1st quartile were 1.56,

95% CI 0.70–3.46, 2.05, 95% CI 0.94–4.47 and 2.93, 95% CI 1.36–6.34) (Bornehag et al., 2004). A similar study in Bulgaria showed a dose-response relationship between wheezing among children age 2–7 and house dust DEHP levels (4^{th} vs. 1^{st} quartile dust DEHP levels, OR = 3.7, 95% CI 1.4–9.9, *p*-trend = 0.02) (Kolarik et al., 2007).

Outdoor air pollution Childhood exposure, limited evidence: A reviewer found overwhelming evidence that ambient air pollution from traffic increases the risk of developing asthma during childhood (Schwartz, 2004). A WHO expert panel reviewed studies published up to 2004 and concluded that there is little evidence for a causal association between childhood asthma prevalence/incidence and air pollution in general, but there is suggestive evidence for a causal association between the prevalence/incidence of childhood asthma symptoms and living in close proximity to traffic (Binkova et al., 2005). Among reviewed studies, cohort studies in Japan, Germany and California found associations, including dose-response relationships, between incident asthma in young children and ambient air levels of one or more pollutants including ozone, NO_2 and PM (Gehring et al., 2002; McConnell et al., 2002; Shima & Adachi, 2000; Shima et al., 2002). Among high-ozone communities in the California cohort study, there was a dose-response relationship between incident asthma and number of team sports engaged in by subjects (OR = 3.3, 95% CI 1.9–5.8) with a somewhat stronger association among children without a history of wheeze at baseline (OR = 4.4, 95% CI 2.1–9.3) (McConnell et al., 2002). The California study also observed associations between incident asthma and team sports participation in both low- and high-PM_{10} communities (low PM_{10}, OR = 1.7, 95% CI 0.9–3.2; high PM_{10}, OR = 2.0, 95% CI 1.1–3.6). A cohort study in the Netherlands found weak associations between incident asthma before age 2 yr and ambient air PM (per interquartile range, OR = 1.12, 95% CI 0.84–1.50) and NO_2 (per interquartile range, OR = 1.18, 95% CI 0.93–1.51) levels (Brauer et al., 2002). The Japanese cohort study reported a moderately strong association between incident asthma in young children and residential proximity to main roads (<50 m vs. rural residence, girls, OR = 4.06, 95% CI 0.91–18.1; boys, OR = 3.75, 95% CI 1.00–14.1) (Shima et al., 2003). A small case-control study in France revealed an association between childhood incident asthma and cumulative traffic density exposure before age 3 (3rd vs. 1st tertile, OR = 2.28, 95% CI 1.14–4.56) (Zmirou et al., 2004). In a new California cohort study, incident asthma by age 5–7 was associated with residential proximity to a main road (<75 vs. >300 m, all children, OR = 1.29, 95% CI 1.01–1.66; long-term residents, OR = 1.46, 95% CI 0.98–2.17) (McConnell et al., 2006). This relationship was limited to girls (OR = 2.51, 95% CI 1.39–4.54; boys, OR = 0.94, 95% CI 0.54–1.64).

Summary Epidemiologic evidence for the role of environmental toxicants in new-onset childhood asthma includes: (a) sufficient evidence—childhood ETS exposure; (b) limited evidence—childhood indoor chlorinated swimming pool use, house dust di(2-ethylhexyl)phthalate, indoor air formaldehyde and residential outdoor air pollution (mainly traffic-related). Although limited, the evidence linking ambient air pollution to incident asthma is quite strong and suggestive of a causal relationship.

Asthma Severity

Pesticides Childhood exposure, organophosphate and pyrethroid insecticides, inadequate evidence: In New York City, daily asthma emergency department visits in the South Bronx did not change significantly during the 1999 West Nile Virus mosquito control campaign in which malathion (an organophosphate insecticide) was aerially sprayed and resmethin (a pyrethroid insecticide) was sprayed from trucks for 4 d (O'sullivan et al., 2005). This study did not measure individual exposure or control for other environmental factors. Another study assessed emergency room visits to all 11 public hospitals in New York City during a 14-mo period including the 2000 West Nile Virus campaign in which pyrethroid pesticides were sprayed from truck from July to September 2000 (Karpati et al., 2004). ZIP codes were used to assign spraying versus nonspraying exposure and residence location at the time of emergency department presentation. No difference in emergency department presentation for asthma was observed among children age <15 yr during the 3 d before and after spraying (RR = 0.78, 95% CI 0.61–1.01). No association was observed among ZIP codes considered that received the heaviest spraying. Although the New York City studies evaluated

the effects of low levels of pesticide exposure among the general population, these studies only considered asthma symptoms severe enough to require presentation to a hospital. It is possible that more subtle respiratory effects may have been experienced. Additionally, an ecologic indicator of exposure was used; therefore the precise level of personal exposure is also unknown.

Childhood exposure, unspecified pesticides, inadequate evidence: A cross-sectional study in New Jersey revealed a slightly elevated risk of peak flow test failure among children in grades 2–3 exposed to indoor residential use of pesticide sprays or powders (OR = 1.12, 95% CI 0.88–1.41) and those in grades 3–4 (OR = 1.30, 95% CI 0.97–1.74) but not those in grade 5 (OR = 0.86, 95% CI 0.50–1.49) (Schneider et al., 2004). This study experienced declining response rates and changes in protocol and staff over the 4-year study period and lacked information on other potentially related environmental influences.

Environmental tobacco smoke Childhood exposure, sufficient evidence: Several reviews concluded that the frequency and severity of symptoms among asthmatic children is associated with postnatal ETS exposure (California Environmental Protection Agency, 2005; DiFranza et al., 2004; Jaakkola & Jaakkola, 2002; World Health Organization, 1999). Three expert panel reviews concluded that this association is causal (California Environmental Protection Agency, 2005; U.S. Department of Health and Human Services, 2006; World Health Organization 1999).

Other indoor air pollutants Childhood exposure, biomass smoke, limited evidence: A WHO review panel found limited evidence for an association between increased childhood asthma severity and exposure to biomass smoke in developing countries (Bruce et al. 2002).

Outdoor air pollution Childhood exposure, sufficient evidence: Reviewers noted evidence that summertime ozone elevations increase childhood asthma severity as indicated by reduced lung function, more symptoms and more episodes requiring medical attention (including ER visits) (Suh et al., 2000). A WHO expert panel reviewed studies published up to 2004 and concluded that there is sufficient evidence for a causal association between childhood asthma exacerbation and air pollution, mainly due to PM and ozone (Binkova et al., 2005). In an ecologic study in Vancouver, Canada, asthma hospitalizations among girls age 6–12 yr in low household income families (based on small area census data) were associated with 4-d average SO_2 levels (OR = 1.18, 95% CI 1.02–1.36); there was no association for girls in higher household income families (OR = 0.99, 95% CI 0.85–1.15) or for boys in either group (Lin et al., 2004). In a new California cohort study, current wheeze among children age 5–7 was associated with residential proximity to a main road (<75 vs. >300 m, all children, OR = 1.40, 95% CI 1.09–1.78; long-term residents, OR = 1.67, 95% CI 1.14–2.43) (McConnell et al., 2006).

Summary There is sufficient epidemiologic evidence for causal associations between childhood asthma severity and postnatal exposure to ETS or outdoor air pollution and limited evidence for an association with indoor exposure to biomass smoke (mainly in developing countries).

Lung Infections

PCBs High-level maternal PCB/PCDF exposure, limited evidence: A retrospective cohort study of Yucheng children age 6 yr revealed a substantially increased prevalence of a history of bronchitis or pneumonia by age 6 mo (exposed vs. comparison children, OR = 7.02, 95% CI 2.74–21.0; calculated from data in paper) (Rogan et al., 1988). A WHO expert group concluded that high-level maternal PCB/PCDF exposure was associated with increased risk of bronchitis among infants (Brouwer et al., 1998).

Background maternal PCB exposure, inadequate evidence: Reviews of epidemiologic studies published up to the mid–1990s found inadequate evidence for an association between risk of infections during infancy and background maternal PCB exposure levels (Longnecker et al., 1997; Tryphonas, 1998). A multicentre Dutch birth cohort study reported no association between a history of pneumonia by age 42 mo and maternal plasma PCB (per natural log increment of maternal plasma PCB, OR = 0.41, 95% CI 0.10–1.63, adjusted for breastfeeding history and duration) (Weisglas-Kuperus et al., 2000). Among Inuit women and infants in northern Quebec, a history of clinically confirmed lower respiratory tract infection by age 12 mo was not associated with maternal plasma PCB–153 levels (4th vs. 1st quartile plasma PCB–153, OR = 1.03, 95% CI 0.72–1.48,

p-trend = .36) (Dallaire et al., 2004). In a similar study, a clinically confirmed history of lower respiratory tract infection by age 5 yr was associated with cord plasma PCB–153 (4th vs. 1st quartile, OR = 1.44, 95% CI 1.20–1.72) with evidence of a dose-response relationship (per log cord plasma PCB–153 increment, OR = 1.14, 95% CI 1.04–1.24) (Dallaire et al., 2006).

Lactational PCB exposure, inadequate evidence: The Dutch birth cohort study revealed an inverse association between a history of pneumonia by age 42 mo and current child plasma PCB, an index of lactational exposure (per natural log increment of child plasma PCB (μg/L), OR = 0.0.01, 95% CI 0.01–0.37, adjusted for breastfeeding vs. formula feeding and duration of breastfeeding) (Weisglas-Kuperus et al., 2000). In a German cross-sectional study of children age 7–10 yr, a history of physician-diagnosed pneumonia was not associated with whole blood PCB levels stratified by whole blood DDE levels (for DDE <0.3 μg/L, PCB >0.48 vs. ≤0 0.48 μg/L, OR = 1.24, 95% CI 0.53–2.92; for DDE ≥0.3 μg/L, PCB >0.48 vs. ≤0 0.48 μg/L, OR = 0.68, 95% CI 0.26–1.76) (Karmaus et al., 2001).

Pesticides Maternal exposure, DDT/DDE, inadequate evidence: A birth cohort study in northern Quebec revealed no association between a history of lower respiratory tract infection before age 6 mo (confirmed by medical chart review) and prenatal plasma DDE (4th vs. 1st quartile, OR = 0.96, 95% CI 0.55–1.66, *p*-trend = 0.89) (Dallaire et al., 2004).

Maternal exposure, other and unspecified pesticides, inadequate evidence: A retrospective cohort study of Ontario farm families revealed no association between a history of persistent cough or bronchitis and parent-reported prenatal farm use of any pesticide (OR = 1.21, 95% CI 0.77–1.90) or specific pesticides (Weselak et al., 2006). This study relied on parent recall of prenatal events often 10 yr or more before interview, raising the possibility of considerable exposure misclassification and attenuation of risk estimates.

Childhood exposure, DDT/DDE or HCB, inadequate evidence: A retrospective cohort study of German children age 7–10 revealed no association between current whole blood DDE levels and a history of physician-diagnosed whooping cough (≥0.3 vs. <0.3 μg/L, OR = 0.61, 95% CI 0.38–0.99) or pneumonia (OR = 0.79, 95% CI 0.45–1.40) (Karmaus et al., 2001). This study reported no association between these outcomes and blood HCB levels.

Environmental tobacco smoke Childhood exposure, sufficient evidence: A meta-analysis of 13 studies concluded that serious lower respiratory infection among young children age 0–6 was associated with ETS exposure (pooled OR = 1.57 95% CI = 1.28–1.91) (Li et al., 1999). Four recent reviews concluded that childhood ETS exposure is an important cause of lower respiratory infections during early childhood (California Environmental Protection Agency, 2005; Jaakkola & Jaakkola, 2002; U.S. Department of Health and Human Services, 2006; World Health Organization, 1999; California Environmental Protection Agency, 2005; Jaakkola & Jaakkola, 2002).

Other indoor air pollutants Childhood exposure, biomass smoke, sufficient evidence: A WHO review panel found sufficient evidence for an association between childhood pneumonia and exposure to biomass smoke in developing countries (Bruce et al. 2002). In developed countries, lower respiratory tract infections in children have been linked to indoor air PM_{10} concentrations related to use of wood-burning stoves ($PM_{10} \geq 65$ vs. <65 $\mu g/m^3$, crude OR = 7.0, 95% CI 0.9–56.9); the authors stated that the OR changed little after adjustment for other factors including ETS (Robin et al., 1996).

Outdoor air pollution Childhood exposure, limited evidence: Reviewers concluded that evidence from time-series and panel studies published up to 2000 supports an association between acute respiratory infection and outdoor air pollutants, especially $PM_{2.5}$ and ozone, but it was not clear whether ambient air pollutants affected respiratory infection incidence, severity or both (Romieu et al., 2002). Another reviewer noted consistent evidence for an association between childhood bronchitis and long-term exposure to PM and some evidence for reduced risk after abatement of such exposure (Schwartz 2004). Recently, a WHO expert panel concluded that air pollutants including PM_{10}, $PM_{2.5}$, NO_2, SO_2 and ozone are associated with upper and lower respiratory symptoms in children, much of which are likely related to infections (Binkova et al., 2005). In a large California retrospective cohort study, postneonatal respiratory deaths were associated with average $PM_{2.5}$ levels within 8 km of the maternal residence (per 10 $\mu g/m^3$ increment, OR = 2.13, 95% CI 1.12–4.05) (Woodruff et al., 2006).

Summary Epidemiologic evidence for the role of environmental toxicants in childhood lung infections includes: (a) sufficient evidence—childhood ETS and biomass smoke exposure; (b) limited evidence—high-level prenatal exposure to PCBs, PCDFs and related toxicants; childhood exposure to outdoor air pollution, mainly from traffic.

Middle Ear Infections

PCBs High-level maternal PCB/PCDF exposure, inadequate evidence: Yucheng children age 8–16 had a statistically nonsignificant increased risk of parent-reported ear infections during the 6 mo before their 1995 examination (mean frequency, exposed vs. unexposed, 0.67 ± 3.88 vs. 0.03 ± 0.22, $p>.05$) (Yu et al., 1998). However, Yucheng children had an increased risk of otolaryngologically confirmed chronic otitis media compared to unexposed children (OR = 3.23, 95% CI 1.70–6.23) (Chao et al., 1997). This study revealed associations between chronic otitis media and current serum PCDF levels (cases vs. controls, proportion with serum PCDF ≥400 ng/kg lipid, 5/15 vs. 0/15, $p = .04$) but not current serum PCB levels (cases vs. controls, proportion with serum PCB ≥4 mg/kg lipid, 5/15 vs. 4/15, $p = .86$).

Background maternal PCB exposure, inadequate evidence: In the Dutch birth cohort, a history of at least 6 ear infections by age 42 mo was weakly associated with maternal plasma levels of 4 noncoplanar PCBs (per natural log increment, OR = 1.37, 95% CI 0.87–2.17, adjusted for breastfeeding history and duration) (Weisglas-Kuperus et al., 2000). Further follow-up of this cohort showed that a history of recurrent otitis media at age 3–7 yr was not associated with maternal plasma PCB (per natural log increment of plasma PCB (μg/L), OR = 0.98, 95% CI 0.53–1.80) (Weisglas-Kuperus et al., 2004). In a cohort of Inuit infants, a history of otitis media by age 1 yr was not associated with prenatal plasma PCB-153 levels (4^{th} vs. 1^{st} quartile, OR = 0.97, 95% CI 0.73–1.28, p-trend = .89) (Dallaire et al., 2004). In a similar study, a clinically confirmed history of acute otitis media by age 5 yr was associated with cord plasma PCB–153 (4th vs. 1st quartile, OR = 1.37, 95% CI 1.20–1.55) with evidence of a dose-response relationship (per log cord plasma PCB–153 increment (μg/g lipid), OR = 1.12, 95% CI 1.05–1.20) (Dallaire et al., 2006).

Lactational PCB exposure, limited evidence: In the North Carolina birth cohort study, the prevalence of a history of ear infections before age 1 was lower (47%) among those in the highest cumulative lactational PCB dose category than that for formula-fed infants (58%) or those in the lowest cumulative lactational PCB dose category (50%); the authors did not include a statistical measure of the trend of prevalence versus PCB dose (Rogan et al., 1987). Among breastfed Quebec Inuit infants in the highest tertile of breast milk PCB levels, there were statistically nonsignificant elevated risks of otitis media (at least once before age 12 mo, 3rd vs. 1st tertile, OR = 1.28, 95% CI 0.92–1.77; at least 3 occurrences before age 1, OR = 1.65, 95% CI 0.49–5.57) (Dewailly et al., 2000). In the Dutch birth cohort, a history of 1 or more ear infections by age 42 mo was not associated with current child plasma PCB levels (per natural log plasma PCB increment, OR = 1.27, 95% CI 0.61–2.64, adjusted for breastfeeding history and duration) but there was an association for the occurrence of at least 6 ear infections by age 42 mo (per natural log plasma PCB increment, OR = 3.06, 95% CI 1.17–7.98) (Weisglas-Kuperus et al., 2000). This study also showed that recurrent otitis media was inversely associated with short lactational exposure (6–16 vs. ≥16 wk, OR = 0.12, 95% CI 0.01–1.07) (Weisglas-Kuperus et al., 2000). Plasma PCB levels at age 3–4 yr are 4–5 times higher among breast-fed compared to formula-fed children; thus plasma PCB levels in young children are a proxy for lactational exposure (Lanting et al., 1998a). Further follow-up of the Dutch birth cohort revealed that a history of recurrent otitis media at age 3–7 yr was associated with cumulative lactational PCB dose based on breast milk PCB levels times weeks of lactation (per natural log increment of lactational PCB dose (μg-week/g lipid), OR = 1.19, 95% CI 1.01–1.41) (Weisglas-Kuperus et al., 2004). Among German children age 7–10, a history of physician-diagnosed ear infections was associated with whole blood PCB levels among the subgroup of children with above-median whole blood DDE levels (whole blood PCB >0.48 vs. ≤0 0.48 μg/L, OR = 3.70, 95% CI 1.64–8.34) but not among children with below-median DDE levels, suggesting a possible interaction between these 2 exposures (Karmaus et al., 2001).

Pesticides Lactational exposure, DDT/DDE, limited evidence: Among breast-fed infants in northern Quebec, at least 1 occurrence of otitis media before age 1 was associated with breast milk levels of DDE (3rd vs. 1st tertile DDE, OR = 1.52, 95% CI 1.05–2.22) (Dewailly et al., 2000). This study observed stronger associations for a history of at least 3 occurrences of otitis media before age 1 yr and breast milk levels of DDE (3rd vs. 1st tertile DDE, OR = 3.48, 95% CI 0.86–14.1). In a cross-sectional study of German children age 7–10 yr, a history of physician-diagnosed otitis media was inversely associated with blood DDE (≥0.3 vs. <0.3 μg/L, OR = 0.50, 95% CI 0.31–0.79) (Karmaus et al., 2001). The latter study did observe an association between otitis media and above-median blood levels of both DDE and HCB (OR = 2.38, 95% CI 1.08–5.25). A birth cohort study in northern Quebec reported a dose-response relationship of borderline statistical significance between a history of otitis media before age 6 mo (confirmed by medical chart review) and prenatal plasma DDE (4^{th} vs. 1^{st} quartile, OR = 1.55, 95% CI 0.90–2.68, *p*-trend = 0.07) (Dallaire et al., 2004).

Lactational exposure, other organochlorine pesticides, inadequate evidence: Among breast-fed infants in northern Quebec, at least 1 occurrence of otitis media before age 1 yr was associated with breast milk levels of HCB (3rd vs. 1st tertile HCB, OR = 1.49, 95% CI 1.10–2.03), dieldrin (OR = 1.26, 95% CI 0.93–1.71) and mirex (OR = 1.36, 95% CI 0.99–1.86) (Dewailly et al., 2000). This study observed stronger associations for a history of at least 3 occurrences of otitis media before age 1 yr and breast milk levels of HCB (3rd vs. 1st tertile HCB, OR = 3.71, 95% CI 1.10–12.6) and dieldrin (OR = 3.50, 95% CI 0.95–13.0) (Dewailly et al., 2000). In a cross-sectional study of German children age 7–10 yr, a history of physician-diagnosed otitis media was unrelated to HCB levels (≥0.2 vs. <0.2 μg/L, OR = 1.25, 95% CI 0.60–2.62, among the subset of children with DDE <0.3 μg/L) (Karmaus et al., 2001). This study did observe an association between otitis media and above-median blood levels of both DDE and HCB (OR = 2.38, 95% CI 1.08–5.25).

Environmental tobacco smoke Childhood exposure, sufficient evidence: A pooled-analysis of seven studies found an association between recurrent middle ear infections and smoking by either or both parents (pooled OR = 1.48, 95% CI = 1.08–2.04) (Strachan & Cook, 1998a). A review of studies published up to 1998 concluded that middle ear disease was associated with parental smoking by either parent with stronger associations among pre-school compared to older children (Cook & Strachan, 1999). Four recent reviews, including two by expert panels, concluded that childhood ETS exposure can cause acute and chronic childhood middle ear infections (California Environmental Protection Agency, 2005; Jaakkola & Jaakkola, 2002; U.S. Department of Health and Human Services, 2006; World Health Organization, 1999).

Other indoor air pollutants Childhood exposure, biomass smoke, limited evidence: A WHO review panel found limited evidence for an association between childhood otitis media and exposure to biomass smoke in developing countries (Bruce et al., 2002).

Outdoor air pollution Childhood exposure, limited evidence: Reviewers found limited evidence for an association between otitis media and ambient air pollution (Bernard et al., 2006). A large cross-sectional study in the former East Germany reported associations between childhood middle ear infections and residential ambient air pollutant levels (per 50 $\mu g/m^3$ total suspended particulate increment, OR = 1.45, 95% CI 0.89–2.37; per 100 $\mu g/m^3$ SO_2 increment, OR = 1.42, 95% CI 0.94–2.15) (Heinrich et al., 2002). In a small Spanish birth cohort study, otitis media before age 1 yr was associated with residence in regions with high ambient SO_2 levels (median annual SO_2, 75 vs. 20 $\mu g/m^3$, OR = 2.01, 95% CI 1.05–3.84), independent of ETS and other potential confounders (Caceres Udina et al., 2004). In a large pregnancy cohort study in the Netherlands and Germany, otitis media by age 2 yr was associated with residential ambient air pollutant levels (Netherlands, per 3 $\mu g/m^3$ $PM_{2.5}$ increment, OR = 1.13, 95% CI 1.00–1.27; per 10 $\mu g/m^3$ NO_2 increment, OR = 1.14, 95% CI 1.03–1.27; similar results for Germany) (Brauer et al., 2006).

Summary Epidemiologic evidence for the role of environmental toxicants in childhood middle ear infections includes: (a) sufficient evidence—childhood ETS exposure; (b) limited evidence—lactational PCB exposure; lactational or childhood DDT/DDE exposure or childhood exposure to biomass smoke or outdoor air pollution, mainly from traffic.

Childhood Cancer

About 10,000 new-onset childhood cancers were anticipated to be diagnosed among children age 0–14 yr in the United States during 2006 (American Cancer Society, 2006). U.S. childhood brain cancer, leukemia, and neuroblastoma incidence rates increased during the mid–1980s and then stabilized, while Hodgkin's disease rates decreased and leukemia rates may have declined slightly (Linet et al., 1999). In contrast, overall childhood cancer incidence rates in Europe increased by 1.0% per year in children age 0–14 and by 1.5% in youth age 15–19 during 1970–1999 (Steliarova-Foucher et al., 2004). Cancer incidence rate trends reflect both true changes in risk over time but also any changes in diagnostic and reporting practices/efficiencies. Although it is not clear whether there have been sustained true increased cancer risks among children, the persistence of this devastating disease justifies enhanced research into environmental and other preventable causes.

Reviewers concluded that epidemiologic studies published up to early 1998 provided fairly consistent evidence of associations between parental occupational or childhood pesticide exposure and risk of childhood cancers, including leukemia, brain cancer, neuroblastoma, non-Hodgkin's lymphoma (NHL), Wilms's tumor, and Ewing's sarcoma (Zahm & Ward, 1998). A recent review noted that 15 case-control, 4 cohort, and 2 ecologic studies have since been published and that 15 of these 21 studies observed statistically significant increased risks between childhood cancer and parental occupational or childhood pesticide exposure (Infante-Rivard & Weichenthal, 2006). The authors concluded that there is an association between pesticide exposure and childhood cancer but the epidemiologic evidence is insufficient to prove a cause–effect relationship.

Although pesticides and some other environmental exposures (e.g., ionizing radiation) may increase overall cancer risk, discussion here focuses on specific types of childhood cancer. As discussed later, and summarized in Table 6, there is limited epidemiologic evidence for associations between several types of childhood cancer and parental or childhood exposure to pesticides, ETS or solvents.

Childhood Leukemia Childhood leukemia appears to have a clonal origin, developing from a single abnormal precursor cell over a period of several months to a leukemia cell burden of about 10^{12} cells (Ford et al., 1998; Ma et al., 1999; Mori et al., 2002; Taub & Ge, 2004). Analysis of routinely collected neonatal blood samples has revealed leukemia clones with specific chromosomal translocations (e.g., MLL-AF4[t(4;11)], MLL-AF4[t(12;21)]) in children who later developed acute lymphatic leukemia (ALL), suggesting that many such cases originate in utero (Gale et al., 1997). It is not known whether the abnormal cells detected in neonatal blood samples lead inevitably to childhood leukemia, but it appears that preleukemic clones can persist during childhood and that only a minority progress to leukemia, suggesting that postnatal exposures may be required for such progression (Maia et al., 2004).

Metals, metalloids Parental or childhood exposure, inadequate evidence: In a Denver case-control study, leukemia was not associated with likely paternal occupational arsenic exposure (based on job title) (OR = 0.7, 95% CI 0.2–2.7) (Feingold et al., 1992). A large population-based case-control study in Quebec found no association between childhood ALL and average prenatal drinking-water arsenic (>5 vs. ≤5 μg/L, OR = 0.94, 95% CI 0.49–1.81) or cumulative prenatal exposure (>95th vs. ≤95th percentile, μg-d/L, OR = 0.70, 95% CI 0.39–1.25); there was also no association with postnatal arsenic exposure indices or with lead or cadmium indices (Infante-Rivard et al., 2001). An ecologic study in Nevada reported no increased leukemia in areas where drinking-water arsenic levels were 10–25 (SIR = 0.61, 95% CI 0.12–1.79) or 35–90 μg/L (SIR = 0.86, 95% CI 0.37–1.70) (Moore et al., 2002).

PCBs Childhood exposure, inadequate evidence: A small German case-control study of childhood leukemia found no association with bone-marrow PCBs (mean concentration, cases vs. controls, 4.21 and 3.38 μg/g lipid, $p = .28$) (Scheele et al., 1992).

TCDD Paternal occupational exposure, inadequate evidence: Among children of sawmill workers in British Columbia, Canada, leukemia was not associated with paternal chlorophenate exposure duration (≥3000 vs. <3000 h cumulated exposure, OR = 0.8, 95% CI 0.2–3.6) (Heacock et al., 2000). An expert panel found insufficient evidence for an association between paternal phenoxy herbicide exposure and childhood cancer (National Academy of Sciences, 2003).

TABLE 6. Role of Environmental Toxicants in Childhood Cancer

Toxicant	Exposure	Leukemia	Lymphoma[k]	Brain	Neuroblastoma	Wilms's tumor	Other cancers
Lead	Prenatal	I			I		
	Paternal				**L**	I	
	Childhood	I					
Other metals, metalloids	Prenatal	As—I Cd—I Pb—I					
	Paternal	As —I		As—I			
	Childhood	As—I Cd—I Pb—I					
PCBs	Childhood	I					
TCDD and related toxicants	Paternal	I			I		
	Childhood	I					
Chlorophenate wood preservatives	Paternal	I		I			
	Childhood			I			
Herbicides	Prenatal	**L**		I		I	Germ cell—I Soft tis sarc—I
	Paternal	I		I			Germ cell—I
	Childhood	I	I	I	I	I	Soft tis sarc—I
Insecticides	Prenatal	**L**	I	**L**	I	I	Germ cell—I
	Paternal	I		I	I		Germ cell—I
	Childhood	**L**	I	**L**	I	I	Germ cell—I Bone—I
Fungicides	Prenatal			I			
	Paternal	I		I			
	Childhood	I	I	I			
Soil fumigants	Prenatal			I			
	Childhood	I	I	I			
Unspecified pesticides	Prenatal	I	I	I	I	I	Germ cell—I Bone—I Soft tis sarc—I Eye tumors - I
	Paternal	I	**L**	**L**	I	I	Germ cell—I Bone—L Soft tis sarc—I Eye tumors—I
	Childhood	I	I	**L**		I	Germ cell—I Bone—I
Active smoking	Prenatal	I	I	I			Germ cell—I
	Paternal[l]	**L**	**L**	**L**			Germ cell—I
Environmental tobacco Smoke	Prenatal	**L**	**L**	I			Germ cell—I
	Childhood	**L**	**L**				
Outdoor air pollution	Prenatal	I	I	I			
	Paternal[m]	**L**					
	Childhood	**L**	I	I			
Drinking water DBPs	Prenatal	I					
	Childhood	I					
Drinking water nitrate, nitrite	Prenatal	I		I			
	Childhood	I					
Hazardous waste disposal sites	Childhood	I					
Various and unspecified solvents	Prenatal	**L**	I	I	I		
	Paternal	I	I	I	I	I	
	Childhood	**L**	I	I			

Note. TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[k]Most studies assessed non-Hodgkin's lymphoma.

[l]Paternal smoking could act as a source of ETS exposure and/or through paternal germ-cell mutations.

[m]Paternal occupational exposure to motor vehicle exhaust emissions.

Childhood exposure, inadequate evidence: Follow-up of Seveso residents age 0–19 yr at the time of the 1976 chlorophenol plant explosion revealed no overall excess of incident cancer by 1986 (obs = 17, exp = 13.6, SIR = 1.2, 95% CI 0.7–2.1); there was a statistically nonsignificant excess of leukemia and other hematopoietic cancers (SIR = 1.6, 95% CI 0.7–3.4) (Pesatori et al., 1993). Much longer follow-up is needed to assess the risk of cancer after longer latent periods.

Pesticides Although pesticides may increase overall childhood cancer risk, discussion here focuses on specific types of cancer. A review of 18 epidemiologic studies published up to early 1998 noted that 13 studies reported increased childhood leukemia risk in relation to parental occupational or childhood pesticide exposure but did not clearly define the most critical exposures with regard to timing (preconceptual vs. gestational vs. childhood) or parent (maternal vs. paternal) (Zahm & Ward, 1998). A recent review noted that the 12 studies published since the Zahm and Ward paper generally support an association between childhood leukemia and pesticide exposure with the greatest risks being childhood exposure to household insecticides and parental exposure to pesticides before or during pregnancy (Infante-Rivard & Weichenthal, 2006). Other reviewers reached similar conclusions (Brown 2006; Buffler et al., 2005).

Maternal exposure, herbicides, limited evidence: As shown in Figure 3, leukemia was associated with prenatal residential herbicide application in case-control studies in Los Angeles (herbicides or other pesticides, OR = 9.0, 95% CI 1.25–394; the high odds ratio was based on 9/1 discordant pairs[3] in a matched-pairs analysis) (Lowengart et al., 1987), Quebec (any herbicide use, OR = 1.84, 95% CI 1.32–2.57; used more than 5 times vs. no use, OR = 3.72, 95% CI 0.72–19.1) (Infante-Rivard et al., 1999), California (prenatal residential herbicide use, OR = 1.6, 95% CI 0.9–3.0) (Ma et al., 2002), United States/Canada (frequency of use ≥median vs. none, OR = 1.84, 95% CI 0.91–3.73, *p*-trend = .13) (Alderton et al., 2006) and France (prenatal outdoor use of herbicides, OR = 5.9, 95% CI 0.7–52, 6 exposed case mothers) (Menegaux et al., 2006). The Quebec study also reported an association between ALL and prenatal use of herbicides alone (OR = 1.56, 95% CI 0.96–2.55) (Infante-Rivard et al., 1999).

Maternal exposure, insecticides, limited evidence: As shown in Figure 4, leukemia was associated with prenatal indoor insecticide use but not residential proximity to agricultural insecticide use. There were elevated risks in case-control studies in Los Angeles (≥1 vs. 0 times/wk, OR = 3.25, 95%

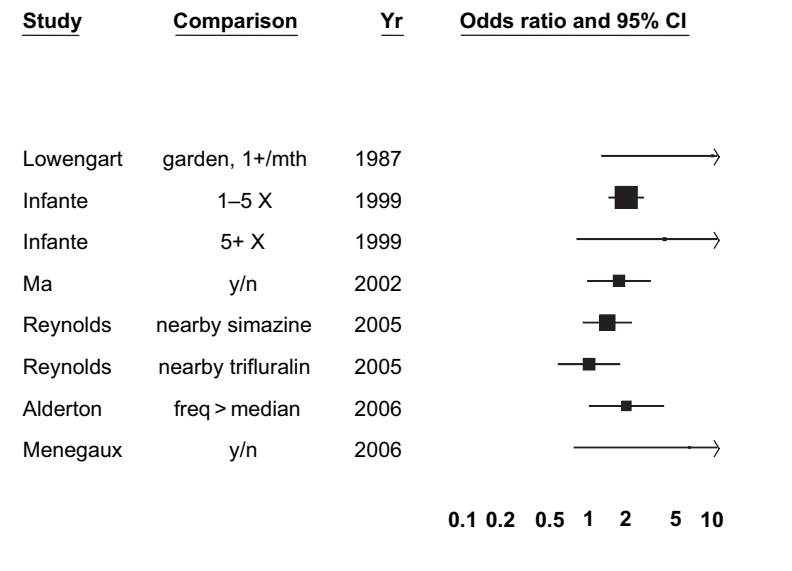

FIGURE 3. Childhood leukemia vs. prenatal herbicide exposure (mth = month, X = times during gestation, y/n = any exposure vs. none).

[3]Ratio of the number of matched pairs in which the case was exposed but not the control to the number of matched pairs in which the control was exposed but not the case.

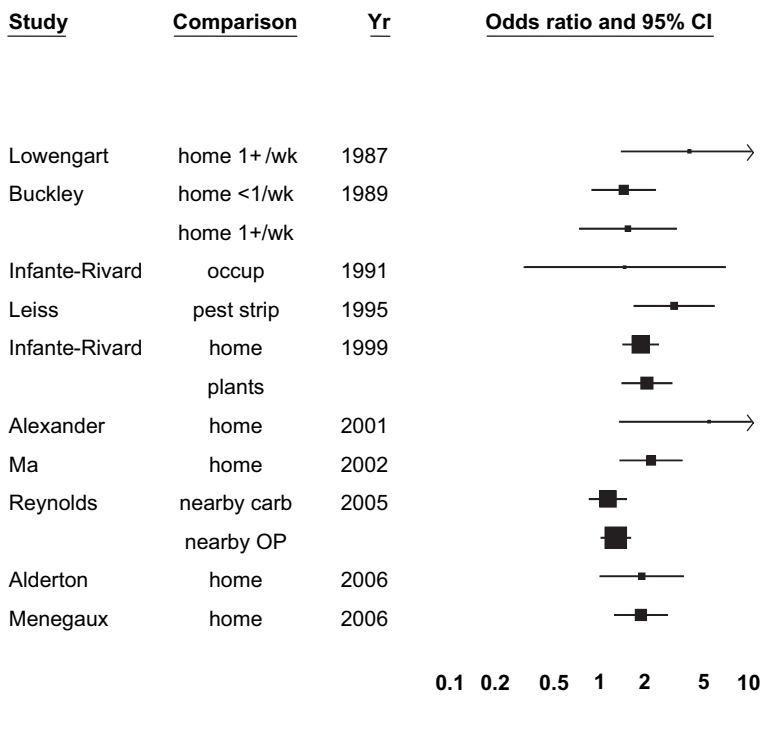

FIGURE 4. Childhood leukemia vs. prenatal insecticide exposure (occup = occupation, carb = carbamates and OP = organophosphates).

CI 1.00–13.7) (Lowengart et al., 1987), United States/Canada (≥1/wk, OR = 1.47, 95% CI 0.69–3.17, *p*-trend = .05) (Buckley et al., 1989), Denver (prenatal use of insecticide pest strips in home, OR = 3.0, 95% CI 1.6–5.7) (Leiss & Savitz, 1995), Quebec (prenatal use of indoor insecticides for cockroaches, ants, flies, bees or wasps, all cases, OR = 1.79, 95% CI 1.34–2.40, cases with CYP1A1m2 polymorphism, OR = 4.73, 95% CI 1.18–18.6) (Infante-Rivard et al., 1999), a seven-country study (leukemia before age 18 mo vs. maternal use of the carbamate insecticide propoxur, OR = 5.14, 95% CI 1.27–20.9) (Alexander et al., 2001), California (prenatal indoor insecticide use, OR = 2.1, 95% CI 1.3–3.5) (Ma et al., 2002), United States/Canada (ALL, any prenatal home extermination, OR = 2.25, 95% CI 1.13–4.49; cases and controls all had Down's syndrome) (Alderton et al., 2006), and France (prenatal home use of insecticides, OR = 1.8, 95% CI 1.2–2.8) (Menegaux et al., 2006). Leukemia was associated with prenatal residential use of insecticides for interior or outdoor plants (any use, OR = 1.97, 95% CI 1.32–2.94; used more than 5 times, OR = 4.01, 95% CI 1.12–14.3) and with prenatal professional indoor insect extermination (OR = 1.68, 95% CI 0.87–3.25) in Quebec (Infante-Rivard et al., 1999). There was a dose-response relationship between leukemia and duration or frequency of prenatal indoor insecticide use in the first United States/Canada study (Buckley et al., 1989). In a recent United States/Canada study, there was a nonmonotonic relationship between ALL risk and frequency of prenatal home extermination (<median vs. none, OR = 3.44, 95% CI 1.41–8.39; ≥median, OR = 1.28, 95% CI 0.46–3.55) (Alderton et al., 2006).

There was no association between leukemia and prenatal occupational insecticide exposure in a Spanish case-control study (OR = 1.40, 95% CI 0.44–4.41, 7 exposed case mothers) (Infante-Rivard et al., 1991). Childhood leukemia was associated with prenatal use of tree insecticides in a Quebec case-control study (any use, OR = 1.70, 95% CI 1.12–2.59; used more than 5 times, OR = 3.27, 95% CI 0.64–16.7) (Infante-Rivard et al., 1999). A French case-control study observed a statistically nonsignificant elevated leukemia risk related to prenatal garden insecticide use (OR = 1.9, 95% CI 0.6–6.5) (Menegaux et al., 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: Elevated leukemia risks were related to prenatal occupational pesticide exposure in case-control studies in Shanghai (ALL,

OR = 3.5, 95% CI 1.1–11.2; ANLL, OR = 2.4, 95% CI 0.5–11.0) (Shu et al., 1988), United States/Canada (crude OR = 2.85, 95% CI 0.82–10.8, calculated from data in paper) (Buckley et al., 1989), Spain (occupation in farming, OR = 1.80, 95% CI 0.60–6.64 (Infante-Rivard et al., 1991), Germany (regional study, OR = 2.59, 95% CI 0.45–20.4, only 4 exposed case mothers) (Meinert et al., 1996), Greece (home or occupational exposure, OR = 3.6, 95% CI 1.2–10.8) (Petridou and Dessypris 2000), Germany (nation-wide, OR = 3.6, 95% CI 1.5–8.8) (Meinert et al., 2000), a seven-country study (leukemia before age 18 mos, OR = 3.67, 95% CI 1.54–8.74) (Alexander et al., 2001), and Israel (occupational exposure of either parent, OR = 2.35, 95% CI 1.10–5.0) (Abadi-Korek et al., 2006). Elevated leukemia risk was also related to maternal outdoor pesticide use in case-control studies in Germany (prenatal or postnatal use, OR = 2.76, 95% CI 1.26–6.30) (Meinert et al., 1996) and France (prenatal, OR = 2.5, 95% CI 0.8–7.2) (Menegaux et al., 2006).

There was no association in case-control studies in the Netherlands (prenatal occupational pesticide exposure, OR = 0.7, 95% CI 0.2–2.5, only 4 exposed case mothers) (van Steensel-Moll et al., 1985), Denver (prenatal outdoor herbicide or insecticide use, OR = 1.1, 95% CI 0.6–1.9) (Leiss & Savitz, 1995) or United Kingdom (periconceptual maternal occupations potentially exposed to agrochemicals, OR = 0.81, 95% CI 0.31–2.12) (McKinney et al., 2003). The consistency of findings are suggestive of an association, but the heterogeneity of exposure indices, the lack of demonstrated dose-response relationships, and the relatively small numbers of exposed case mothers in most studies preclude firm conclusions.

Paternal occupational exposure, major pesticide classes, inadequate evidence: In the Quebec study, leukemia risk was elevated in relation to preconceptual paternal occupational exposure to herbicides (OR = 2.05, 95% CI 0.93–4.56), insecticides (OR = 1.38, 95% CI 0.87–2.18) and fungicides (OR = 5.11, 95% CI 1.46–17.8) (Infante-Rivard & Sinnett 1999).

Paternal occupational exposure, unspecified pesticides, inadequate evidence: Elevated leukemia risk was associated with paternal occupational pesticide exposure in case-control studies in Italy (OR = 5.6, 95% CI 1.3–24.3, 5 case fathers worked in farming) (Magnani et al., 1990), United States/Canada (1–1000 d cumulated exposure vs. none during period from 1 yr before birth to date of diagnosis, OR = 1.0, 95% CI 0.4–2.4); >1000 d vs. none, OR = 2.7, 95% CI 1.0–7.0, *p*-trend = .04) (Buckley et al., 1989), United Kingdom (paternal occupation in farming, OR = 1.98, 95% CI 0.66–5.96) (Gardner et al., 1990), and Germany (occupational pesticide exposure in year before conception, OR = 1.5, 95% CI 1.1–2.2) (Meinert et al., 2000).

Leukemia was not associated with paternal occupational pesticide exposure in case-control studies in Quebec (paternal work as farmer based on birth certificate information, OR = 0.70, 95% CI 0.39–1.21) (Fabia & Thuy, 1974), the Netherlands (paternal work in agriculture, forestry or horticulture, OR = 0.9, 95% CI 0.5–1.5; self-reported occupational pesticide exposure, OR = 1.0, 95% CI 0.6–1.7) (van Steensel-Moll et al., 1985), Germany (paternal occupational pesticide exposure in year before pregnancy, OR = 1.29, 95% CI 0.46–3.62) (Meinert et al., 1996), Sweden (OR = 0.90, 95% CI 0.37–2.19) (Feychting et al., 2001), or the United Kingdom (periconceptual paternal occupations potentially exposed to agrochemicals, OR = 0.83, 95% CI 0.58–1.19) (McKinney et al., 2003). In a Norwegian retrospective cohort study, leukemia risk among offspring of farmers (84% of whom were males) was not elevated compared to nonfarm children (all farm children, SIR = 0.96, 95% CI 0.82–1.11; children on farms reporting pesticide expenditures, SIR = 1.06, 95% CI 0.75–1.49) (Kristensen et al., 1996a). Two cohort studies reported normal leukemia risks among offspring of licensed pesticide applicators: a Swedish study (OR = 0.43, 95% CI 0.19–0.86) (Rodvall et al., 2003) and a U.S. study (OR = 0.91, 95% CI 0.47–1.75) (Flower et al., 2004). Despite the dose-response relationship observed in one study, the inconsistent findings, heterogeneous exposure indices and negative results of two cohort studies of licensed pesticide applicators provide inadequate evidence of an association.

Childhood exposure, herbicides, inadequate evidence: The Quebec study reported an association between leukemia and childhood residential herbicide use (with or without residential use of other pesticides, OR = 1.41, 95% CI 1.06–1.86) but not with residential use of herbicides alone (OR = 0.88, 95% CI 0.58–1.33) (Infante-Rivard et al., 1999). An ecologic study in Maryland observed borderline associations between leukemia and residence at diagnosis <3.2 km from well

water containing detectable levels of the herbicides atrazine (OR = 1.43, 95% CI 0.89–2.30) and metolachlor (OR = 1.48, 95% CI 0.93–2.36) but not simazine (OR = 0.97, 95% CI 0.48–1.96) (Thorpe & Shirmohammadi, 2005). There was a statistically nonsignificant elevated leukemia risk related to childhood residential herbicide use in a French case-control study (OR = 1.4, 95% CI 0.8–2.4) (Menegaux et al., 2006). An ecologic study in California found no association between total leukemia before age 15 yr and childhood residential proximity to agricultural use (≥90th vs. <1st percentile, lb/mi^2) of the herbicides simazine (a triazine herbicide, OR = 0.79, 95% CI 0.45–1.40) or trifluralin (a dinitroaniline herbicide, OR = 0.87, 95% CI 0.46–1.63) (Reynolds et al., 2002a). Further analysis restricted to ALL before age 15 yr revealed a slightly elevated risk related to simazine use (≥75th vs. <1st percentile, lb/mi^2, OR = 1.21, 95% CI 0.86–1.71) but not trifluralin (OR = 0.81, 95% CI 0.49–1.34) (Reynolds et al., 2005a). A California case-control study restricted to ALL before age 5 revealed elevated risks related to childhood residential proximity to agricultural use (≥50th vs. <1st percentile, lb/mi^2) of simazine (OR = 1.29, 95% CI 0.81–2.05) but not trifluralin (OR = 0.92, 95% CI 0.51–1.65) (Reynolds et al., 2005b).

Leukemia was not associated with childhood residential herbicide use in Denver (OR = 0.9, 95% CI 0.5–1.8) (Leiss & Savitz, 1995), California (birth to age 1, OR = 0.7, 95% CI 0.4–1.2; age 1–2, OR = 1.1, 95% CI 0.7–2.0; age 2–3, OR = 1.1, 95% CI 0.6–2.1) (Ma et al., 2002) or in a United States/Canada study (≥median frequency of use vs. none, OR = 1.07, 95% CI 0.42–2.67, *p*-trend = .66) (Alderton et al., 2006).

Childhood exposure, insecticides, limited evidence: As shown in Figure 5, leukemia was associated with childhood indoor residential use of insecticides but not residential proximity to agricultural insecticide use. Leukemia risk was elevated in relation to childhood indoor insecticide use in case-control studies in United States/Canada (≥1×/wk, OR = 2.02, 95% CI 0.91–4.57, *p*-trend = .04) (Buckley et al., 1989), Denver (insecticide pest strips[4] in home, birth to 2 yr before diagnosis,

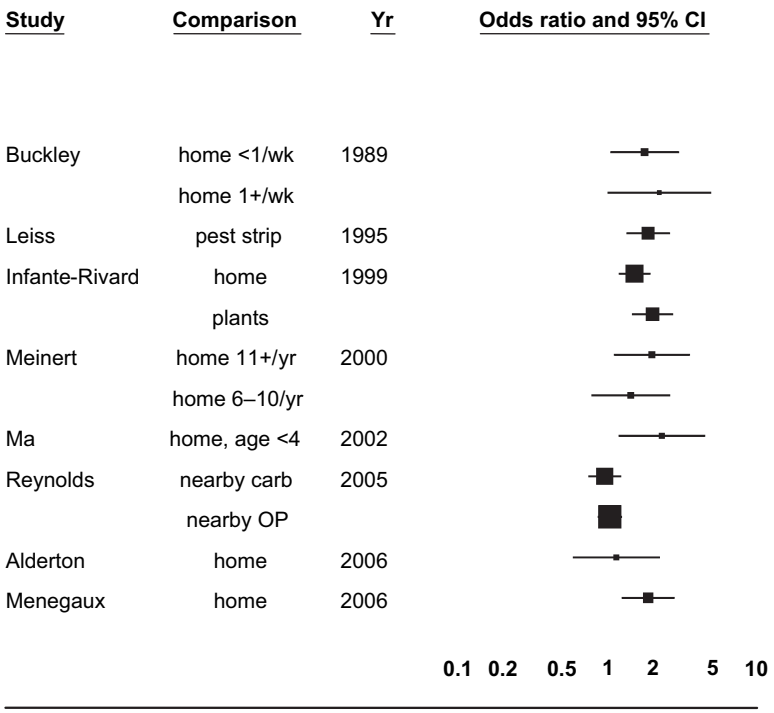

FIGURE 5. Childhood leukemia vs. childhood insecticide exposure (carb = carbamates, OP = organophosphates).

[4]Pest strips contained dichlorvos, a highly volatile organophosphate insecticide; it is a known mutagen and animal carcinogen causing leukemia and lung and mammary-gland tumors.

OR = 1.7, 95% CI 1.2–2.4; <2 yr before diagnosis, OR = 2.6, 95% CI 1.7–3.9) (Leiss & Savitz, 1995), Quebec (indoor insecticide use for cockroaches etc., all ALL cases, OR = 1.38, 95% CI 1.07–1.77; ALL cases with CYP1A1m2 polymorphism, OR = 3.95, 95% CI 0.81–19.2) (Infante-Rivard et al., 1999), Germany (indoor insecticide use >10 vs. <1×/yr, OR = 1.8, 95% CI 1.0–3.3, *p*-trend = .12) (Meinert et al., 2000), California (indoor insecticide use, birth to age 1, OR = 1.7, 95% CI 1.0–2.9; age 1–2, OR = 1.6, 95% CI 1.0–2.7; age 2–3, OR = 1.2, 95% CI 0.7–2.1) (Ma et al., 2002), United States/Canada (frequency of use ≥median vs. none, OR = 1.63, 95% CI 0.84–3.30, p = .21) (Alderton et al., 2006) and France (indoor insecticide use, OR = 1.7, 95% CI 1.1–2.4; childhood use of insecticide shampoo, OR = 1.9, 95% CI 1.1–3.2) (Menegaux et al., 2006). The French study also reported an association between leukemia and childhood use of insecticidal shampoos (OR = 1.9, 95% CI 1.1–3.2) (Menegaux et al., 2006). Dose-response relationships between leukemia and frequency of childhood residential indoor insecticide use were apparent in Germany (*p*-trend = .12) (Meinert et al., 2000) and California (per increment in frequency of use, birth to age 1, OR = 1.2, 95% CI 1.0–1.4; age 1–2, OR = 1.1, 95% CI 1.0–1.3) (Ma et al., 2002). Childhood indoor insecticide use was not associated with leukemia in the Denver case-control study (home extermination, <2 yr before diagnosis, OR = 0.9, 95% CI 0.5–1.4) (Leiss & Savitz, 1995). The apparent interaction between indoor insecticide exposure and the CYP1A1m2 polymorphism in the Quebec study may indicate a role for P-450 enzyme activation; however, this appears to be the only study of interactions between genetic polymorphisms and pesticide exposure in childhood cancer and more research is urgently needed.

ALL was associated with childhood outdoor residential insecticide use in case-control studies in Quebec (tree insecticides, OR = 1.41, 95% CI 1.01–1.97) (Infante-Rivard et al., 1999), California (ALL age <5, childhood residential proximity, agricultural use of organophosphate insecticide, ≥50th vs. <1st percentile, lb/mi^2, OR = 1.22, 95% CI 0.96–1.56) (Reynolds et al., 2005b), and France (OR = 2.4, 95% CI 1.3–4.3) (Menegaux et al., 2006). The California study also observed elevated risks of leukemia before age 5 yr related to childhood residential proximity to agricultural use of the organochlorine miticide dicofol (OR = 1.83, 95% CI 1.05–3.22) but not propargite (OR = 0.96, 95% CI 0.62–1.49) or the broad classes of organochlorine (OR = 1.29, 95% CI 0.78–2.13) or carbamate insecticides (OR = 1.08, 95% CI 0.80–1.47) (Reynolds et al., 2005b). An ecologic study in California found no association between total leukemia before age 15 yr and childhood residential proximity to agricultural use (≥90th vs. <1st percentile, lb/mi^2) of organochlorine (OR = 0.70, 95% CI 0.39–1.23), organophosphate (OR = 0.91, 95% CI 0.70–1.18) or carbamate insecticides (OR = 1.03, 95% CI 0.75–1.41) (Reynolds et al., 2002a). Further analysis restricted to ALL before age 15 revealed no association with agricultural use of organochlorine (≥75th vs. <1st percentile, lb/mi^2, OR = 0.73, 95% CI 0.47–1.15), organophosphate (OR = 0.94, 95% CI 0.77–1.14), or carbamate insecticides (OR = 0.87, 95% CI 0.67–1.13) or propargite (OR = 1.03, 95% CI 0.76–1.39) (Reynolds et al., 2005a). The consistency of findings and evidence of dose-response relationships provide relatively strong evidence of an association.

Childhood exposure, fungicides, inadequate evidence: Leukemia was associated with childhood residential garden fungicide use in a French case-control study (OR = 2.5, 95% CI 1.0–6.2) (Menegaux et al., 2006). An ecologic study in California found no association between leukemia and childhood residential proximity to agricultural use (≥90th vs. <1st percentile, lb/mi^2) of dithiocarbamate fungicides (OR = 0.89, 95% CI 0.61–1.30) (Reynolds et al., 2002a). This study did report elevated leukemia risk related to agricultural use of the chlorinated isophthalic acid fungicide chlorothalonil (OR = 1.27, 95% CI 0.90–1.80). Further analysis, restricted to ALL before age 15 yr and using different cut points of pesticide use intensity, revealed no association with agricultural use of dithiocarbamate fungicides (≥75th vs. <1st percentile, lb/mi^2, OR = 0.92, 95% CI 0.70–1.19) (Reynolds et al., 2005a). A California case-control study restricted to ALL before age 5 yr revealed no association with childhood residential proximity to agricultural use (≥50th vs. <1st percentile, lb/mi^2) of dithiocarbamate fungicides (OR = 1.01, 95% CI 0.71–1.42) and a statistically nonsignificant elevated risk related to childhood residential proximity to agricultural use of chlorothalonil (OR = 1.33, 95% CI 0.88- 2.01) (Reynolds et al., 2005b).

Childhood exposure, soil fumigants, inadequate evidence: An ecologic study in California found no association between total leukemia and childhood residential proximity to agricultural use (≥90th vs. <1st percentile, lb/mi^2) of the soil fumigant metam sodium (OR = 0.92, 95% CI 0.48–1.73) (Reynolds et al., 2002a). A subsequent case-control study restricted to ALL before age 5 revealed an association with childhood residential proximity to agricultural use (≥50th vs. <1st percentile, lb/mi^2) of metam sodium (OR = 2.05, 95% CI 1.01–4.17) but not methyl bromide (OR = 0.89, 95% CI 0.60–1.33) (Reynolds et al., 2005b).

Childhood exposure, residential use of unspecified pesticides, inadequate evidence: A case-control study in northwestern Germany reported an association between leukemia and prenatal or childhood garden pesticide use (crude OR = 2.76, 95% CI 1.26–6.30, calculated from data in paper) but did not distinguish between prenatal or childhood exposure (Meinert et al., 1996). Childhood outdoor residential pesticide use was not associated with childhood leukemia in case-control studies in Denver (yard insecticide or herbicide use, OR = 0.9, 95% CI 0.5–1.8) (Leiss & Savitz, 1995) or a nationwide German study (residential garden pesticide exposure use, OR = 1.0, 95% CI 0.8–1.2) (Meinert et al., 2000).

Environmental tobacco smoke Prenatal active smoking, inadequate evidence: Prenatal active smoking was not associated with childhood leukemia in a meta-analysis of 8 studies (summary OR = 1.05, 95% CI 0.82–1.34) (Boffetta et al., 2000). A Quebec study reported elevated risks in relation to 2nd or 3rd trimester maternal active smoking among subgroups of childhood leukemia based on CYP1A1 polymorphisms (e.g., 3rd trimester smoking >20 vs. 0 cigarettes/d, OR = 2.8 (95% CI 0.8–9.8) for CYP1A1*2A and 5.4 (95% CI 0.8–37.3) for CYP1A1*4 polymorphisms (Infante-Rivard et al., 2000). A case-control study in France revealed no overall association between childhood leukemia and prenatal active smoking (OR = 1.2, 95% CI 0.7–2.1); case-only analyses showed associations with prenatal smoking among infants with CYP1A1 (*1/2A or *2A/2A) (OR = 2.2, 95% CI 1.0–4.9) or GSTM1 null polymorphisms (OR = 2.3, 95% CI 1.2–4.4) (Clavel et al., 2005). A subsequent report of this study revealed no association between ALL or ANLL and postnatal maternal or paternal smoking (e.g., ALL, maternal smoking birth to interview, ≥20 cigarettes/d, OR = 0.6, 95% CI 0.5–1.6) (Menegaux et al., 2005). A population-based case-control study in California revealed no association between preconceptual or prenatal active smoking and ALL or AML (e.g., ALL, prenatal smoking, OR = 0.93, 95% CI 0.58–1.51) (Chang et al., 2006).

Prenatal ETS exposure, limited evidence: Few studies have assessed the independent effect of prenatal ETS exposure and childhood cancer risk, i.e., independent from maternal or paternal active smoking. An expert group convened by the State of California found inadequate evidence of a causal association between childhood leukemia and prenatal ETS exposure (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood leukemia and prenatal or postnatal ETS exposure but not sufficient for a firm conclusion (U.S. Department of Health and Human Services, 2006).

Paternal active smoking, limited evidence: A meta-analysis of 4 epidemiologic studies indicated a weak association between childhood ALL and paternal smoking (summary OR = 1.17, 95% CI 0.96–1.42) (Boffetta et al., 2000). An expert group convened by the State of California found limited evidence of a causal association between childhood leukemia and preconceptual paternal smoking (California Environmental Protection Agency, 2005). A large UK case-control study reported no association between childhood leukemia and paternal preconceptual smoking (≥20 vs. 0 cigarettes/d, OR = 1.01, 95% CI0.87–1.17) (Pang et al., 2003). In a population-based case-control study in California, preconceptual paternal smoking was associated with AML (OR = 3.84, 95% CI 1.04–14.2) and to a lesser degree with ALL (OR = 1.32, 95% CI 0.86–2.04) (Chang et al., 2006).

Childhood exposure, limited evidence: The California expert panel found inadequate evidence of a causal association between childhood leukemia and childhood ETS exposure (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood leukemia and prenatal or postnatal ETS exposure but insufficient for a firm conclusion (U.S. Department of Health and Human Services, 2006). In a population-based case-control study in California, ALL was associated with postnatal maternal

active smoking among the subgroup of children whose fathers smoked preconceptually (OR = 3.94, 95% CI 1.25–12.4) (Chang et al., 2006).

Outdoor air pollution Based on studies of experimental animals and occupationally exposed adults, diesel and gasoline engine emissions, respectively, are classified as probable and possible human carcinogens (International Agency for Research on Cancer, 1989). However, a WHO expert panel noted that the few available studies of childhood cancer and outdoor air pollution had inconsistent results and there was inadequate evidence for a causal association (Binkova et al., 2005). A systematic review of eight case-control and seven ecologic studies of all childhood cancers combined and air pollution noted that four relatively small case-control studies (including two in Denver) reported associations and these studies all had methodologic limitations (Raaschou-Nielsen & Reynolds, 2006). Two case-control studies with high statistical power, validated exposure assessment methods, substantial exposure gradient and low potential for bias or confounding, reported no association (Raaschou-Nielsen et al., 2001; Reynolds et al., 2004). However, some of the studies that reported no association between air pollution exposure indices and all childhood cancer types combined did observe associations with specific types of childhood cancer (see later discussion).

Maternal exposure, inadequate evidence: A large Danish case-control study reported no association between childhood leukemia and cumulative prenatal exposure to benzene based on outdoor air sampling near the maternal residence (≥90th vs. <50th percentile of ppb-days, OR = 0.8, 95% CI 0.4–1.9) or NO_2 (Raaschou-Nielsen et al., 2001). A large California-wide case-control study revealed no association between leukemia and traffic density near the maternal residence at birth (≥90th vs. <29th percentile of vehicle-miles/mi^2, OR = 0.92, 95% CI 0.73–1.15) (Reynolds et al., 2004). A case-control study in France reported an association between leukemia and prenatal residential proximity to car repair garages or gasoline stations (adjoining property, OR = 2.2, 95% CI 0.9–5.7) but not heavy-traffic roads (<50 vs. ≥50 m, OR = 1.3, 95% CI 0.5–3.2) (Steffen et al., 2004).

Paternal exposure, motor vehicle emissions, limited evidence: Reviewers concluded that the preponderance of epidemiological evidence suggests an association between childhood leukemia/lymphoma and paternal vehicle-related occupations likely exposed to motor vehicle emissions or solvents (Olshan & van Wijngaarden, 2003).

Childhood residential exposure, limited evidence: A case-control study in Denver, CO, revealed a dose-response relationship between leukemia and traffic density on the street of residence at diagnosis (≥10,000 vs. <500 vehicles/d, OR = 4.7, 95% CI 1.6–13.5) (Savitz & Feingold, 1989). This association occurred among cases age 0–4 (OR = 5.6, 95% CI 1.9–16.7) but not older children. In a re-analysis of the Denver study, leukemia was associated with the highest traffic density on any street within 0.25 km of residence at diagnosis (≥500 vs. <500 vehicles/d, OR = 2.08, 95% CI 1.06–4.07) (Pearson et al., 2000). In a Swedish ecologic study, motor vehicle density in the municipality of residence was associated with AML (≥20 vs. <5 vehicles/km^2, OR = 1.62, 95% CI 0.91–2.91) but not ALL (OR = 0.88, 95% CI 0.69–1.12) among persons age 0–24 (Nordlinder & Jarvholm, 1997). A small Swedish case-control study (only 39 cases) revealed a statistically nonsignificant and imprecise association between childhood leukemia and average ambient air NO_2 levels (an indicator of motor vehicle emissions) near the residence during the year of diagnosis (≥50 vs. <40 $\mu g/m^3$, OR = 2.7, 95% CI 0.3–20.6) (Feychting et al., 1998). In a UK case-control study, there were elevated leukemia risks for children living <100 m from a main road (OR = 1.61, 95% CI 0.90–2.87) or gasoline station (OR = 1.99, 95% CI 0.73–5.43) (Harrison et al., 1999). In a California ecologic study, leukemia was weakly associated with traffic density near the childhood residence (≥90th vs. <25th percentile of vehicles/d/mi^2, OR = 1.15, 95% CI 0.97–1.37) (Reynolds et al., 2002b). An extension of this study reported a similar association between leukemia and airborne levels, in the census tract of childhood residence at diagnosis, of 25 hazardous air pollutants (HAP) classified as known, probable or possible human carcinogens by the U.S. versus <25th percentile of carcinogenic HAP index, OR = 1.21, 95% CI 1.03–1.42, *p*-trend<.05) (Reynolds et al., 2003). A small case-control study of leukemia in Los Angeles County revealed an association with traffic density near the childhood residence of longest duration (5th vs. 1st quintile, OR = 1.9, 95% CI 0.9–3.7) which weakened after

adjustment for electric wire code (OR = 1.4, 95% CI 0.7–3.0) (Langholz et al., 2002). A case-control study in France reported an association between leukemia and childhood residential proximity to car repair garages or gasoline stations (adjoining property, OR = 4.0, 95% CI 1.5–10.3) but not heavy-traffic roads (<50 vs. ≥50 m, OR = 1.3, 95% CI 0.6–2.9) (Steffen et al., 2004). The latter study also noted a dose-response relationship between leukemia and duration of childhood residence near a car repair garage or gasoline station (≥36 vs. 0 mo, OR = 4.7, 95% CI 1.2–18.5, *p*-trend < .05). An Italian case-control study reported an association between leukemia and ambient air benzene levels, estimated from modeling of vehicle density on roads <0.3 km from childhood residence (>10 vs. <0.1 $\mu g/m^3$, OR = 3.91, 95% CI 1.36–11.3, *p*-trend = .005) (Crosignani et al., 2004). In a Taiwanese case-control study, residential proximity to 4 petrochemical production complexes (involved in petroleum cracking and production of many products including vinyl chloride monomer, polyethylene, acrylates, MTBE) was associated with leukemia among persons age 20–29 yr (per log exposure score increment, OR = 1.54, 95% CI 1.14–2.09) but not with childhood leukemia (OR = 1.04, 95% CI 0.79–1.38) (Yu et al., 2006). In a large Danish case-control study, leukemia was not associated with cumulative childhood exposure to ambient air benzene (90th vs. <50th percentile of ppb-days, OR = 0.4, 95% CI 0.1–1.6) or NO_2 (Raaschou-Nielsen et al., 2001) near the residence at diagnosis.

Drinking-water disinfection by-products contaminants MX comprised 49% of mutagenic activity in Massachusetts municipal water supplies (Wright et al., 2002). Among DBPs studied to date, known animal carcinogens include chloroform, bromoform, BDCM, HAAs, haloacetonitriles, bromate and MX (Komulainen, 2004).

Prenatal or childhood exposure, inadequate evidence: A large population-based case-control study of ALL in Quebec reported no association with prenatal THM exposure indices (>95th vs. ≤95th percentile average THM, OR = 1.05, 95% CI 0.46–2.39; >95th vs. ≤95th percentile cumulative THM, OR = 0.83, 95% CI 0.39–1.76) (Infante-Rivard et al., 2001). There was a statistically nonsignificant elevated ALL risk among children above the 95th percentile of cumulative childhood (OR = 1.54, 95% CI 0.78–3.03) but not average childhood exposure (OR = 1.08, 95% CI 0.55–2.13). Case-only analyses within this study revealed strong but imprecise associations between ALL and average childhood THM levels above 100 μg/L among GSTT1-null (OR = 9.1, 95% CI 1.4–58) and CYP2E1*5 children (OR = 4.1, 95% CI 0.8–22) (Infante-Rivard et al., 2002). There were similar associations with other THM exposure indices among children with such polymorphisms but the imprecise odds ratios (because of small numbers) preclude strong inferences.

Drinking water nitrate Prenatal or childhood exposure, inadequate evidence: The Quebec study case-control study described above revealed no association between childhood ALL and time-weighted average drinking water nitrate level (>2 vs. ≤2 mg/L, prenatal, OR = 0.7, 95% CI 0.3–1.7; postnatal, OR = 0.6, 95% CI 0.2–1.6); there were similar results when exposure was modeled as cumulative exposure (Infante-Rivard et al., 2001).

Hazardous waste disposal sites Childhood residential proximity, inadequate evidence: A small case-control study in Woburn, MA, revealed a statistically nonsignificant elevated risk of childhood leukemia related to prenatal or childhood consumption of contaminated drinking water (main contaminant was trichloroethylene), OR = 2.4, 95% CI 0.5–11) (Massachusetts Department of Public Health, 1997). An ecologic study in the United Kingdom found no association between leukemia and childhood residential proximity to hazardous waste disposal sites (<2 vs. ≥2 km, OR = 0.93, 95% CI 0.81–1.06) (Jarup et al., 2002). In a large U.S. case-control study, Wilms's tumor risk was reduced among offspring of women living within 1.6 km of a NPL site (OR = 0.35, 95% CI 0.12–0.99); there was a similar relationship with childhood residential proximity (Tsai et al., 2006).

Solvents Maternal exposure, specified solvents, inadequate evidence: A large Quebec case-control study revealed associations between ALL and prenatal occupational exposure to specific solvents or solvent categories including methylene chloride (probable or definite exposure, OR = 3.22, 95% CI 0.88–11.7), toluene (OR = 1.98, 95% CI 1.06–3.72), mineral spirits (OR = 1.74, 95% CI 0.99–3.06), alkanes (OR = 1.78, 95% CI 1.09–2.91), and mononuclear aromatic hydrocarbons (OR = 1.67, 95% CI 1.13–2.48) (Infante-Rivard et al., 2005).

Maternal exposure, unspecified solvents, limited evidence: The Children's Cancer Study Group (United States and Canada) found a dose-response relationship between childhood acute nonlymphoblastic leukemia and cumulative prenatal occupational solvent exposure (>1000 vs. 0 days, OR = 2.2, 95% CI 0.9–5.4, *p*-trend = 0.05) (Buckley et al., 1989). In a much larger United States–Canada study, childhood acute lymphocytic leukemia was associated with prenatal occupational exposure to solvents or products containing solvents (solvents, OR = 1.6, 95% CI 1.1–2.3; paints or thinners, OR = 1.7, 95% CI 1.2–2.3) (Shu et al., 1999). A pooled analysis of three German population-based case-control studies indicated that acute lymphocytic leukemia was associated with prenatal occupations likely exposed to paints or lacquers (OR = 2.0, 95% CI 1.2–3.3) but not with solvents per se (OR = 1.3, 95% CI 0.8–1.9) (Schuz et al., 2000). A U.S. case-control study revealed an association between ALL and periconceptual household painting (≥5 vs. 0 rooms, OR = 1.7, 95% CI 1.1–2.7, *p*-trend = 0.01) (Freedman et al., 2001). A large Danish case-control study found no association between childhood leukemia and cumulative prenatal residential exposure to ambient air benzene (90th vs. <50th percentile of ppb-days, OR = 0.8, 95% CI 0.4–1.9) (Raaschou-Nielsen et al., 2001). In a large case-control study, the subgroup of childhood ALL cases with K-*ras* mutations was associated with prenatal occupational exposure to solvents, degreasers or cleaning agents (OR = 3.1, 95% CI 1.0–9.7) but not paints or thinners (OR = 1.0, 95% CI 0.2–4.4) (Shu et al., 2004). A large Quebec case-control study revealed no association between ALL and prenatal occupational exposure to the broad category of solvents (OR = 1.00, 95% CI 0.78–1.28) (Infante-Rivard et al., 2005).

Paternal occupational exposure, unspecified solvents, inadequate evidence: Reviewers noted that all five epidemiologic studies of childhood leukemia and paternal occupational solvent exposure published up to 1993 found positive associations; significantly associated solvents included chlorinated solvents and benzene (Colt & Blair, 1998). A review noted that studies published since the 1998 Colt and Blair review generally did not support an association between childhood leukemia/lymphoma and paternal occupational solvent exposure (Olshan & van Wijngaarden, 2003). Among subsequently reported studies, there was no association between childhood leukemia and paternal occupational exposure to solvents or products containing solvents in a United States–Canada study (solvents, OR = 1.1, 95% CI 0.9–1.3; paints or thinners, OR = 1.0, 95% CI 0.8–1.2) (Shu et al., 1999), a pooled analysis of three German population-based case-control studies (solvents, OR = 1.0, 95% CI 0.8–1.2; paints or lacquers, OR = 1.1, 95% CI 0.9–1.4) (Schuz et al., 2000), or a Swedish study (OR = 1.3, 95% CI 0.8–2.0) (Feychting et al., 2001). In a large case-control study, the subgroup of childhood ALL cases with K-*ras* mutations was not associated with preconceptual paternal occupational exposure to solvents, degreasers or cleaning agents or paints/thinners (OR = 1.0, 95% CI 0.2–4.4) (Shu et al., 2004).

Childhood exposure, unspecified solvents, limited evidence: The Children's Cancer Study Group (United States and Canada) reported a nonmonotonic dose-response relationship between childhood acute nonlymphoblastic leukemia and frequency of household use of petroleum products (≥4 vs. 0 times/month, OR = 1.8, 95% CI 0.7–4.3, *p*-trend = 0.02) (Buckley et al., 1989). A record-based case-control study in the United Kingdom found borderline associations between childhood leukemia and residential proximity to main roads (<100 vs. ≥100 m, OR = 1.6, 95% CI 0.9–2.9) and gasoline stations (OR = 2.0, 95% CI 0.7–5.4) (Harrison et al., 1999). A large Danish case-control study found no association between childhood leukemia and cumulative childhood residential exposure to ambient air benzene (90^{th} vs. $<50^{th}$ percentile of ppb-days, OR = 0.4, 95% CI 0.1–1.6) (Raaschou-Nielsen et al., 2001). A large U.S. case-control study revealed an association between childhood ALL and childhood artwork involving solvent exposure during the year before diagnosis (high frequency vs. unexposed, OR = 4.1, 95% CI 1.1–15.1, *p*-trend = 0.07) (Freedman et al., 2001).

Summary Limited epidemiologic evidence supports a role for environmental toxicants in childhood leukemia, including (a) prenatal residential or occupational exposure to herbicides, insecticides, ETS or unspecified solvents; (b) paternal occupational exposure to motor vehicle exhaust emissions or active smoking (not clear if paternal smoking acts through germ-cell mutations or fetal/childhood ETS exposure); (c) childhood residential exposure to insecticides, ETS, outdoor air pollution (mainly traffic-related) or unspecified solvents.

Childhood Lymphoma

Pesticides Among seven studies published by early 1998, three reported increased childhood nonHodgkin's lymphoma (NHL) risks related to indoor insecticide use during pregnancy or childhood (two studies) or residence on farms with relatively high pesticide exposures (one study); the authors noted that each study had few exposed cases or case parents (Zahm & Ward, 1998). A recent review of the four studies published since Zahm and Ward's report concluded that they provided further evidence for an association between NHL and pesticide exposure, especially residential indoor insecticide use during pregnancy or childhood for which there were dose-response relationships (Infante-Rivard & Weichenthal, 2006).

Maternal exposure, insecticides, inadequate evidence: The United States/Canada case-control study reported a dose-response relationship between NHL and frequency of prenatal indoor insecticide use (1–2 vs. 0×/wk, OR = 2.62, 95% CI 0.96–7.18; ≥3×/wk, OR = 7.33, 95% CI 0.84–64, *p*-trend = .05) (Buckley et al., 2000). This study also reported a dose-response relationship between NHL and frequency of prenatal outdoor insecticide use (any use vs. none, OR = 2.98, 95% CI 1.44–6.16, *p*-trend = .002) (Buckley et al., 2000). In the Denver case-control study, lymphoma was not associated with 3rd trimester home extermination (OR = 1.2, 95% CI 0.4–3.9) or indoor use of insecticide pest strips (OR = 1.4, 95% CI 0.7–2.5) (Leiss & Savitz, 1995). Although suggestive, the findings of Buckley et al. require replication.

Maternal exposure, unspecified pesticides, inadequate evidence: The United States/Canada case-control study reported statistically nonsignificant elevated NHL risks related to occupational pesticide exposure of either parent (OR = 1.74, 95% CI 0.82–3.69) and prenatal use of garden pesticide sprays (≥1/mo vs. never, OR = 1.71, 95% CI 0.67–4.37) (Buckley et al., 2000). A German case-control study observed an association between NHL and self-reported prenatal occupational pesticide exposure (OR = 11.8, 95% CI 2.2–64, 4 exposed case mothers) (Meinert et al., 2000). In the Denver case-control study, lymphoma was not associated with 3rd trimester outdoor use of herbicides and/or insecticides (OR = 0.5, 95% CI 0.2–1.2, 6 exposed case mothers) (Leiss & Savitz, 1995). The small number of studies, heterogeneity of exposure indices, and weak findings preclude firm conclusions.

Paternal occupational exposure, unspecified pesticides, limited evidence: As shown in Figure 6, there was a slightly elevated risk of Hodgkin's disease among Norwegian farm children (parents worked on farm at least 500 hr/yr, compared to nonfarm families, SIR = 1.17, 95% CI 0.85–1.56)

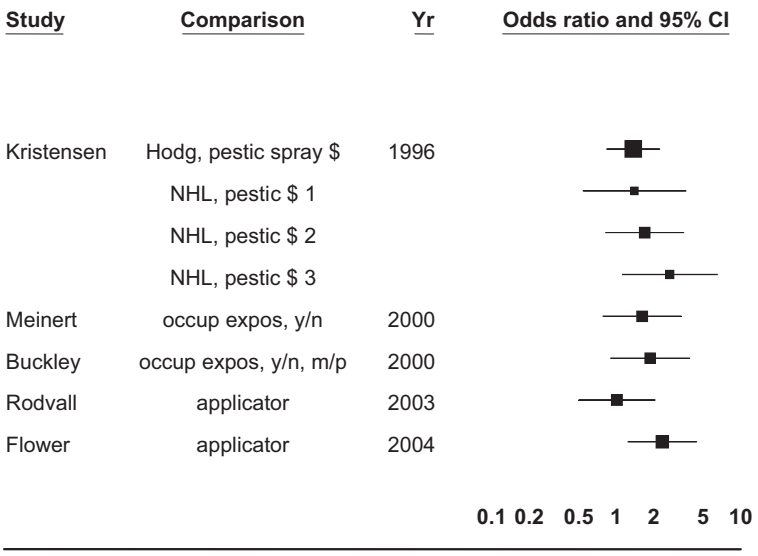

FIGURE 6. Childhood lymphoma vs. paternal exposure to unspecified pesticides (Hodg = Hodgkin's Disease, pestic spray $ = expenditures on pesticide spraying equipment, pestic $ 1 = low expenditures on pesticides, 2 = medium, 3 = high, m/p = prenatal or paternal).

(Kristensen et al., 1996a). There was also a dose-response relationship between NHL risk and pesticide expenditures on Norwegian farms (level 1 vs. none, OR = 1.30, 95% CI 0.49–3.42; level 2, OR = 1.57, 95% CI 0.75–3.30; level 3, OR = 2.50, 95% CI 1.02–6.15). In a United States/Canada case-control study, there was a statistically nonsignificant elevated risk of NHL related to self-reported occupational pesticide exposure of either parent (OR = 1.74, 95% CI 0.82–3.69) (Buckley et al., 2000). A case-control study in Germany found a statistically nonsignificant elevated risk of NHL related to paternal occupational pesticide exposure in the year before conception (OR = 1.5, 95% CI 0.7–3.1) (Meinert et al., 2000). Among offspring of licensed pesticide applicators, lymphoma risk was not elevated in a Swedish study (SIR = 0.94, 95% CI 0.44–1.79, 8 observed cases) (Rodvall et al., 2003) but was increased in the AHS cohort (SIR = 2.18, 95% CI 1.13–4.19, 9 observed cases) (Flower et al., 2004). The relatively consistent findings, including the results of the AHS cohort (likely the best cohort study of pesticide risks ever done) and dose-response relationship provide limited evidence of an association.

Childhood exposure, residential use or proximity to agricultural use of herbicides, inadequate evidence: In the California ecologic study, there was no association between NHL and childhood residential proximity to agricultural use of the herbicides trifluralin (≥75th vs. <1st percentile, OR = 0.47, 95% CI 0.08–2.78) or simazine (OR = 0.76, 95% CI 0.14–4.06) (Reynolds et al., 2005a). Similarly, there was no association between Hodgkin's disease and childhood residential proximity to agricultural use of trifluralin (OR = 1.13, 95% CI 0.40–3.17) or simazine (OR = 0.59, 95% CI 0.25–1.41).

Childhood exposure, insecticides, inadequate evidence: In a case-control study in Denver, lymphoma was associated with childhood house extermination (OR = 1.8, 95% CI 1.1–2.9) but not with indoor use of insecticide pest strips (OR = 1.3, 95% CI 0.4–2.7) (Leiss & Savitz, 1995). A German case-control study revealed a dose-response relationship between NHL and childhood indoor insecticide use (>10 vs. <1 time/yr, OR = 2.8, 95% CI 1.1–7.2, *p*-trend = .02) (Meinert et al., 2000).

In a California-wide ecologic study, there was no association between childhood NHL and childhood residential proximity to agricultural use of organochlorine (75th vs. <1st percentile, lb/mi^2, OR = 1.11, 95% CI 0.50–2.47), organophosphate (OR = 0.83, 95% CI 0.50–1.37) or carbamate insecticides (OR = 0.84, 95% CI 0.49–1.43) (Reynolds et al., 2005a). This study found statistically nonsignificant elevated risks of Hodgkin's disease related to organochlorine (OR = 1.31, 95% CI 0.70–2.46) and carbamate insecticides (OR = 1.30, 95% CI 0.77–2.20) and dicofol (1.43, 95% CI 0.70–2.95) but not organophosphate insecticides (OR = 1.12, 95% CI 0.71–1.76) or propargite (OR = 0.85, 95% CI 0.39–1.86).

Childhood exposure, fungicides, inadequate evidence: In the California ecologic study, there was no association between childhood residential proximity to agricultural use of dithiocarbamate fungicides and NHL (OR = 0.52, 95% CI 0.23–1.19) but Hodgkin's disease risk was elevated (OR = 1.38, 95% CI 0.78–2.44) (Reynolds et al., 2005a). This study found no association between NHL or Hodgkin's disease and childhood residential proximity to agricultural use of soil fumigants (methyl bromide, metam sodium) or the fungicide chlorothalonil.

Childhood exposure, soil fumigants, inadequate evidence: The California ecologic study observed no association between NHL or Hodgkin's disease and childhood residential proximity to agricultural use of the soil fumigants methyl bromide or metam sodium (Reynolds et al., 2005a).

Childhood exposure, unspecified pesticides, inadequate evidence: As noted earlier, children on Norwegian farms reporting pesticide expenditures had an increased risk of NHL (highest vs. no expenditure, OR = 2.50, 95% CI 1.02–6.15) with evidence of a dose-response relationship (Kristensen et al., 1996a). Given the design of the Norwegian study, farm pesticide exposures were indices of both prenatal parental and childhood exposures. NHL was associated with direct childhood exposure to herbicides or insecticides in a United States/Canada case-control study (yes vs. no, OR = 2.35, 95% CI 1.37–4.03, *p*-trend = .001 based on exposure frequency); the report did not distinguish between indoor and outdoor exposure (Buckley et al., 2000). In the Denver case-control study, lymphoma was not associated with postnatal outdoor use of herbicides and/or insecticides (OR = 0.8, 95% CI 0.3–1.8) (Leiss & Savitz, 1995). Although suggestive, the small number of studies and heterogeneous exposure indices preclude firm conclusions.

Tobacco smoke Prenatal active smoking, inadequate evidence: A meta-analysis of 6 epidemiologic studies found no association between childhood NHL and prenatal active smoking (summary OR = 1.13, 95% CI 0.85–1.49) (Boffetta et al., 2000).

Prenatal ETS exposure, limited evidence: An expert group noted inadequate evidence for an association between childhood lymphomas and prenatal and postnatal ETS exposure (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood lymphoma and prenatal or postnatal ETS exposure (U.S. Department of Health and Human Services, 2006).

Paternal active smoking, limited evidence: A meta-analysis of 4 epidemiologic studies observed an association between childhood NHL and paternal smoking (summary OR = 2.08, 95% CI 1.08–3.98) (Boffetta et al., 2000). An expert group convened by the State of California found limited evidence of a causal association between childhood lymphomas and preconceptual paternal smoking; their report noted that paternal smoking might act through preconceptual paternal germ-cell mutations or by increasing prenatal ETS exposure (California Environmental Protection Agency, 2005).

Childhood ETS exposure, limited evidence: An expert group noted inadequate evidence for this association (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood lymphoma and prenatal or postnatal ETS exposure (U.S. Department of Health and Human Services, 2006).

Outdoor air pollution Maternal exposure, major ambient air pollutants, inadequate evidence: A large Danish case-control study revealed associations between childhood Hodgkin's disease and cumulative prenatal residential exposure to ambient air NO_2 (90th vs. <50th percentile of ppb-days, OR = 6.7, 95% CI 1.7–26.0, *p*-trend = 0.02) and benzene (90th vs. <50th percentile of ppb-days, OR = 4.3, 95% CI 1.5–12.4, *p*-trend = 0.005) (Raaschou-Nielsen et al., 2001).

Childhood exposure, major ambient air pollutants, inadequate evidence: In a Swedish ecologic study, motor vehicle density in the municipality of residence was not associated with NHL among persons age 0–24 yr (≥20 vs. <5 vehicles/km^2, OR = 1.09, 95% CI 0.59–2.05) (Nordlinder & Jarvholm, 1997). The Danish case-control study reported no association between childhood lymphomas and cumulative childhood residential exposure to ambient air benzene (90th vs. <50th percentile of ppb-days, OR = 0.4, 95% CI 0.1–2.0) or NO_2 (Raaschou-Nielsen et al., 2001).

Solvents Maternal exposure, benzene, inadequate evidence: As noted earlier, cumulative prenatal ambient air benzene exposure was associated with childhood Hodgkin's disease (≥90th vs. <50th percentile of ppb-days, OR = 4.3, 95% CI 1.5–12.4, *p*-trend = .005) (Raaschou-Nielsen et al., 2001).

Paternal occupational exposure, inadequate evidence: Reviewers noted that all 5 reviewed studies of childhood leukemia/lymphoma and paternal occupational solvent exposure found ORs exceeding 2 but there were no data for lymphoma alone (Colt & Blair, 1998).

Childhood exposure, benzene, inadequate evidence: As noted earlier, childhood lymphomas were not associated with cumulative childhood exposure to ambient air benzene (≥90th vs. <50th percentile of ppb-days, OR = 0.4, 95% CI 0.1–2.0) (Raaschou-Nielsen et al., 2001).

Summary There is limited epidemiologic evidence for the role of environmental toxicants in childhood lymphomas including prenatal ETS exposure, paternal occupational exposure to unspecified pesticides, paternal active smoking (not clear whether paternal smoking acts through germ-cell mutations or fetal/childhood ETS exposure) and childhood ETS exposure.

Childhood Brain Cancer

Arsenic Paternal occupational exposure, inadequate evidence: In a Denver case-control study, brain cancer was not associated with likely paternal occupational arsenic exposure (based on job title) (OR = 1.3, 95% CI 0.4–4.1) (Feingold et al., 1992).

Pesticides A review noted that 12 of 16 case-control studies published by early 1998 revealed increased childhood brain cancer risks related to pesticide exposure with statistically significant relationships in 7 studies (Zahm & Ward, 1998). Risks were generally highest for parental pesticide use in the home, garden, or on pets. The only cohort study observed an association with paternal employment in farming and one of the case-control studies found an association with prenatal

household insecticide use or at least 1 yr of farm residence. A review of the nine studies published since the Zahm and Ward report found general support for an association between childhood brain cancer and pesticide exposure, especially prenatal and indoor residential insecticide use, but there were no statistically significant dose-response relationships (Infante-Rivard & Weichenthal, 2006).

Maternal exposure, herbicides, inadequate evidence: There was no association between brain cancer and prenatal residential herbicide use in Missouri (lawn herbicides, OR = 1.1, 95% CI 0.5–2.5) (Davis et al., 1993) or Denver (outdoor insecticide or herbicide use, OR = 0.6, 95% CI 0.3–1.1) (Leiss & Savitz, 1995). A large United States/Canada case-control study reported no association between maternal occupational herbicide exposure and astrocytoma (OR = 1.3, 95% CI 0.5–3.7) or PNET (OR = 0.5, 95% CI 0.2–1.5) (van Wijngaarden et al., 2003). In a California case-control study, brain tumors before age 5 yr were not associated with prenatal residential proximity to agricultural use of the herbicides simazine (≥50th vs. <1st percentile of lb/mi^2, OR = 1.06, 95% CI 0.49–2.26) or trifluralin (OR = 0.88, 95% CI 0.26–2.98) (Reynolds et al., 2005b).

Maternal exposure, insecticides, limited evidence: As shown in Figure 7, prenatal residential insecticide use was related to elevated childhood brain tumor risks in Missouri (OR = 1.8, 95% CI 0.8–4.0; insecticide pest strips in home, OR = 5.2, 95% CI 1.2–22.2) (Davis et al., 1993), France (OR = 1.8, 95% CI 0.8–4.1) (Cordier et al., 1994), the United States/Canada (astrocytoma, any prenatal use, OR = 1.5, 95% CI 0.8–2.7; used at least weekly, OR = 2.2, 95% CI 0.6–7.4) (Bunin et al., 1994), Australia (home extermination, OR = 2.0, 95% CI 1.0–3.9) (McCredie et al., 1994a), Denver (insecticide pest strips in home, OR = 1.5, 95% CI 0.9–2.4; house extermination, OR = 1.3, 95% CI 0.7–2.1) (Leiss & Savitz, 1995), and the western United States (direct prenatal use of flea/tick insecticides, all cases, OR = 2.2, 95% CI 1.1–4.2; cases age <5, OR = 5.4, 95% CI 1.3–22.3) (Pogoda and Preston-Martin, 1997). The western United States study also revealed associations between brain cancer and prenatal number of pets treated with insecticides for fleas/ticks (1 pet, OR = 1.4, 95% CI 0.9–2.4; >1 pet, OR = 2.0, 95% CI 1.0–4.0, p-trend = .04). Among children in households with indoor insecticide use during pregnancy or childhood, brain cancer risk was

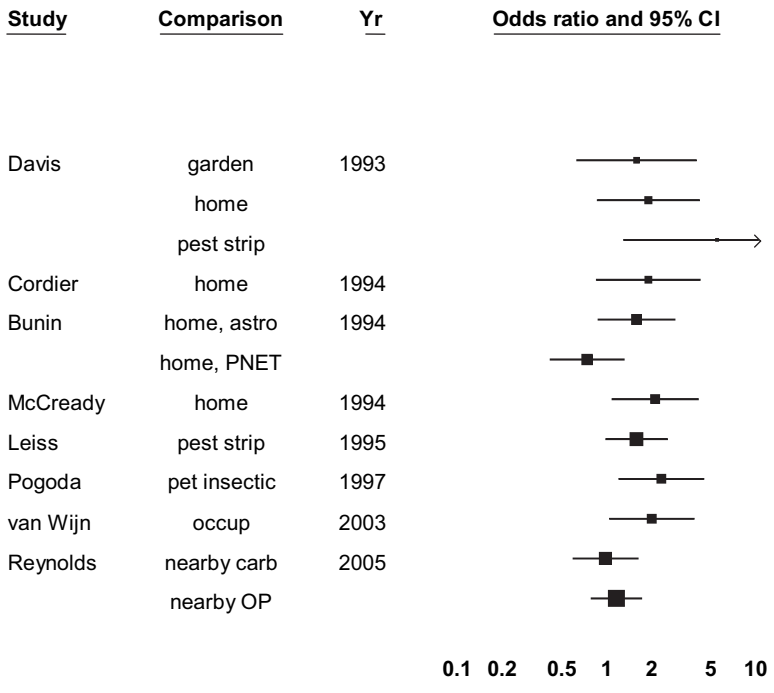

FIGURE 7. Childhood brain cancer vs. prenatal insecticide exposure (astro = astrocytoma, PNET = primitive neuroectodermal tumor, carb = carbamates, OP = organophosphates).

strongly associated with inefficient polymorphisms at C–108 in PON1, the gene that encodes paraoxonase, an organophosphate detoxifying enzyme (CC, OR = 1.0 (referent); CT, OR = 2.6, 95% CI 1.2–5.5; TT, OR = 6.6, 95% CI 1.5–29.7) (Nielsen et al., 2005). There was no association between PNET and prenatal indoor insecticide use in the United States/Canada study (any prenatal use, OR = 0.7, 95% CI 0.4–1.4; used at least weekly, OR = 1.0, 95% CI 0.2–4.9) (Bunin et al., 1994).

Prenatal outdoor residential insecticide use was related to elevated childhood brain tumor risks in Missouri (carbaryl, OR = 1.5, 95% CI 0.7–3.3; diazinon, OR = 4.6, 95% CI 1.2–17.9) (Davis et al., 1993). A large United States/Canada case-control study reported an association between maternal occupational insecticide exposure and astrocytoma (OR = 1.9, 95% CI 1.1–3.3) but not PNET (OR = 1.0, 95% CI 0.6–1.7) (van Wijngaarden et al., 2003). In a California case-control study, brain tumors before age 5 yr were not associated with prenatal residential proximity to agricultural use of organochlorine (≥50th vs. <1st percentile of lb/mi^2, OR = 0.73, 95% CI 0.32–1.65), organophosphate (OR = 1.10, 95% CI 0.74–1.66) or carbamate insecticides (OR = 0.93, 95% CI 0.56–1.57), propargite (OR = 1.06, 95% CI 0.50–2.28), or dicofol (OR = 0.65, 95% CI 0.27–1.61) (Reynolds et al., 2005b).

In sum, there were elevated brain cancer risks in six of seven case-control studies of residential indoor insecticide use with statistical significance apparent in four studies, a dose-response relationship in one study, and increased risk among children with inefficient polymorphisms at C–108 in PON1, the gene that encodes paraoxonase, an organophosphate detoxifying enzyme.

Maternal exposure, fungicides, inadequate evidence: A large United States/Canada case-control study reported an association between maternal occupational fungicide exposure and astrocytoma (OR = 1.6, 95% CI 0.9–2.7) but not PNET (OR = 0.7, 95% CI 0.4–1.2) (van Wijngaarden et al., 2003). In a California case-control study, brain tumors before age 5 yr were not associated with prenatal residential proximity to agricultural use of dithiocarbamate fungicides (≥50th vs. <1st percentile of lb/mi^2, OR = 0.89, 0.49–1.64) or chlorothalonil (OR = 1.18, 95% CI 0.58–2.38) (Reynolds et al., 2005b).

Maternal exposure, other specified pesticides, inadequate evidence: In a California case-control study, brain tumors before age 5 yr were not associated with prenatal residential proximity to agricultural use of the soil fumigants dimethyl bromide (OR = 0.80, 95% CI 0.44–1.46) or metam sodium (OR = 0.91, 95% CI 0.27–3.08) (Reynolds et al., 2005b).

Maternal exposure, unspecified pesticides, inadequate evidence: Elevated brain tumor risk was related to prenatal pesticide exposure in case-control studies in France (prenatal farm residence, OR = 2.5, 95% CI 0.4–16.1, 4 exposed case mothers) (Cordier et al., 1994), the United States/Canada (farm residence, PNET, OR = 3.7, 95% CI 0.8–23.9) (Bunin et al., 1994), western U.S. states (prenatal agricultural pesticide use, OR = 1.8, 95% CI 0.77–4.2) (Holly et al., 1998), and a seven-country study (prenatal farm residence, OR = 1.3, 95% CI 1.0–1.8; maternal agricultural pesticide use, OR = 2.0, 95% CI 1.2–3.2) (Efird et al., 2003).

In the United States/Canada study, astrocytomas were not associated with prenatal farm residence (OR = 0.5, 95% CI 0.1–1.8, 4 exposed case mothers) (Bunin et al., 1994). Brain cancer was not associated with prenatal pesticide exposure in Australia (maternal farm residence or farm work, OR = 0.9, 95% CI 0.3–2.6) (McCredie et al., 1994a), Europe (OR = 0.5, 95% CI 0.2–1.4, 5 exposed case mothers) (Cordier et al., 1997), or a seven-country study (maternal occupation in agriculture, during 5 yr before birth, OR = 1.1, 95% CI 0.7–1.9; during pregnancy, OR = 1.4, 95% CI 0.6–3.0) (Cordier et al., 2001). The inconsistent findings, lack of statistical significance in most of the positive studies and the lack of demonstrated dose-response relationships comprise inadequate evidence for an association.

Paternal exposure, chlorophenate wood preservatives, inadequate evidence: Among children of sawmill workers in British Columbia, Canada, there was a statistically nonsignificant elevated brain cancer risk related to paternal occupational chlorophenate exposure duration (≥3560 vs. <3560 h cumulated exposure, OR = 1.5, 95% CI 0.4–6.9) (Heacock et al., 2000).

Paternal exposure, broad pesticide classes, inadequate evidence: A large United States/Canada case-control study reported associations between astrocytoma brain tumors and paternal occupational exposure to herbicides (astrocytoma, OR = 1.6, 95% CI 1.0–2.7), insecticides (OR = 1.5, 95%

CI 0.9–2.4) and fungicides (OR = 1.6, 95% CI 1.0–2.6); PNET brain tumors were associated with paternal exposure to herbicides (OR = 1.5, 95% CI 0.9–2.6) but not insecticides or fungicides (van Wijngaarden et al., 2003). These findings require replication and exploration of dose-response relationships.

Paternal occupational exposure, unspecified pesticides, limited evidence: There was a dose-response relationship between nonastrocytic neuroepithelial brain tumors and pesticide expenditures in a Norwegian record-based cohort study of farm families (level 1 expenditures, OR = 2.00, 95% CI 0.85–4.74; level 2, OR = 2.93, 95% CI 1.54–5.60; level 3, OR = 3.28, 95% CI 1.39–7.76) (Kristensen et al., 1996a). This study noted a particularly high risk of such tumors among children age <5 yr on grain farms with pesticide purchases (OR = 8.01, 95% CI 1.62–39.7). Because of the design of the Norwegian study, pesticide exposure indices reflect both prenatal parental and childhood exposures. Brain cancer risk was elevated among children of licensed pesticide applicators in the AHS cohort (SIR = 1.60, 95% CI 0.89–2.89) (Flower et al., 2004) but not in a Swedish record-based cohort (SIR = 1.03, 95% CI 0.60–1.65) (Rodvall et al., 2003).

When paternal pesticide exposure was inferred from job titles, without other evidence of exposure, increased childhood brain cancer risk was noted in studies in Ohio (preconceptual paternal occupation in farming, brain cancer deaths, OR = 2.0, 95% CI 1.0–4.1) (Wilkins & Koutras, 1988), another Ohio study (preconceptual paternal occupation in farming, brain cancer incident cases, OR = 2.7, 95% CI 0.8–9.1) (Wilkins & Sinks, 1990), 3 U.S. states (preconceptual paternal occupation in agriculture, OR = 1.8, 95% CI 0.6–6.0) (Kuijten et al., 1992), France (preconceptual paternal occupation in agriculture (OR = 2.0, 95% CI 1.0–4.1) (Cordier et al., 1997), a seven-country study (paternal occupation in agriculture during 5 yr before birth, OR = 1.3, 95% CI 1.0–1.8) (Cordier et al., 2001), and Sweden (potential paternal preconceptual occupational pesticide exposure, RR = 2.36, 95% CI 1.27–4.39) (Feychting et al., 2001). There was no association in case-control studies in Quebec (occupation as farmer, OR = 0.56, 95% CI 0.22–1.26) (Fabia and Thuy 1974) or the United Kingdom (occupation in farming, OR = 0.70, 95% CI 0.35–1.38) (McKinney et al., 2003). The relatively consistent findings and dose-response relationship are suggestive of an association.

Childhood exposure, herbicides, inadequate evidence: Brain cancer was associated with childhood residential herbicide use in a case-control study in Missouri (OR = 2.4, 95% CI 1.0–5.7) (Davis et al., 1993) but not in Denver (use of herbicides or insecticides in yard, OR = 0.5, 95% CI 0.2–0.9) (Leiss & Savitz, 1995) or the western United States (OR = 1.2, 95% CI 0.3–4.9, 4 exposed case mothers) (Pogoda and Preston-Martin, 1997). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of the herbicides simazine (≥90th vs. <1st percentile, OR = 1.12, 95% CI 0.69–1.82) and trifluralin (OR = 0.58, 95% CI 0.27–1.25) (Reynolds et al., 2002a).

Childhood exposure, insecticides, limited evidence: As shown in Figure 8, indoor residential insecticide use was associated with elevated brain cancer risks in case-control studies in Baltimore (household insect extermination, OR = 2.29, 95% CI 0.96–5.95) (Gold et al., 1979), Missouri (indoor use of insecticides, OR = 3.4, 95% CI 1.1–10.6; indoor insecticidal pest strips, OR = 3.7, 95% CI 1.0–13.7; Kwell insecticidal shampoo, OR = 4.6, 95% CI 1.0–21.3) (Davis et al., 1993), France (home extermination, OR = 2.0, 95% CI 1.0–4.1) (Cordier et al., 1994), Denver (insecticide pest strips, OR = 1.4, 95% CI 0.7–2.9; house extermination, OR = 1.4, 95% CI 0.6–2.7) (Leiss & Savitz, 1995), and Los Angeles (failure to evacuate house after indoor insecticide use, OR = 1.6, 95% CI 1.0–2.6) (Pogoda & Preston-Martin, 1997). A German case-control study reported statistically nonsignificant and non-dose-related elevated brain cancer risks related to indoor insecticide use (1×/yr vs. 0, OR = 1.38, 95% CI 0.84–2.25; >1/yr, OR = 1.19, 95% CI 0.81–1.77) (Schuz et al., 2001).

The western United States study found no association with any indoor insecticide use (OR = 1.2, 95% CI 0.8–2.0) or flea/tick insecticide use (OR = 1.0, 95% CI 0.7–1.4) (Pogoda & Preston-Martin, 1997). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of organochlorine (≥90th vs. <1st percentile, OR = 0.86, 95% CI 0.44–1.67), organophosphate (OR = 0.71, 95% CI 0.50–1.02) or carbamate

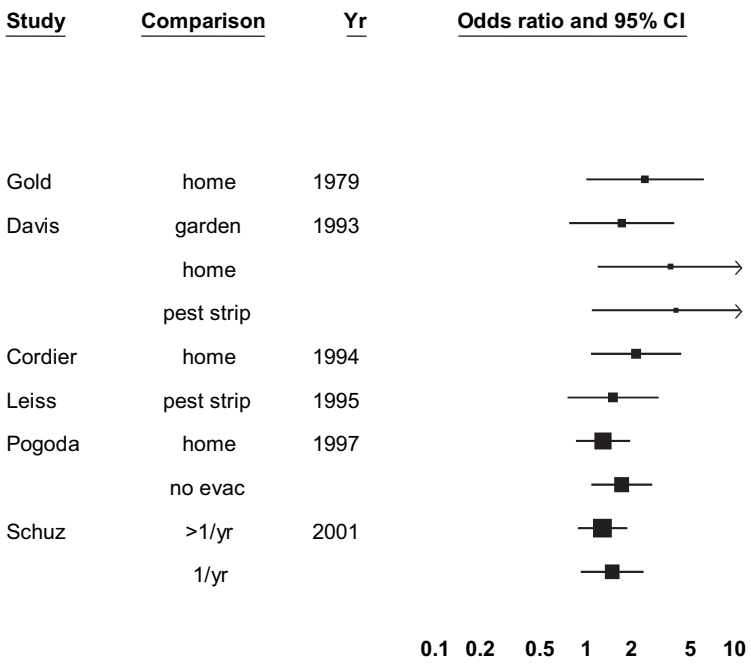

FIGURE 8. Brain cancer versus childhood insecticide exposure (no evac = indoor extermination without home evacuation).

insecticides (OR = 0.76, 95% CI 0.48–1.19) (Reynolds et al., 2002a). The consistency of findings is suggestive of an association but further research is needed to explore dose-response relationships and specific insecticides or groups of toxicologically related insecticides.

Childhood exposure, fungicides, inadequate evidence: An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of dithiocarbamate fungicides (≥90th vs. <1st percentile, OR = 0.59, 95% CI 0.33–1.04) or chlorothalonil (OR = 0.47, 95% CI 0.23–0.97) (Reynolds et al., 2002a).

Childhood exposure, other specified pesticides, inadequate evidence: There was no association between brain cancer and childhood residential use of wood preservatives (OR = 1.26, 95% CI 1.00–1.59) (Schuz et al., 2001). An ecologic study in California found no association between brain gliomas and childhood residential proximity to agricultural use of the soil fumigants methyl bromide (≥90th vs. <1st percentile, OR = 0.63, 95% CI 0.38–1.05) and metam sodium (OR = 0.37, 95% CI 0.09–1.41) (Reynolds et al., 2002a).

Childhood exposure, unspecified pesticides, limited evidence: Brain tumors were associated with outdoor residential pesticide use or proximity to agricultural pesticide use in case-control studies in Baltimore (childhood farm residence, OR = 4.00, 95% CI 1.21–17.7) (Gold et al., 1979), France (farm residence, OR = 6.7, 95% CI 1.2–38.0) (Cordier et al., 1994), the United States/Canada (residence on farm for at least 1 yr, PNET, OR = 5.0, 95% CI 1.1–46.8) (Bunin et al., 1994), the western states in the United States (farm residence before age 6 mo, OR = 1.9, 95% CI 0.96–3.8; farm residence for over 1 yr, OR = 1.7, 95% CI 0.88–3.1) (Holly et al., 1998), and a seven-country study (childhood farm residence, OR = 1.3, 95% CI 1.0–1.7; beginning before age 6 mo, OR = 1.6, 95% CI 1.1–2.2) (Efird et al., 2003). As noted earlier, there was a dose-response relationship between nonastrocytic neuroepithelial brain tumors and pesticide expenditures in a Norwegian record-based cohort study of farm families, especially among children age <5 yrliving on grain farms (Kristensen et al., 1996a). The design of the Norwegian study precluded clear distinction between prenatal parental and childhood pesticide exposures.

No association was apparent in studies in Ontario (childhood pesticide exposure, OR = 0.94, 95% CI 0.47–1.90) (Howe et al., 1989), United States/Canada (childhood farm residence, OR = 0.4,

95% CI 0.1–1.6) (Bunin et al., 1994) or Australia (lived or worked on farm, OR = 0.6, 95% CI 0.2–1.9, only 4 exposed cases) (McCredie et al., 1994b). Although there was uncertainty about the timing of pesticide exposure in the Norwegian cohort, the observation of associations in the larger studies, the strength of associations (odds ratios in 3 studies exceeded 4) and the fact that 2 of the 3 studies with negative findings had less than 100 cases is suggestive of an association.

Environmental tobacco smoke The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood brain cancer and prenatal and postnatal ETS exposure (U.S. Department of Health and Human Services, 2006).

Prenatal active smoking, inadequate evidence: A meta-analysis of 12 epidemiologic studies indicated no association between childhood brain and other central nervous system cancers and prenatal active smoking (summary OR = 1.04, 95% CI 0.92–1.18) (Boffetta et al., 2000).

Prenatal ETS exposure, limited evidence: The California expert panel found no substantial evidence for an association between childhood brain tumors and prenatal active smoking or ETS exposure (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood brain cancer and prenatal or postnatal ETS exposure but insufficient for a firm conclusion (U.S. Department of Health and Human Services, 2006).

Paternal smoking, limited evidence. A meta-analysis of 10 epidemiologic studies indicated a weak association between childhood brain cancer and prenatal paternal smoking (summary OR = 1.22, 95% CI 1.05–1.40) (Boffetta et al., 2000). In an international case-control study, brain cancer before age 1 yr was weakly associated with preconceptual paternal smoking (OR = 1.4, 95% CI 0.9–2.1); there was no such association among older children (Filippini et al., 2002). A recent very large UK case-control study reported no association between central nervous system tumors and preconceptual paternal smoking (OR = 1.03, 95% CI 0.82–1.28) (Pang et al., 2003). See also next section.

Childhood exposure, limited evidence. The California expert panel found limited evidence of a causal association between childhood brain cancer and postnatal ETS exposure, mainly related to paternal smoking but stated that this association may reflect an effect of preconceptual paternal smoking (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is suggestive evidence of a causal relationship between childhood brain cancer and prenatal or postnatal ETS exposure but insufficient for a firm conclusion (U.S. Department of Health and Human Services, 2006).

Outdoor air pollution Maternal exposure, inadequate evidence: In a large Danish case-control study, childhood CNS tumors were not associated with cumulative prenatal exposure to ambient air benzene (≥90th vs. <50th percentile of ppb-days, OR = 0.4, 95% CI 0.1–1.3) or NO_2 (Raaschou-Nielsen et al., 2001). A large California-wide case-control study revealed a weak association between CNS tumors and traffic density near the maternal residence at birth (≥90th vs. <29th percentile of vehicle-miles/mi^2, OR = 1.22, 95% CI 0.87–1.70) (Reynolds et al., 2004).

Childhood exposure, inadequate evidence: A case-control study in Denver, Colorado revealed a dose-response relationship between traffic density on the street of residence at diagnosis and brain tumors among children age 0–4 yr (≥10,000 vs. <500 vehicles/d, OR = 5.2, 95% CI 1.4–19.6) but not those in older children (OR = 1.5, 95% CI 0.5–5.9) (Savitz and Feingold, 1989). A small Swedish case-control study (only 33 cases) revealed a statistically nonsignificant and imprecise association between childhood CNS tumors and average NO_2 levels (an indicator of motor vehicle emissions) near the residence during the year of diagnosis (≥50 vs. <40 μg/m^3, OR = 5.1, 95% CI 0.4–61) (Feychting et al., 1998). Childhood CNS tumors were not associated with cumulative childhood exposure to ambient air benzene (≥90th vs. <50th percentile of ppb-days, OR = 0.6, 95% CI 0.2–1.7) or NO_2 (Raaschou-Nielsen et al., 2001). In a California ecologic study, brain tumors were weakly associated with traffic density near the childhood residence (≥90th vs. <25th percentile of vehicles/d/mi^2, OR = 1.14, 95% CI 0.90–1.45) (Reynolds et al., 2002b). An extension of this study reported no association between brain gliomas and airborne levels, in the census tract of childhood residence at diagnosis, of 25 hazardous air pollutants (HAP) classified as known, probable, or possible human carcinogens by the U.S. EPA (≥90th vs. <25th percentile of carcinogenic HAP index, OR = 0.98, 95% CI 0.80–1.21, *p*-trend > .05) (Reynolds et al., 2003).

Drinking-water nitrate/nitrite Maternal exposure, nitrate, inadequate evidence: In a California/Washington State case-control study, childhood brain tumors were associated with drinking water nitrite levels at the maternal residence (≥1 vs. <1 mg/L, OR = 8.8, 95% CI 2.1–46) but not nitrate levels (≥10 vs. <10 mg/L, OR = 0.6, 95% CI 0.3–1.1) (Mueller et al., 2001). A large international case-control study revealed no association between childhood brain tumors and drinking water nitrate or nitrite levels at the residence where the mother lived during the relevant pregnancy (nitrate ≥50 vs. <10 mg/L, OR = 1.0, 95% CI 0.4–2.2; nitrite ≥5 vs. <1 mg/L, OR = 2.1, 95% CI 0.6–7.4) (Mueller et al., 2004). However, there was an association between astroglial brain tumors and tap water nitrite levels (OR = 5.7, 95% CI 1.2–27).

Solvents Prenatal occupational exposure, unspecified solvents, inadequate evidence: A population-based case-control study in France reported an association between childhood brain tumors and maternal employment in occupations likely exposed to solvents during the 5 yr before the child's birth (high vs. no exposure, OR = 2.4, 95% CI 1.2–4.9) (Cordier et al., 1997). A large Danish case-control study found no association between childhood CNS tumors and cumulative prenatal residential exposure to ambient air benzene (90th vs. <50th percentile of ppb-days, OR = 0.4, 95% CI 0.1–1.3) (Raaschou-Nielsen et al., 2001).

Paternal occupational exposure, unspecified solvents, inadequate evidence: In a Texan case-control study, childhood CNS tumor deaths were associated with paternal occupations with likely solvent exposure including printing (OR = 4.5, 95% CI 1.4–14.7) and petroleum refining (OR = 2.7, 95% CI 0.9–7.8) but not painting (OR = 1.0, 95% CI 0.3–3.3) (Johnson et al., 1987). The authors reported a summary odds ratio of 5.0 ($p < 0.05$) for this association based on 7 studies published up to 1982. During recent years, childhood CNS tumors were not associated with paternal occupational solvent exposure in studies in Denver (preconceptual exposure, yes vs. no, OR = 1.2, 95% CI 0.2–8.5) (Feingold et al., 1992), France (paternal employment in occupations likely exposed to solvents during 5 yr before child's birth, high vs. no exposure, OR = 1.2, 95% CI 0.7–1.9) (Cordier et al., 1997), or Sweden (OR = 1.2, 95% CI 0.7–1.9) (Feychting et al., 2001).

Childhood exposure, benzene, inadequate evidence: A large Danish case-control study found no association between childhood CNS tumors and cumulative childhood residential exposure to ambient air benzene (90th vs. <50th percentile of ppb-days, OR = 0.6, 95% CI 0.2–1.7) (Raaschou-Nielsen et al., 2001).

Summary There is limited epidemiologic evidence for the role of environmental toxicants in childhood brain cancer including: (a) prenatal occupational or residential exposure to insecticides; (b) paternal occupational exposure to unspecified pesticides or active smoking (not clear if paternal smoking acts through germ-cell mutations or fetal/childhood ETS exposure); (c) childhood residential exposure to insecticides or unspecified pesticides.

Neuroblastoma

Lead Maternal occupational exposure, inadequate evidence: One case-control study reported an association between childhood neuroblastomas and self-reported prenatal occupational lead exposure (OR = 4.7, 95% CI 1.3–18.2); the association was somewhat attenuated when exposure was defined as self-reported plus expert-rated potential for such exposure (OR = 3.5, 95% CI 0.7–22.6) (Kerr et al., 2000).

Paternal occupational exposure, limited evidence: Associations between childhood neuroblastomas and self-reported paternal occupational lead exposure were observed in case-control studies in New York State (OR = 2.4, 95% CI 1.2–4.8) (Kerr et al., 2000) and the United States/Canada (OR = 2.6, 95% CI 0.9–7.1) (De Roos et al., 2001). The association in the New York study persisted when exposure was defined as self-reported plus expert-rated potential for such exposure (OR = 2.2, 95% CI 0.9–5.4) (Kerr et al., 2000).

TCDD Paternal occupational exposure, TCDD, inadequate evidence: A case-control study of neuroblastoma found an association with self-reported paternal occupational dioxin exposure but the OR was imprecise (OR = 6.9, 95% CI 1.3–68, 7 exposed case fathers) (Kerr et al., 2000).

Pesticides Among five studies of neuroblastoma published by early 1998, two reported associations with parental pesticide exposure through employment in agriculture and one with parental residential garden pesticide use during childhood (Zahm & Ward, 1998). A review of neuroblastoma

studies published since the Zahm and Ward paper noted that all four found associations with parental occupational pesticide exposure and one observed an association with residential use of pesticides including herbicides (Infante-Rivard & Weichenthal, 2006).

Maternal exposure, insecticides, inadequate evidence: A case-control study in New York State reported an association between neuroblastoma and maternal occupational insecticide exposure (OR = 2.6, 95% CI 1.5–4.5) (Kerr et al., 2000). In the United States/Canada case-control study, neuroblastoma was associated with prenatal or childhood indoor insecticide use for ants or cockroaches (use confirmed by both parents, OR = 1.8, 95% CI 1.0–3.1) and, among cases age 1 yr or older, with any indoor insecticide use (OR = 1.9, 95% CI 1.1–3.2) (Daniels et al., 2001).

Maternal exposure, unspecified pesticides, inadequate evidence: A large United States/Canada case-control study reported statistically nonsignificant elevated risks of neuroblastoma related to maternal occupation in farming (OR = 2.2, 95% CI 0.6–8.8, 7 exposed case mothers) and florist/garden stores (OR = 2.4, 95% CI 0.6–9.9, 6 exposed case mothers) (Olshan et al., 1999). A subsequent report of this study revealed that neuroblastomas were associated with maternal application of garden pesticides (OR = 2.2, 95% CI 1.3–3.8) (Daniels et al., 2001). The few studies, limited sample size and heterogeneity of exposure indices preclude firm conclusions.

Paternal occupational exposure, insecticides, inadequate evidence: A case-control study in New York State reported an association between neuroblastoma and paternal occupational insecticide exposure (OR = 1.8, 95% CI 1.1–3.1) (Kerr et al., 2000).

Paternal occupational exposure, unspecified pesticides, inadequate evidence: In a Norwegian cohort study, neuroblastoma risk was increased among offspring of farmers (mainly male) who reported field vegetable farming and purchased pesticides (compared to farm families with neither trait, RR = 2.51, 95% CI 1.03–6.13) (Kristensen et al., 1996a). A large United States/Canada case-control study reported that neuroblastoma was associated with certain potentially exposed paternal occupations (landscaping or grounds keeping, OR = 2.3, 95% CI 1.0–5.2) but not farming (OR = 0.9, 95% CI 0.4–1.8) (Olshan et al., 1999). A later report of this study indicated that neuroblastomas were not associated with paternal application of garden pesticides (OR = 1.1, 95% CI 0.8–1.5) (Daniels et al., 2001). The AHS cohort revealed no association between neuroblastoma and paternal occupation as licensed agricultural pesticide applicators (SIR = 1.26, 95% CI 0.40–3.89) but there were only three cases (Flower et al., 2004). The findings of the Norwegian cohort and the large United States/Canada case-control study are suggestive of an association but further research is needed to clarify the role of specific pesticides or related groups of pesticides, critical exposure windows and dose-response relationships. Further follow-up of the AHS cohort would also be valuable.

Childhood exposure, herbicides, inadequate evidence: The United States/Canada case-control study also reported elevated neuroblastoma risk related to prenatal or childhood herbicide use (use confirmed by both parents, OR = 2.2, 95% CI 1.1–4.3); there was no association among infants below age 1 yr (Daniels et al., 2001).

Childhood exposure, insecticides, inadequate evidence: A recent report of the United States/Canada case-control study noted elevated neuroblastoma risk among children age 1 or older related to prenatal or childhood insecticide use indoors (OR = 1.9, 95% CI 1.1–3.2) and in gardens (OR = 1.7, 95% CI 0.8–3.6) (Daniels et al., 2001).

Solvents Parental occupational exposure, unspecified solvent, inadequate evidence: A large United States–Canada case-control study of neuroblastoma found associations with likely occupational solvent exposure during the 2 yr before the child's birth among fathers (OR = 1.5, 95% CI 1.0–2.1) but not mothers (OR = 1.2, 95% CI 0.7–2.1) (De Roos et al., 2001). For paternal solvent exposure, associations were stronger (and statistically significant) for lacquer thinner, mineral spirits, and turpentine (ORs of 1.9 to 3.5).

Summary There is limited epidemiologic evidence that childhood neuroblastoma is associated with paternal occupational lead exposure.

Wilms's Tumor

Pesticides A review of the six studies of Wilms' tumor published by early 1998 noted that none of the three that assessed postnatal parental pesticide exposure (occupational use or residential

gardening) found an association (Zahm & Ward, 1998). The only study that examined household extermination (mainly insecticide use) observed an association and the two studies that focused on parental occupational exposures before birth both found associations. A review of the two studies published since Zahm and Ward's report noted that both observed statistically nonsignificant increased risks related to parental occupational pesticide exposure based on only two or three exposed case parents (Infante-Rivard & Weichenthal, 2006).

Maternal exposure, herbicides, inadequate evidence: In a United States/Canada case-control study, Wilms's tumor was not associated with residential herbicide use at any time during pregnancy or childhood (OR = 1.0, 95% CI 0.7–1.4) (Cooney et al., 2007).

Maternal exposure, insecticides, inadequate evidence: A German case-control study reported a statistically nonsignificant elevated risk of Wilms's tumor related to prenatal or childhood indoor residential insecticide use (≥1 vs. <1×/yr, OR = 1.27, 95% CI 0.78–2.08) (Schuz et al., 2001). In the United States/Canada case-control study, Wilms's tumor was associated with indoor residential insecticide use at any time during pregnancy or childhood (OR = 1.4, 95% CI 1.0–1.8) (Cooney et al., 2007).

Maternal exposure, unspecified pesticides, inadequate evidence: A case-control study in Brazil, a country with relatively high Wilms's tumor incidence rates, revealed a dose-response relationship between this tumor and frequency of preconceptual/prenatal occupational exposure to agricultural pesticides (≥10 vs. 0 times, OR = 129, 95% CI 6.4–2570, 6 exposed case and 1 exposed control mothers, *p*-trend = .03) (Sharpe et al., 1995). There were statistically nonsignificant elevated risks of Wilms's tumor in case-control studies in Germany (maternal occupational pesticide exposure, OR = 2.52, 95% CI 0.50–12.6, 2 exposed case mothers) (Schuz et al., 2001) and the United States (prenatal residential or occupational pesticide exposure, OR = 1.32, 95% CI 0.83–2.09) (Tsai et al., 2006). In the United States/Canada case-control study, Wilms's tumor was associated with indoor residential use of any pesticide at any time during pregnancy or childhood (OR = 1.3, 95% CI 1.0–1.7) (Cooney et al., 2007). Larger studies are needed to clarify the role of specific pesticides or related groups of pesticides, critical exposure windows and dose-response relationships.

Paternal occupational exposure, unspecified pesticides, inadequate evidence: The Brazil study revealed a dose-response relationship between Wilms' tumor and frequency of preconceptual paternal occupational exposure to agricultural pesticides (≥10 vs. 0 times, OR = 3.2, 95% CI 1.2–9.0, *p*-trend = .02) (Sharpe et al., 1995). A Norwegian retrospective cohort study reported elevated risks of Wilms' tumor among offspring of farmers (mainly male) who reported ownership of pesticide spraying equipment (OR = 2.54, 95% CI 0.98–6.58) and those with orchards or greenhouses and pesticide spraying equipment (OR = 8.87, 95% CI 2.67–29.5) (Kristensen et al., 1996a). Although this study lacked detailed pesticide use information, it had the advantage of not relying on potentially biased parental recall of exposures. A mortality study in England found no association between Wilms's tumor and paternal occupation in agriculture (PMR = 0.88, 95% CI 0.20–3.84) (Pearce & Parker 2000). The AHS cohort revealed a statistically nonsignificant elevated risk of Wilms's tumor related to paternal occupation as licensed agricultural pesticide applicators (SIR = 1.56, 95% CI 0.50–4.84, only 3 cases) (Flower et al., 2004). The two studies with negative findings are not compelling because one was a proportional mortality study limited to information on death records and the other was a cohort study with only three observed cases.

Childhood exposure, herbicides, inadequate evidence: In the U.S./Canada case-control study, Wilms's tumor was not associated with residential herbicide use at any time during pregnancy or childhood (OR = 1.0, 95% CI 0.7–1.4) (Cooney et al., 2007).

Childhood exposure, insecticides, inadequate evidence: The German study reported a statistically nonsignificant elevated risk of Wilms' tumor related to prenatal or childhood indoor residential insecticide use (≥1 vs. <1×/yr, OR = 1.27, 95% CI 0.78–2.08) (Schuz et al., 2001). In a United States/Canada case-control study, Wilms' tumor was associated with indoor residential insecticide use at any time during pregnancy or childhood (OR = 1.4, 95% CI 1.0–1.8) (Cooney et al., 2007).

Childhood exposure, unspecified pesticides, inadequate evidence: The German study reported no association between Wilms's tumor and childhood residence on farms (OR = 0.8, 95% CI 0.3–2.3), residential garden pesticide use (OR = 0.8, 95% CI 0.4–1.5) or childhood paternal occupational

pesticide exposure (OR = 0.97, 95% CI 0.39–2.37) (Schuz et al., 2001). In the United States/Canada case-control study, Wilms's tumor was associated with indoor residential use of any pesticide at any time during pregnancy or childhood (OR = 1.3, 95% CI 1.0–1.7) (Cooney et al., 2007).

Other toxicants Paternal exposure, inadequate evidence: Reviewers found inadequate evidence for an association between Wilms's tumor and paternal occupational lead exposure (Colt & Blair, 1998).

Summary There was inadequate epidemiologic evidence for an association between Wilms' tumor and any of the environmental contaminants examined here.

Bone Tumors

Pesticides A review of the three studies of Ewing's sarcoma published by early 1998 noted that all found elevated risks related to parental pesticide exposure (statistically significant in two studies) (Zahm & Ward, 1998). Reviewers noted that the only study published since the Zahm and Ward review found increased Ewing's sarcoma risk related to agricultural employment of at least 1 parent (Infante-Rivard & Weichenthal, 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: Maternal occupation in farming was associated with increased risk of childhood bone cancer in Ontario (2.7, 95% CI 0.8–9.3), especially among women with at least 5 yr exposure (OR = 2.9, 95% CI 0.5–15.3) and the subgroup of Ewing's sarcoma (OR = 7.8, 95% CI 1.9–32) (Hum et al., 1998). An Australian case-control study reported a statistically nonsignificant elevated risk of Ewing's sarcoma among children and young adults in relation to periconceptual maternal occupation in farming (OR = 2.8, 95% CI 0.5–15.8) and ever-handling of pesticides (OR = 2.3, 95% CI 0.5–12) (Valery et al., 2002).

Paternal exposure, unspecified pesticides, limited evidence: Ewing's sarcoma was associated with paternal occupational pesticide exposure in a California case-control study (OR = 8.8, 95% CI 1.8–42.7) (Holly et al., 1992). The Ontario study showed that osteosarcoma risk was elevated in relation to paternal occupation in farming (OR = 2.1, 95% CI 0.8–5.7) and bone cancer risk (any histologic type) was increased in relation to paternal work in farming for at least 5 yr (OR = 2.4, 95% CI 0.9–6.4) (Hum et al., 1998). The Australian case-control study reported statistically nonsignificant elevated risks of Ewing's sarcoma related to periconceptual paternal occupation in farming (OR = 3.5, 95% CI 1.0–11.9) and ever-handling of pesticides (OR = 2.0, 95% CI 0.8–4.9) (Valery et al., 2002). In the AHS cohort, there was a statistically nonsignificant increased risk of bone cancer among offspring of licensed pesticide applicators (SIR = 2.19, 95% CI 0.82–5.84, based on 4 cases) (Flower et al., 2004). A U.S. case-control study of Ewing's sarcoma observed no association with likely prenatal paternal pesticide exposure (OR = 0.7, 95% CI 0.2–2.9) (Moore et al., 2005).

Childhood exposure, insecticides, inadequate evidence: In a California case-control study, Ewing's sarcoma was not associated with childhood indoor insecticide use (OR = 0.6, 95% CI 0.3–1.2) or residence on or next to a farm (OR = 1.0, 95% CI 0.3–4.0) (OR = 0.6, 95% CI 0.3–1.2) (Holly et al., 1992). A U.S. case-control study of Ewing's sarcoma observed an association between childhood residential indoor insecticide use and Ewing's sarcoma among boys (OR = 3.0, 95% CI 1.1–8.1) but not girls (OR = 1.1, 95% CI 0.4–3.2) (Moore et al., 2005).

Childhood exposure, unspecified pesticides, inadequate evidence: A U.S. case-control study reported statistically nonsignificant elevated risks of Ewing's sarcoma among girls who had ever lived on farms (OR = 6.4, 95% CI 0.7–58.4) but not among boys (OR = 0.9, 95% CI 0.4–2.2) and but not in relation to postnatal parental occupational pesticide exposure (OR = 0.9, 95% CI 0.2–3.7) (Moore et al., 2005).

Germ-Cell Tumors Germ-cell tumors arise from male or female germ cells and can occur at almost any anatomic site and be benign or malignant.

Pesticides Maternal exposure, herbicides, insecticides, inadequate evidence: A U.S. case-control study revealed no association between germ-cell tumors and prenatal residential use of indoor insecticides (used ≥2 vs. 0 types of insecticides, OR = 1.2, 95% CI 0.8–1.6, p-trend = .48) and a statistically nonsignificant, modestly elevated risk related to prenatal residential herbicide use (ever vs. never, OR = 1.3, 95% CI 0.9–1.7) (Chen et al., 2006).

Maternal exposure, unspecified pesticides, inadequate evidence: A United States/Canada case-control reported elevated risks of germ-cell tumors (ovarian, testicular, nongonadal) related to maternal occupational or residential pesticide exposure (OR = 2.4, 95% CI 0.9–6.9) (Shu et al., 1995). In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had an increased risk of germ-cell tumors (OR = 2.34, 95% CI 0.88–6.24; 5 exposed case fathers); there was potential prenatal pesticide exposure because the women lived on farms and 58% of them reported mixing or applying pesticides (Flower et al., 2004). In another U.S. case-control study, prenatal pesticide exposure at work was not associated with germ-cell tumors (>50th percentile of cumulative exposure vs. unexposed, OR = 0.9, 95% CI 0.5–1.7, *p*-trend = 0.93) but was related to an elevated risk of dysgerminoma, a specific histological type of germ-cell tumor (ever exposed vs. never, OR = 1.9, 95% CI 0.9–4.2) (Chen et al., 2005b). Three studies observed elevated risks of germ-cell tumors related to prenatal occupational or residential pesticide exposure. However, none of the relationships were statistically significant, one was limited to a histologic subtype and the role of maternal versus paternal exposure in the AHS cohort is not clear.

Paternal exposure, herbicides, insecticides, inadequate evidence: A U.S. case-control study revealed no association between germ-cell tumors and preconceptual/perinatal paternal residential use of herbicides (ever vs. never, OR = 1.0, 95% CI 0.7–1.3) or insecticides (used ≥2 vs. 0 types of insecticides, OR = 1.1, 95% CI 0.8–1.6, *p*-trend = .64) (Chen et al., 2006).

Paternal exposure, unspecified pesticides, inadequate evidence: The United States/Canada case-control reported elevated risks of germ-cell tumors (ovarian, testicular, nongonadal) related to paternal occupational pesticide exposure (OR = 1.8, 95% CI 0.7–5.0) (Shu et al., 1995). In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had an increased risk of germ-cell tumors (OR = 2.34, 95% CI 0.88–6.24; 5 exposed case fathers) (Flower et al., 2004). In a U.S. case-control study, preconceptual paternal pesticide exposure at work was not associated with germ-cell tumors (>50th percentile of cumulative exposure vs. unexposed, OR = 0.9, 95% CI 0.6–1.3, *p*-trend = 0.49) or any histological subtype (Chen et al., 2005b). Two of the three studies observed statistically nonsignificant elevated risks of germ-cell tumors related to self-reported paternal occupational pesticide exposure.

Childhood exposure, insecticides, inadequate evidence: A U.S. case-control study revealed no association between germ-cell tumors and childhood residential indoor insecticide use (used ≥2 vs. 0 types of insecticides, OR = 1.0, 95% CI 0.7–1.5, *p*-trend = .99) (Chen et al., 2006).

Childhood exposure, unspecified pesticides, inadequate evidence: In the AHS cohort study, children of licensed pesticide applicator-farmers (almost entirely men) had a statistically nonsignificant increased risk of germ-cell tumors (OR = 2.34, 95% CI 0.88–6.24; 5 exposed case fathers) (Flower et al., 2004). Given their residence on farms known to use pesticides, and evidence that children of pesticide applicators have substantially higher urinary organophosphate insecticide metabolites compared to other children (Fenske et al., 2005), there clearly was the potential for childhood pesticide exposure.

Tobacco smoke Maternal active smoking, inadequate evidence: In a large United States-Canada case-control study, childhood germ-cell tumors were not associated with prenatal active smoking (≥20 cigarettes/d, OR = 1.1, 95% CI 0.6–2.1) or ETS exposure (OR = 1.0, 95% CI 0.6–1.3) (Chen et al., 2005a).

Paternal smoking, inadequate evidence: The United States–Canada case-control study revealed no association between childhood germ-cell tumors and paternal active smoking (smoked 16 or more years before pregnancy, OR = 1.3, 95% CI 0.7–2.2, *p*-trend = .13; smoked 16 or more years before pregnancy, OR = 1.3, 95% CI 0.6–2.7, *p*-trend = .21) (Chen et al., 2005a).

Eye Tumors Most childhood eye tumors are retinoblastomas. There was an increased risk of adult eye tumor death among farmers licensed to apply pesticides in Italy (SMR = 2.38, 95% CI 0.65–6.09) (Torchio et al., 1994), but most adult eye tumors are melanomas and the relevance to childhood eye tumors, apart from demonstrating the potential vulnerability of the eye to environmental carcinogens, is not clear.

Pesticides Maternal exposure, unspecified pesticides, inadequate evidence: A U.S. case-control study reported an association between nonheritable retinoblastoma and maternal grandparent

occupation in farming (OR = 10.0, 95% CI 1.4–433; based on 10 case-only and 1 control-only exposed matched pairs) (Bunin et al., 1990).

Paternal exposure, unspecified pesticides, inadequate evidence: In a Norwegian retrospective cohort study, childhood eye tumors were associated with parental (mainly paternal) pesticide purchases for field vegetable farming (compared to no field vegetable farming and no pesticide purchases, RR = 3.17, 95% CI 0.93–10.9) (Kristensen et al., 1996a). The AHS cohort revealed a statistically nonsignificant elevated retinoblastoma risk among children of licensed agricultural pesticide applicators (SIR = 1.63, 95% CI 0.41–6.53, only 2 cases) (Flower et al., 2004).

Soft-Tissue Sarcoma

Pesticides Soft tissue sarcomas comprise relatively rare and diverse histological subtypes of largely unknown causation (the only proven cause of adult soft-tissue sarcomas is high-dose radiation). Among adults, soft-tissue sarcomas have been linked to occupational exposure to herbicides or multiple pesticides in several studies conducted in various countries (Briggs et al., 2003; Hoar Zahm et al., 1988) (Hansen et al., 1992; Hoppin et al., 1999; Kogevinas et al., 1997; Lynge 1998; Vineis et al., 1987), but other studies found no association (Fleming et al., 1999; Johnson et al., 1990; Pahwa et al., 2003; Wiklund et al., 1988).

Maternal exposure, herbicides, unspecified pesticides, inadequate evidence: A case-control study in Denver reported that childhood soft-tissue sarcoma was not associated with prenatal residential herbicide use (OR = 0.8, 95% CI 0.5–1.3) (Leiss & Savitz, 1995). In a relatively large case-control study in Germany, childhood soft-tissue sarcomas were associated with maternal occupational pesticide exposure (result stated without supporting data in paper) (Meinert et al., 2000).

Paternal exposure, unspecified pesticides, inadequate evidence: The AHS cohort revealed no association between soft-tissue sarcoma and paternal occupation as licensed agricultural pesticide applicators (SIR = 1.17, 95% CI 0.38–3.62, only 3 cases) (Flower et al., 2004).

Childhood exposure, herbicides, inadequate evidence: A case-control study in Denver reported that childhood soft-tissue sarcoma was associated with postnatal lawn herbicide use (OR = 4.1, 95% CI 1.0–16.0) (Leiss & Savitz, 1995).

Adult Cancers

This section describes adult cancer risks linked to prenatal or childhood environmental exposures, with level of epidemiologic evidence summarized in Table 7. About 130,000 new cancer cases annually occur among persons age 15–49 in the United States (Wu et al., 2005). Cancer incidence rates for this age range increased during 1969–1996 in Canada for lung (women), testicular and thyroid cancers, melanoma, and NHL (Marrett et al., 2002).

Testicular Cancer Reviewers concluded that available evidence from human and animal studies supports a hypothesis that testicular cancer is associated with a prenatal exposure to exogenous estrogens (Storgaard et al., 2006). However, there have been few epidemiologic studies of testicular cancer and prenatal exposure to environmental toxicants.

PCBS Maternal exposure, inadequate evidence: A recent Swedish case-control study observed an association between testicular cancer and maternal plasma PCB levels (>median vs. ≤median, OR = 3.8, 95% CI 1.4–10.0) (Hardell et al., 2003). Further investigation revealed an

TABLE 7. Role of Early-Life Exposure to Environmental Toxicants in Adult Cancer

Toxicant	Exposure	Testicular	Breast	Lung	Other
Arsenic	Prenatal			I	
	Childhood			I	
PCBs	Prenatal	I			
Organochlorine pesticides	Prenatal	I			
Unspecified pesticides	Prenatal	I			
	Paternal	I			
Environmental tobacco smoke	Childhood		**L**	S	Pancreas—I Chronic lymphocytic leukemia—I
Drinking-water nitrate	Childhood	I			

association between testicular cancer and maternal plasma PCB-TEQ (>median vs. ≤median, OR = 3.3, 95% CI 1.3–8.4) (Hardell et al., 2006).

Pesticides Maternal exposure, organochlorine pesticides, inadequate evidence: A small case-control study reported that testicular cancer was marginally associated with the subjects' plasma HCB (≥median vs. <median plasma levels, OR = 1.7, 95% CI 0.8–3.6) and DDE levels (OR = 1.7, 95% CI 0.8–3.7) and strongly associated with their mothers' plasma HCB levels (OR = 4.4, 95% CI 1.7–12) (Hardell et al., 2003). This study found no association with maternal plasma DDE (OR = 1.3, 95% CI 0.5–3.0) and a statistically nonsignificant relationship with sum of chlordanes (OR = 1.9, 95% CI 0.7–5.0).

Maternal occupational exposure, unspecified pesticides, inadequate evidence: Testicular cancer in Denmark was not associated with prenatal employment in agriculture (OR = 1.2, 95% CI 0.6–2.7) (Moller, 1997).

Paternal occupational exposure, unspecified pesticides, inadequate evidence: In a retrospective cohort study of Norwegian farm families, there was a slightly elevated testicular cancer risk among offspring (relative to national rates, SIR = 1.24, 95% CI 1.01–1.52), but risk was not related to expenditures on farm pesticides (any expenditure vs. none, OR = 0.89, 95% CI 0.60–1.32) (Kristensen et al., 1996a).

Drinking water nitrate Childhood exposure, inadequate evidence: In a Norwegian retrospective cohort study, testicular cancer among offspring in farm families was associated with parental farm use of high nitrogen fertilizers (OR = 2.0, 95% CI 1.5–2.6) (Kristensen et al., 1996b). A population-based case-control study in Denmark reported an association between testicular cancer and a history of having lived for most of childhood in 3 counties with ground water nitrate levels exceeding 25 mg/L (OR = 1.4, 95% CI 1.1–1.8) (Moller, 1997). However, the excess risk was largely limited to men who grew up in urbanized regions of the three counties served by low-nitrate communal water supplies; thus, nitrate per se probably was not responsible for the observed association.

Summary There is inadequate epidemiologic evidence for a role of prenatal or childhood exposure to environmental toxicants in adult testicular cancer.

Breast Cancer

Environmental tobacco smoke Childhood exposure, evidence: An expert group convened by the State of California found sufficient evidence of a causal association between breast cancer and ETS exposure, particularly among premenopausal women and those exposed early in life (California Environmental Protection Agency, 2005). The California report also noted that ETS contains these carcinogens known to cause breast cancer in experimental animals: benzene, dibenz[a,h]anthracene, four dibenzopyrenes, two nitrosamines, eight aliphatic compounds, and three arylamines/nitroarenes. The U.S. Surgeon General reviewed findings from 7 prospective cohort and 14 case-control studies of breast cancer and ETS exposure and concluded that the evidence was suggestive of a causal relationship but not conclusive (U.S. Department of Health and Human Services, 2006). The strongest associations were generally based on case-control studies and premenopausal breast cancer. The Surgeon General noted that there was inconsistent evidence for increased breast cancer risk related to ETS exposure during childhood or adolescence.

A pooled analysis of data from 53 studies that compared ever and never smokers showed no association between breast cancer and active smoking (pooled OR = 1.03, 95% CI 0.98–1.07) (Hamajima et al., 2002). However, smoking has effects that may increase or decrease breast cancer risk. For instance, active smokers have lower urinary estrogen levels and increased estradiol 2-hydroxylation compared to nonsmokers, characteristics associated with reduced breast cancer risk (U.S. Department of Health and Human Services, 2006). However, tobacco smoke mutagens and aromatic DNA adducts are detectable in breast fluid or tissues. In active smokers, but not ETS-exposed nonsmokers, the anti-estrogenic effects of smoking may offset any increased breastcancer risk from tobacco smoke carcinogens (U.S. Department of Health and Human Services, 2006).

Summary There is limited epidemiologic evidence for an association between adult breast cancer and lifetime ETS exposure; thus, childhood ETS exposure may contribute to lifetime breast cancer risk in women.

Lung Cancer

Arsenic Maternal or childhood exposure, inadequate evidence: An ecologic study in Chile noted increased lung cancer death rates among persons who were likely exposed to high arsenic levels in drinking water prenatally (SMR = 7.0, 95% CI 5.4–8.9) or during early childhood (SMR = 6.1, 95% CI 3.5–9.9) (Smith et al., 2006).

Environmental tobacco smoke Childhood exposure, sufficient evidence: The U.S. Surgeon General reviewed 8 cohort and over 40 case-control studies and concluded that there is sufficient evidence that ETS causes adult lung cancer (U.S. Department of Health and Human Services, 2006). Thus, childhood ETS exposure contributes to lifetime exposure and risk of adult lung cancer.

Summary There is sufficient evidence that childhood ETS exposure contributes to lifetime ETS exposure and increased lung cancer risk.

Other Adult Cancers

Environmental tobacco smoke Childhood exposure, inadequate evidence: A large Canadian case-control study observed a slightly elevated risk of pancreatic cancer among persons exposed to ETS during both childhood and adulthood (OR = 1.21, 95% CI 0.60–2.44) (Villeneuve et al., 2004). In a large case-control study restricted to nonsmokers, lifetime duration of residential and occupational ETS exposure was associated with adult chronic lymphocytic leukemia (≥53 vs. 0 yr, OR = 2.18, 95% CI 1.10–4.32, p-trend = 0.001) and to a lesser degree with acute myelogenous leukemia (≥53 vs. 0 yr, OR = 1.74, 95% CI 0.83–3.66, p-trend = 0.27) (Kasim et al., 2005).

Summary There is inadequate evidence for associations between other adult cancers and prenatal or childhood exposure to environmental chemical contaminants.

Other Health Outcomes

Table 8 summarizes the level of epidemiologic evidence for associations between environmental contaminants and postnatal growth and pubertal development, and Table 9 addresses sudden infant death syndrome (SIDS), tooth abnormalities, chloracne, renal tubular damage, and chromosomal abnormalities.

Postnatal Growth in Height

Lead Maternal exposure, inadequate evidence: In the Cleveland birth cohort, height at age 4 was not associated with average maternal and cord blood lead levels (change in height (% of 1 SD) per unit change in blood lead (μg/dl), β = –0.26 ± 3.37, p = .94) (Greene & Ernhart, 1991).

TABLE 8. Role of Environmental Toxicants in Child Growth and Pubertal Development

Toxicant	Exposure	Postnatal growth in height	Delayed menarche	Delayed pubic hair development, girls	Delayed breast development	Delayed male external genital development	Delayed male pubic hair development
Lead	Prenatal	I					
	Childhood	**L**	**L**		I		
Methylmercury	Prenatal	I					
	Lactational	I					
PCBs	Prenatal	High-level: L Low-level: I	I	I	I	I	I
	Lactational or childhood	I	I	I	I	I	I
PBBs	Prenatal	I	I	I	I		
DDT/DDE	Prenatal	I					
	Lactational or childhood	I					
Environmental tobacco smoke	Prenatal	I					
	Childhood	I					
Phthalates	Childhood				Early breast development: I	I	

TABLE 9. Role of Environmental Toxicants in other Child Health Outcomes

Toxicant	Exposure	Renal tubular damage	Chromosomal abnormalities	Other diseases
Lead	Childhood	**S**		Dental caries –**L**
Mercury	Childhood	Organic Hg—**L** Elemental Hg—I		
Arsenic	Prenatal		I	
	Childhood		**L**	
Cadmium	Childhood	I		
PCBs, PCDFs, related toxicants	Prenatal			Allergies/low-level PCBs—I
	Childhood			Chloracne/high-level PCBs—**S** Allergies/low-level PCBs—I
TCDD	Childhood			Chloracne/high-level TCDD—**S**
Unspecified pesticides	Prenatal			Allergies—I
Active smoking	Prenatal			SIDS—**S**
Environmental tobacco	Prenatal		I	
smoke	Infancy		I	SIDS—**S**
Outdoor air pollution	Prenatal		I	
	Infancy			SIDS—**L**
Drinking water DBPs	Prenatal		I	
Hazardous waste disposal sites	Prenatal		I	
Incinerators	Prenatal		I	
Unspecified solvents	Prenatal		I	
	Paternal		I	

Note. TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Childhood exposure, limited evidence: In the Cincinnati birth cohort, there was an inverse dose-response relationship between infant blood lead at age 3 months and growth in stature from age 3 to 15 months (regression slope b = –0.015 cm per μg/dL, $p = .013$). (Shukla et al., 1989). Further follow-up revealed an inverse association between stature at age 33 months and the interaction term between average blood lead from age 3 to 15 months times that for age 18 to 33 months ($\beta = -1.81 \pm 0.80$ cm, $p = .025$) (Shukla et al., 1991). In the Cleveland birth cohort, height at age 4 yr was inversely associated with blood lead at age 6 mo (change in height (% of 1 SD) per unit change in blood lead (μg/dl), $\beta = -3.91 \pm 2.07$, $p = .06$) but not current blood lead ($\beta = 1.62 \pm 1.40$, $p = .25$) (Greene & Ernhart, 1991). Three large cross-sectional studies based on NHANES II and III found inverse dose-response relationships between height and current blood lead levels extending below 10 μg/dl with no evidence of a threshold. Among children age 1–7, height was inversely associated with current blood lead levels in NHANES II (change in height per unit change in current blood lead (μg/dL), $\beta = -0.12 \pm 0.0005$ cm, $p < 0.0001$) (Schwartz et al., 1986). Similarly, height was inversely associated with current blood lead level among all children in NHANES III (boys and girls age 1–7, $\beta = -0.157 \pm 0.032$ cm, $p < 0.0001$) (Ballew et al., 1999) and among the subset of girls age 8–18 (difference in height, current blood lead ≥ 3 vs. <1.0 μg/dL, regression slope r = –0.51 cm, $p < 0.001$) (Selevan et al., 2003). A small birth cohort study in Massachusetts revealed no association between height at age 6–8 and log tooth dentin lead levels ($\beta = -0.9 \pm 1.1$ (SE), $p > 0.05$) (Kim et al., 1995). A cross-sectional study of Italian children age 11–13 revealed an inverse association between height and log current blood lead levels (boys, $\beta = -27.4 \pm 11.5$ (SE) cm, $p = 0.02$) (Vivoli et al., 1993). Similarly, a cross-sectional study of Greek children age 6–9 reported an inverse association between height and current blood lead (μg/dL) ($\beta = -0.086 \pm 0.037$ (SE) cm, $p = 0.02$) (Kafourou et al., 1997).

Methylmercury Maternal exposure, inadequate evidence: A small birth cohort study in the Faroe Islands reported an inverse association between height at age 18 mo and cord blood mercury (change in height per log cord blood mercury increment, $\beta = -0.88$ cm, 95% CI –1.85 to 0.09); this association persisted at age 42 mo but was not statistically significant (–0.97 cm, 95% CI –2.42 to 0.49) (Grandjean et al., 2003).

Lactational exposure, inadequate evidence: The Faroe Islands cohort observed inverse associations between cumulative lactational mercury exposure (cord blood mercury times breast-feeding duration in weeks) and height at age 18 mo (change in height per log lactational mercury increment, $\beta = -0.73$ cm, 95% CI –1.30 to –0.12) but not height at age 42 mo ($\beta = -0.34$ cm, 95% CI –1.16 to 0.48) (Grandjean et al., 2003).

PCBs and related compounds High-level prenatal PCB exposure, limited evidence: Compard to unexposed children, Yucheng children up to age 8 were 3% shorter (95% CI –4 to –1) (Rogan et al., 1988). Further follow-up revealed a persistent height deficit up at ages 6–13 yr (exposed vs. unexposed, difference –3.1 cm, $p < .01$) (Guo et al., 1994). Reviewers concluded that growth in height during childhood was reduced among offspring of women prenatally exposed to cooking oil highly contaminated by PCBs, PCDFs, and related toxicants (Guo et al., 1995; Longnecker et al., 1997).

Low-level maternal exposure, inadequate evidence: The Dutch birth cohort study reported that cord blood PCB was inversely associated with growth in height from birth to age 3 mo (change in height per unit change in natural log PCB, $\beta = -0.28 \pm 0.12$ cm, $p = .03$) but not with height changes during mo 3–7, 7–18, or 18–42 (Patandin et al., 1998). A Michigan birth cohort study found no association between height at age 4 yr and prenatal PCB exposure (stated without supporting data) (Jacobson et al., 1990b). The North Carolina birth cohort study observed no association between prenatal PCB exposure and height at age 12–14 yr in girls or boys (average height vs. increasing prenatal maternal PCB level, *p*-trend was 0.75 for girls and 0.24 for boys) (Gladen et al., 2000). In another Michigan birth cohort, there was no association between prenatal serum PCB and height of daughters age 5–24 (PCB ≥9.0 vs. ≤5.0 μg/L, $\beta = 0.2$ inches, 95% CI –0.8 to 1.3) (Blanck et al., 2002). A birth cohort study in New York City revealed no association between height at intervals up to age 17 and 3rd trimester maternal serum PCB concentrations (unit change in natural log of height at each age per unit change in natural log of maternal serum PCBs, girls, –0.6 cm, 95% CI –3.2 to 2.0; boys, 0.5 cm, 95% CI –1.4 to 2.3) (Lamb et al., 2006). A retrospective cohort study of Swedish fishermen's wives revealed no association between maternal plasma PCB–153 concentrations and child height at age 4 or 7 (normal birth weight children, mean difference in height at age 7, maternal plasma PCB–153 ≥250 vs. <250 ng/g lipid, $\beta = -0.31$, 95% CI –2.05 to 1.43) (Rylander et al., 2007).

Lactational or childhood PCB exposure, inadequate evidence: A Michigan birth cohort study found no association between height at age 4 yr and lactational PCB exposure (stated without supporting data) (Jacobson et al., 1990b). The Dutch birth cohort study reported that growth in height from 3 to 7 mo was inversely related to cumulative lactational dioxin-TEQ based on cord blood PCDD/PCB concentrations and breast-feeding duration (weeks) (change in height per unit change in cumulative exposure, $\beta = -0.21$ cm, $p = .04$); changes in height from birth to age 3 mo, from 7 to 18 mo, and from 18 to 42 mo were not associated with lactational PCDD/PCB-TEQ exposure (Patandin et al., 1998). The North Carolina birth cohort study observed no association between cumulative lactational PCB exposure and height at age 12–14 (average height vs. increasing lactational PCB intake, *p*-trend was .13 for girls and 0.92 for boys) (Gladen et al., 2000). The North Carolina birth cohort study observed no association between lactational PCB exposure and height at age 12–14 (Gladen et al., 2000). A German cohort study found no association between growth in height from age 7–8 yr to 10–11 yr and baseline blood PCB levels (result stated without supporting data) (Karmaus et al., 2002). In a small Faroe Islands birth cohort, growth in height from birth to age 42 mo was inversely associated with lactational PCB exposure (change in height per doubling of serum PCB at age 54 mo, –0.63 cm, 95% CI –1.12 to–0.13) (Grandjean et al., 2003).

PBBs Maternal exposure, inadequate evidence: A Michigan birth cohort study reported no association between prenatal serum PBB and height of daughters at age 5–24 yr (change in height, PCB ≥7.0 vs. ≤1.0 μg/L, $\beta = 0.61$ inches, 95% CI –0.50 to 1.7) (Blanck et al., 2002).

Pesticides Prenatal or lactational DDT/DDE exposure, inadequate evidence: A birth cohort study in North Carolina revealed a favourable association between height of adolescent boys and increasing breast milk DDE concentration categories (p-trend = .05) (Gladen et al., 2000). This study found no association between adolescent height of girls and breast milk DDE or between height of either gender and lactational DDE exposure; there was no adjustment for maternal height or prenatal smoking. Among girls in a German birth cohort, heights (adjusted for birth weight, breast-feeding duration, prenatal smoking, and other potential confounders) at ages 4–6 wk, 3–4 mo, 6–7 mo, 10–12 mo, 21–24 mo, 43–48 mo, 8 yr, and 9 yr were inversely associated with blood DDE quartiles measured at age 7–8 yr; the difference for girls at age 10 yr was not significant and there was only one significant difference for boys (Karmaus et al., 2002). In the U.S. Collaborative Perinatal Project (pregnant women recruited during 1959–1966), follow-up of a subsample of sons at age 20 revealed no association between height and quintiles of prenatal serum DDE (Gladen et al., 2004).

Environmental tobacco smoke Maternal or childhood exposure, ETS, inadequate evidence: A longitudinal cohort study in California found no association between height at age 5 yr and prenatal ETS exposure of nonsmoking mothers (confirmed by serum cotinine levels at 1st prenatal visit) (Eskenazi & Bergmann, 1995). The California expert panel review found inadequate evidence of a causal association between childhood growth in height and prenatal or childhood ETS exposure and noted that this relationship has been much less studied than postnatal growth and prenatal active smoking (California Environmental Protection Agency, 2005).

Summary There is limited epidemiologic evidence that high-level prenatal exposure to PCBs, PCDFs and related toxicants and childhood lead exposure can reduce childhood growth in height.

Adolescent Reproductive Development: Age at Menarche

Lead Childhood exposure, limited evidence: A large cross-sectional study of age 8–16 girls based on NHANES III found associations between delayed onset of menarche and current blood lead among non-Hispanic white girls (likelihood of reaching menarche, blood lead ≥ 3 vs. < 1 μg/dL, OR = 0.74, 95% CI 0.55–1.002) and African-American girls (OR = 0.78, 95% CI 0.63–0.98) but not among Mexican-American girls OR = 0.90, 95% CI 0.73–1.11) (Selevan et al., 2003). These estimates were based on current blood lead levels over the range 0.7–22 μg/dL and were adjusted for age, family size, urban residence, poverty and body mass index. An independent analysis of NHANES III data found an inverse association between likelihood of having attained menarche and current blood lead levels among girls of all ethnicities/races combined (OR = 0.19, 95% CI 0.08–0.43) (Wu et al., 2003).

PCBs Prenatal or lactational exposure, inadequate evidence: The North Carolina birth cohort study reported no association between age at menarche and indices of transplacental or lactational PCB exposure (average age at menarche, highest vs. lowest maternal or cord serum PCB level, 12.6 vs. 12.7, p-trend over 4 exposure categories was 0.46) or cumulative lactational PCB exposure (average age at menarche, highest vs. lowest cumulative lactational PCB dose, 12.8 vs. 12.9, p-trend over 4 cumulated exposure categories was 0.69) (Gladen et al., 2000). The Michigan cohort observed no association between age at menarche and maternal serum PCB levels (change in age at menarche per unit change in maternal serum PCB, $\beta = -0.01 \pm 0.04$ yr, $p = .76$) (Vasiliu et al., 2004).

PBBs Prenatal exposure, inadequate evidence: A Michigan birth cohort study observed an association between maternal serum PBB levels and likelihood of being post-menarche among breast-fed (≥7 vs. ≤1 μg/L, OR = 3.4, 95% CI 1.3–9.0) but not formula-fed daughters (OR = 0.8, 95% CI 0.3–1.8) (Blanck et al., 2000).

Age at Reproductive System Maturation: Pubic Hair (Girls)

Lead Childhood exposure, limited evidence: A large cross-sectional study of age 8–16 girls based on NHANES III found associations between delayed pubic hair development and current blood lead level among African-American girls (likelihood of reaching a successive stage of pubic hair development, blood lead ≥ 3 vs. <1 μg/dL, OR = 0.64, 95% CI 0.41–0.97) and Mexican American girls (OR = 0.76, 95% CI 0.63–0.91) but not among non-Hispanic white girls (OR = 0.82, 95%

CI 0.47–1.42) (Selevan et al., 2003). An independent analysis of NHANES III data found an inverse association between likelihood of having attained at least Tanner stage 2 pubic hair development and current blood lead levels among girls of all ethnicities/races combined (OR = 0.27, 95% CI 0.08–0.93) (Wu et al., 2003).

PCBs Prenatal, lactational or childhood exposure, inadequate evidence: The North Carolina birth cohort study reported that adolescent girls with high lactational PCB exposure had earlier onset of pubic hair of borderline statistical significance (average age at Tanner stage H3, highest vs. lowest lactational PCB exposure [estimated from breast milk PCB levels and breastfeeding duration], 11.7 vs. 12.6, *p*-trend over 4 cumulated exposure categories was 0.08) (Gladen et al., 2000). There was no association with maternal or cord serum PCB (average age at Tanner stage H3, highest vs. lowest maternal or cord serum PCB level, 10.5 vs. 12.0, *p*-trend over 4 exposure categories was 0.31). In a Belgian cross-sectional study of adolescents, delayed pubic hair development was not associated with current serum level of TCDD-like activity (per doubling of serum CALUX assay for TCDD activity, OR = 1.0, p = .97) or with serum PCBs (per doubling of sum of 3 noncoplanar PCB congeners, OR = 1.2, *p* = .59) (Den Hond et al., 2002).

PBBs Prenatal or lactational PBB exposure, inadequate evidence: A Michigan birth cohort study observed an association between maternal serum PBB levels and likelihood of Tanner pubic hair development stage H2 or greater among breast-fed (maternal serum PCB ≥5 vs. ≤1 μg/L, OR = 19.5, 95% CI 2.8–138) but not formula-fed daughters (OR = 0.9, 95% CI 0.2–4.3) (Blanck et al., 2000). The wide confidence intervals of these odds ratio reflect the small numbers of breast-fed or formula-fed subjects in the highest maternal serum PBB category.

Age at Breast Development

Lead Childhood blood lead levels, inadequate evidence: A large cross-sectional study of age 8–16 girls based on NHANES III found associations between delayed breast development and current blood lead level among African-American girls (likelihood of reaching a successive stage of breast development, blood lead ≥ 3 vs. <1 μg/dL, OR = 0.62, 95% CI 0.41–0.96) and Mexican-American girls (OR = 0.70, 95% CI 0.54–0.91) but not among non-Hispanic white girls (OR = 0.75, 95% CI 0.37–1.51) (Selevan et al., 2003). An independent analysis of NHANES III data found no association between likelihood of at least Tanner stage 2 breast development and current blood lead levels among girls of all ethnicities/races combined (OR = 1.20, 95% CI 0.51–2.85) (Wu et al., 2003).

PCBs Prenatal or lactational exposure, inadequate evidence: The North Carolina study found no association between age at breast development and maternal or cord serum PCB level (average age at Tanner stage B3, highest vs. lowest maternal or cord serum PCB level, 10.1 vs. 11.1, *p*-trend over 4 exposure categories was .41) or cumulative lactational PCB exposure (average age at Tanner stage B3, highest vs. lowest cumulative lactational PCB dose, 11.6 vs. 11.9, *p*-trend over 4 cumulated exposure categories was .69) (Gladen et al., 2000). A Belgian cross-sectional study of youth age 15–19 yr observed an association between delayed breast development and serum TCDD activity (per doubling of serum CALUX assay TCDD activity, OR = 2.3, p = .02) but not with serum PCBs (per doubling of sum of 3 noncoplanar PCB congeners, OR = 0.7, p = .49) (Den Hond et al., 2002).

PBBs Prenatal or lactational PBB exposure, inadequate evidence: The Michigan birth cohort study observed no association between maternal serum PBB levels and likelihood of Tanner breast development stage B2 or greater among breast-fed (maternal serum PCB ≥5 vs. ≤1 μg/L, OR = 1.2, 95% CI 0.2–6.4) or formula-fed daughters (OR = 0.5, 95% CI 0.2–1.9) (Blanck et al., 2000).

Phthalates Childhood exposure, inadequate evidence: In a small case-control study of premature breast development among girls age less than 8 in Puerto Rico, affected girls had higher serum levels of dimethyl-, diethyl- and dibutylphthalate, DEHP and mono-(2-ethylhexyl)phthalate (metabolite of DEHP) compared to controls (Colon et al., 2000). The presence of phthalate diesters in serum is suggestive of contamination, as ingested diesters are rapidly metabolized to monoesters in the gastrointestinal tract (McKee, 2004). Combined with the high endemic rate of premature breast development in Puerto Rico, interpretation of these findings is difficult and confirmatory studies have not yet been published.

Age at Reproductive System Maturation: Male External Genitalia

PCBs, TCDD *Age at external genitalia development* Prenatal, lactational or childhood PCB exposure, inadequate evidence: The North Carolina birth cohort study reported slightly earlier attainment of Tanner male genital development stage G3 among breast-fed boys with high lactational PCB exposure (average age at G3, highest vs. lowest cumulative lactational PCB dose, 11.5 vs. 12.4, *p*-trend over 4 PCB dose categories was .07); there was no association with transplacental PCB exposure (average age at G3, highest vs. lowest cord or maternal serum PCB level, 12.4 vs. 13.0, *p*-trend = .78) (Gladen et al., 2000). In a small birth cohort study in the Faroe Islands, external genital development among boys age 14 yr was not associated with cord tissue PCB levels (mean testicular volume by ascending cord tissue PCB tertile, 6.8, 8.9, 7.5 ml, *p*-trend = .30; average Tanner stage of external genital development by ascending cord tissue PCB tertile, 2.1, 2.5, 2.1, *p*-trend = .25) (Mol et al., 2002). A Belgian cross-sectional study of youths age 15–19 yr reported an association between nonattainment of adult-stage male genital development and current serum PCBs (per doubling of sum of 3 noncoplanar congeners, OR = 3.8, $p = .06$) but not serum TCDD activity (OR = 1.3, $p = .46$) (Den Hond et al., 2002).

Age at pubic hair development Prenatal, lactational or childhood PCB exposure, inadequate evidence: The North Carolina birth cohort study reported slightly earlier attainment of Tanner pubic hair development stage H3 among breast-fed boys with high lactational PCB exposure (average age at H3, highest vs. lowest cumulative lactational PCB dose, 12.5 vs. 12.9, *p*-trend = .35); there was no association with transplacental PCB exposure (average age at H3, highest vs. lowest cord or maternal serum PCB level, 13.1 vs. 13.1, *p*-trend = .93) (Gladen et al., 2000). A Belgian cross-sectional study of youths age 15–19 yr reported an association between nonattainment of adult-stage pubic hair development and current serum PCBs (per doubling of sum of 3 noncoplanar congeners, OR = 2.7, p = .06) but not serum TCDD activity (OR = 1.1, $p = .62$) (Den Hond et al., 2002). In a small birth cohort study in the Faroe Islands, Tanner stage of pubic hair and genital development among boys age 14 yr was not associated with cord tissue PCB levels (average Tanner stage by ascending cord tissue PCB tertile, 1.9, 2.4, 1.9, *p*-trend = .63) (Mol et al., 2002).

Phthalates Infant exposure, inadequate evidence: A small birth cohort study (13 males) found normal testicular volume and phallic length among adolescent boys who had been neonatally exposed to DEHP during extracorporeal membrane oxygenation with estimated cumulative doses of 42–140 mg/kg/bw (Rais-Bahrami et al., 2004).

Summary There is limited epidemiologic evidence for an association between childhood lead exposure and delayed menarche. There is inadequate evidence for associations between prenatal or childhood exposures to environmental toxicants and age at breast or pubic hair development in girls and age at genital development in boys.

Sudden Infant Death Syndrome

Tobacco smoke Maternal active smoking, sufficient evidence: The U.S. Surgeon General concluded that there is sufficient evidence of a causal relationship between SIDS and prenatal active smoking (U.S. Department of Health and Human Services, 2004).

Infant exposure, ETS, sufficient evidence: In a meta-analysis of 4 studies that controlled for prenatal smoking, SIDS was associated with postnatal maternal smoking (pooled OR = 1.94, 95% CI 1.55–2.43) (Anderson & Cook, 1997). These reviewers noted that 2 of the 3 available studies involving infants of nonsmoking mothers found associations between SIDS and paternal smoking with odds ratios of 1.63 (95% CI 1.11–2.40) and 3.41 (95% CI 1.98–5.88). A WHO expert group review concluded that prenatal active smoking is a major cause of SIDS and that there is limited evidence that childhood ETS exposure increases the risk of SIDS (World Health Organization, 1999). An expert panel found sufficient evidence of a causal association between SIDS and childhood ETS exposure, independent of prenatal smoking (California Environmental Protection Agency, 2005). The U.S. Surgeon General concluded that there is sufficient evidence of a causal relationship between SIDS and ETS exposure during early infancy (U.S. Department of Health and Human Services, 2006). A large multicentre European case-control study revealed that SIDS was associated with maternal smoking,

especially among mothers who shared their bed with their infant (OR = 17.7, 95% CI 10.3–30.3); SIDS was also associated with the number of cigarettes smoked daily in the home (≥30 vs. 0 cigarettes/d, OR = 3.31, 95% CI 1.84–5.96) (Carpenter et al., 2004).

Outdoor air pollution Infant exposure, limited evidence: Among studies published up to 2003, reviewers found limited evidence, mainly from ecologic studies, for an association between SIDS and ambient air pollution (Glinianaia et al., 2004b; Tong & Colditz, 2004). One review noted little consistency in study design and pollutant measurement and the potential for prenatal smoking to be a confounder (Tong & Colditz, 2004). Based on air quality data and a relative risk estimate from a large cohort study, the estimated proportion of SIDS deaths in 23 U.S. metropolitan areas attributable to PM_{10} levels exceeding 12 μg/m^3 was 16% (95% CI 9–23) (Kaiser et al., 2004). In a large California retrospective cohort study, SIDS was not associated with average $PM_{2.5}$ levels within 8 km of the maternal residence (per 10 μg/m^3 increment, OR = 0.82, 95% CI 0.55–1.23) (Woodruff et al., 2006).

Summary There is sufficient epidemiologic evidence that prenatal active smoking and ETS exposure during infancy can cause SIDS; limited evidence supports an association between SIDS and outdoor air pollution levels near the maternal/infant residence.

Allergies

PCBs Maternal exposure, inadequate evidence: A small Dutch nested case-control study observed no association between prenatal plasma levels of 4 dioxin-like PCB congeners (118, 138, 153, 180) and the prevalence at age 42 mo of parent-reported eczema (OR = 1.18, 95% CI 0.82–1.71) or allergic reactions to food, pollen, dust, or household pets (OR = 0.62, 95% CI 0.29–1.32) (Weisglas-Kuperus et al., 2000). In a follow-up study at age 7 yr, there was no association between prenatal plasma PCB levels and a history of allergic reactions (OR = 0.95, 95% CI 0.59–1.52) (Weisglas-Kuperus et al., 2004).

Childhood exposure, inadequate evidence: The Dutch case-control study reported that children's current plasma levels of four PCB congeners were not related to a history of eczema (OR = 0.92, 95% CI 0.41–2.08) but were inversely associated with a history of allergic reactions (OR = 0.01, 95% CI 0.01–0.37) (Weisglas-Kuperus et al., 2000). Follow-up at age 7 yr revealed no relationship between lactational PCB exposure (estimated from breast milk PCB levels and duration of breastfeeding) and a history of allergic reactions (OR = 1.09, 95% CI 0.97–1.22) (Weisglas-Kuperus et al., 2004).

Pesticides Prenatal exposure, unspecified pesticides, inadequate evidence: The Ontario farm family study found several associations between childhood hay fever or other allergic conditions and prenatal farm pesticide use (any pesticide, OR = 1.58, 95% CI 1.19–2.08; herbicides, OR = 1.56, 95% CI 1.15–2.11; insecticides, OR = 1.48, 95% CI 1.07–2.03; fungicides, OR = 1.69, 95% CI 1.15–2.47; 2,4-D, OR = 1.66, 95% CI 1.11–2.49; and organophosphate insecticides, OR = 1.55, 95% CI 1.02–2.36) (Weselak et al., 2007). When analyzed by gender, the associations among males were stronger and those for females were not statistically significant. ORs also tended to higher for children who were 12 yr of age or greater at the time of the survey. Potential limitations associated with this study include the retrospective data collection, no information on age of diagnosis or the type and quantity of pesticides used, and multiple comparisons. In addition, no information on potential postnatal confounders was collected.

Paternal exposure, unspecified herbicides, inadequate evidence Vietnam veterans reported more often that their children had a history of allergies (crude OR = 1.6, 95% CI 1.2–2.1) but not allergic rhinitis (crude OR = 1.3, 95% CI 0.9–1.9) compared to non-Vietnam veterans (Centers for Disease Control. 1989).

Summary There is inadequate epidemiologic evidence for associations between allergic conditions and prenatal or childhood exposure to environmental chemical contaminants.

Dental Caries

Lead Childhood exposure, limited evidence: A large cross-sectional study based on NHANES III found a dose-response relationship between dental caries of primary or permanent teeth and current relatively low blood lead levels, independent of potential confounders (>4.1 vs. ≤2.3 μg/dl,

OR = 1.66, 95% CI 1.12–2.48) (Moss et al., 1999). A small cohort study and an intervention study found associations between current blood lead levels and deciduous but not permanent tooth dental caries (Campbell et al., 2000; Gemmel et al., 2002).

Summary There is limited evidence for an association between childhood dental caries and childhood lead exposure.

Chloracne

PCBs High-level childhood exposure, sufficient evidence: Chloracne occurred among children exposed to high levels of PCBs, PCDFs and related toxicants during the Yucheng incident (prevalence of acne or acne scars at age 1 mo to 8 yr, exposed vs. unexposed children, 20/117 vs. 10/106, $p = .05$) (Rogan et al., 1988). When followed to age 12–14 yr, the prevalence of chloracne scars and comedones among Yucheng children was similar to that of an unexposed comparison group (exposed vs. unexposed, prevalence 10.0 vs. 8.1%, $p > .05$) (Hsu et al., 1995).

TCDD High-level childhood exposure, sufficient evidence: After the massive release of relatively pure TCDD into air at Seveso, 88% of the 187 cases detected through screening were children age less than 15 (Del Corno et al., 1985). A review of the Seveso incident concluded that TCDD caused chloracne at doses that cause no other obvious health effects (Sweeney & Mocarelli, 2000). A retrospective cohort study revealed that, compared to unexposed persons, postnatally exposed persons had greatly increased risks of physician-diagnosed chloracne (men, OR = 13.8, 95% CI 5.6–46.0; women, OR = 17.8, 95% CI 7.9–51.0) (Guo et al., 1999).

Summary There is sufficient epidemiologic evidence that high-level childhood exposure to TCDD can cause chloracne and limited evidence that prenatal exposure to high-level PCB/PCDF can cause chloracne.

Renal Tubular Damage This section discusses associations between increased urinary protein excretion, a sign of renal tubular damage and environmental exposures (see also Table 9).

Lead Childhood exposure, sufficient evidence: Reviewers concluded that lead impairs renal tubular resorptive function, causing aminoaciduria, glucosuria and hyperphosphaturia at blood lead levels as low as 10 μg/dl (Goyer, 1990; Loghman-Adham, 1997). Four cross-sectional studies (Bernard et al., 1995; Fels et al., 1998; Staessen et al., 2001; Verberk et al., 1996) and a birth cohort study (Factor-Litvak et al., 1999) reported dose-response relationships between childhood urinary protein markers of renal tubular damage and blood lead levels. These findings occurred at low to moderate blood lead levels and were independent of potential confounders. A large cross-sectional study in three European countries observed inverse dose-response relationships between blood lead and serum cystatin C and β2-microglobulin levels (de Burbure et al., 2006). This study also reported dose-response relationships between urinary proteins and an interaction term based on the product of blood lead and urinary cadmium levels.

Mercury Childhood exposure, organic mercury, limited evidence: A cross-sectional study of infants exposed to diapers treated with a phenyl mercuric fungicide in Argentina reported an association between urinary γ-glutamyl transpeptidase and urinary mercury excretion rates with an apparent threshold of about 6 μg/kg body wt/day (Gotelli et al., 1985).

Childhood exposure, elemental mercury, inadequate evidence: Two cross-sectional studies found no association between urinary protein levels among children or youth and number of amalgam tooth surfaces or urinary mercury levels (de Burbure et al., 2003; Herrstrom et al., 1995).

Cadmium Childhood exposure, inadequate evidence: Three cross-sectional studies found no association between childhood urinary protein levels and blood cadmium (Bernard et al., 1995; Staessen et al., 2001) or urinary cadmium levels (Noonan et al., 2002). A cross-sectional study of children living near nonferrous smelters in France found a correlation between urinary *N*-acetyl-beta-D-glucosaminidase (NAG) and log blood cadmium (partial $r = .25$, $p = .0002$) (de Burbure et al., 2003).

Summary Epidemiologic evidence for the role of environmental toxicants in childhood renal tubular damage (causing proteinuria) includes: (a) sufficient evidence—childhood lead exposure; (b) limited evidence—childhood organic mercury exposure (phenylmercuric mercury used in diaper rinses).

Chromosomal Abnormalities The level of epidemiologic evidence for associations between chromosomal abnormalities is summarized in Table 9.

Arsenic Maternal exposure, inadequate evidence: In a Swedish retrospective cohort study, there was an elevated risk of chromosomal abnormalities (OR = 2.58, 95% CI 0.90–6.70) among infants of women living in parishes near a copper smelter known to emit arsenic, lead, mercury, and cadmium (Wulff et al., 1996).

Childhood exposure, limited evidence: In a small cross-sectional study of Argentinean children, the frequency of micronuclei per 1,000 lymphocytes was substantially higher among children living in regions with drinking water arsenic levels averaging about 200 μg/L (high vs. low drinking water arsenic regions, 35 ± 4.6 vs. 5.6 ± 1.6, $p < 0.05$) (Dulout et al., 1996). In a Swedish retrospective cohort study, infants of women living near a copper smelter had an increased risk of chromosomal abnormalities (RR = 2.58, 95% CI 0.90–6.70) (Wulff et al., 1996). A cross-sectional study of young children in a Mexican mining town with high soil arsenic and lead concentrations found associations between Comet tail length and moment and urinary arsenic levels (note—Comet tail length and moment reflect DNA single- and double-stranded breaks) (Yanez et al., 2003). Reviewers concluded that there is limited evidence that inorganic arsenic causes chromosomal abnormalities in humans (Agency for Toxic Substances and Disease Registry, 2000a).

Environmental tobacco smoke Maternal or childhood exposure, inadequate evidence: A meta-analysis of studies published during 1980–2004 concluded that children exposed to ETS and neonates prenatally exposed to maternal smoking, respectively, had hemoglobin adduct concentrations 1.4 and 6.7 times those of unexposed subjects but sister chromatid exchange frequency was not associated with either exposure (Neri et al., 2006).

Outdoor air pollution Maternal exposure, inadequate evidence: A retrospective cohort study in France observed no association between chromosomal abnormalities and traffic density near the prenatal residence (>50,000 vs. <10,000 vehicles/d, OR = 0.90, 95% CI 0.60–1.37) (Cordier et al., 2004).

Drinking-water disinfection by-products Maternal exposure, inadequate evidence: A retrospective cohort study in Sweden found no association between chromosome abnormalities at birth and prenatal residence in communities using hypochlorite (compared to unchlorinated water, OR = 0.8, 95% CI 0.5–1.3) or chlorine dioxide-treated drinking water (OR = 0.7, 95% CI 0.4–1.2) (Kallen and Robert 2000). A similar study in Canada found a nonmonotonic dose-response relationship between chromosomal abnormalities at birth and periconceptual community drinking water chloroform levels (50–74 vs. <50 μg/L, OR = 1.3, 95% CI 0.8–2.2; 75–99 μg/L, OR = 1.9, 95% CI 1.1–3.3; ≥100 μg/L, OR = 1.4, 95% CI 0.8–2.8); chromosome abnormalities were not associated with BDCM levels (Dodds & King, 2001).

Hazardous waste disposal Maternal exposure, inadequate evidence: In a population-based case-control study, chromosome abnormalities were weakly associated with prenatal residential proximity to hazardous waste disposal sites (<1.6 vs. ≥1.6 km, OR = 1.18, 95% CI 0.90–1.55); the association was stronger for the subgroup of sites containing plastics (OR = 1.46, 95% CI 1.01–2.11) (Geschwind et al., 1992). A European study case-control study revealed an association between chromosomal abnormalities and prenatal residential proximity to any of 23 hazardous waste disposal sites (≤3 vs. 3–7 km, OR = 1.49, 95% CI 1.03–2.17) (Vrijheid et al., 2002a). However, there was a nonmonotonic dose-response relationship between hazard categories based on expert-rated potential for toxicant exposure via air or water and structural chromosome abnormalities (high vs. low hazard, OR = 1.65, 95% CI 0.83–3.29, p-trend = 0.31) (Vrijheid et al., 2002b).

Incinerators Maternal exposure, inadequate evidence: In a French retrospective cohort study, chromosome abnormalities were not associated with prenatal residence in communities with solid waste incinerators (OR = 1.01, 95% CI 0.86–1.20) (Cordier et al., 2004).

Solvents Maternal exposure, unspecified solvents, inadequate evidence: A hospital-based case-control study in France reported no association between chromosomal abnormalities and prenatal occupational solvent exposure (OR = 0.7, 90% CI 0.2–1.7) (Cordier et al., 1992).

Paternal occupational exposure, inadequate evidence: A Norwegian cohort study of offspring of male printers revealed no increased risk of Down syndrome (compared to other occupations, SIR = 1.4, 95% CI 0.65–2.5) (Kristensen et al., 1993).

Summary Limited epidemiologic evidence supports an association between childhood chromosomal abnormalities and childhood exposure to high drinking water arsenic levels.

CONCLUSION

This review identifies known and suspected relationships between environmental chemical contaminants and adverse pregnancy and child health outcomes as well as many supported by inadequate epidemiologic evidence. Known causes of adverse pregnancy and childhood health outcomes include:

Maternal exposures:

- methylmercury
- high-level exposure (delayed developmental milestones and cognitive, motor, auditory and visual deficits)
- PCBs, PCDFs, and related toxicants
- high-level exposure (neonatal tooth abnormalities, cognitive and motor deficits)
- residential environment
- active smoking (delayed conception, preterm birth, FGD, SIDS)
- ETS (preterm birth)

Childhood exposures:

- lead
- low-level exposure (cognitive deficits and renal tubular damage)
- methylmercury
- high-level exposure (visual deficits)
- TCDD
- high-level exposure (chloracne)
- indoor air contaminants
- ETS (SIDS, new-onset asthma, increased asthma severity, lung infections, middle ear infections, adult lung and breast cancers)
- biomass smoke (lung infections)
- outdoor air pollutants (increased asthma severity)

Among proven environmental hazards, several are supported by epidemiologic studies of highly exposed populations (e.g., MeHg, PCBs/PCDFs). Lead and ETS, however, produce adverse effects after relatively low level prenatal or childhood exposure. For instance, there are dose-response relationships between full-scale IQ deficits and blood lead levels below 10 μg/dl, the current U.S. Centers for Disease Control and Prevention (CDC) action level. The CDC stated these reasons for not reducing the current lead action level : (1) No effective clinical interventions are known to lower the blood lead levels for children with levels less than 10 μg/dl or to reduce the risk for adverse developmental effects, (2) children cannot be accurately classified as having blood lead levels above or below a value less than 10 μg/dl because of the inaccuracy inherent in laboratory testing, and (3) no evidence exists of a threshold below which adverse effects are not experienced; thus, any decision to establish a new level of concern would be arbitrary and provide uncertain benefits (Centers for Disease Control and Prevention, 2006). There appears to be no lead exposure threshold for neurotoxicity in children, suggesting a need for public health policies aimed at virtual elimination of lead exposure related to housing (paint, plumbing), ambient air, consumer products and drinking water.

Many relationships between relatively low-level environmental exposures and adverse pregnancy or child health outcomes were supported by limited epidemiologic evidence (see Tables 1–9).

For many of the relationships supported by limited or inadequate epidemiologic evidence, there is a scarcity of published studies, as opposed to inconsistencies among several large, high-quality studies. For instance, several environmental exposures are known to exacerbate existing asthma but there has been less research on the role of environmental factors in asthma onset. About 20 epidemiologic studies have linked childhood leukemia to pesticide exposure (Bérubé, 2006), but most have lacked the statistical power and exposure quantification and specificity needed to produce strong evidence for or against causal relationships.

The burden of adult disease attributable to preconceptual, prenatal, or childhood environmental exposures is largely nonquantifiable at present. Known links include chronic disability from environment-related childhood diseases (birth defects, asthma, cancer). There is limited evidence for associations between childhood exposure to ETS and breast cancer.

The dose and timing of exposure to toxicants are important determinants of adverse effects on developing tissues (Faustman et al., 2000). For instance, prenatal or early childhood exposures to lead, MeHg and PCBs produce more severe neurotoxicity compared to similar exposures of adults. However, there are many knowledge gaps concerning the role of early-life low-level exposure to environmental toxicants in child health and development. Major challenges include the need to identify the potential health effects of both specific exposures (e.g., a specific type of pesticide) and multiple exposures. To date, relatively few epidemiologic studies of child health and development have assessed potential interactions between two or more toxicants.

A child-centered agenda for research and risk assessment should include (Landrigan, 1999): (1) exploration and quantification of unique exposure patterns among children, (2) adoption of more sensitive methods to test chemicals for developmental toxicity, (3) clinical and epidemiologic studies to identify child health outcomes of environmental toxicants, and (4) cellular and molecular research on the pathogenesis of pediatric environmental illness. Although the U.S. federal government has moved in the direction recommended by Landrigan, Canada and most other countries have not. A reviewer recently recommended that Canada conduct an analysis of the economic and social costs of adverse child health outcomes related to environmental hazards to support investments in research in this field (Bérubé, 2006). This review proposed that Canada invest initially in biomonitoring of children's and pregnant women's environmental exposures and initiate a longitudinal cohort study of environmental influences on child health and development. Developed countries in particular should show leadership and strengthen national and international population and laboratory research on the role of environmental contaminants in fetal, child and adult health and development. One of the most pressing needs is large-scale, dedicated funding of new research infrastructure (scientists, laboratories, childhood disease registries) and large-scale epidemiologic research programs and projects. Only adequate funding will permit the conduct of high quality epidemiologic studies that incorporate strong statistical power, robust exposure assessment and sufficient size to explore dose-response relationships, biomarkers of exposure and susceptibility, and the potential roles of confounding variables.

Longitudinal studies of relatively large populations (e.g., Framingham Heart Study, U.S. Nurses Health Study) have provided a wealth of knowledge about risk factors for heart disease, cancer and other adult health conditions. The equivalent investigations of child health and the environment would be large longitudinal studies with intensive environmental exposure assessments beginning before conception or during early pregnancy and prolonged follow-up to identify health outcomes during pregnancy, infancy, childhood, adolescence and adulthood. Such studies, initiated in Europe and at the planning stage in the United States, are extremely valuable and will provide a wealth of information on a wide variety of potential health outcome and environmental exposure relationships (Golding et al., 2001; National Institute of Child Health and Human Development 2002). Given the unique prenatal and childhood environments in diverse geographic regions, other national and international bodies with mandates for environmental health should fund similar longitudinal studies. With advances in understanding of the human genome and molecular markers of environmental contaminant exposure and improved epidemiologic study design, it seems likely that

future studies will be able to better define the range and risks of environmental health outcomes in children.

National and smaller scale biomonitoring systems have documented successes and emerging issues, including:

- Declining levels of blood lead (Annest JL et al., 1983), serum or urinary cotinine (indicators of ETS exposure) (Pirkle et al., 2006) and breast milk *p,p'*-DDT/*p,p'*-DDE (the latter is the major metabolite of DDT) (Atuma et al., 1998).
- Increasing levels of PBDEs (flame retardants) in breast milk (Meironyte et al., 1999).
- Unexpectedly high urinary levels among children and adults of metabolites of several phthalates used in many consumer products including cosmetics, pharmaceutical coatings, food containers/packaging and toys (Centers for Disease Control and Prevention, 2005b).
- Low levels of TCDD: This potent toxicant was detectable in only 0.7% of U.S. serum samples from persons age 6 yr or older, and observed levels were far below those associated with health effects in occupationally or accidentally exposed persons (Centers for Disease Control and Prevention, 2005b).
- Widespread maternal and fetal plasma bisphenol A concentrations in the range showing reproductive toxicity in experimental animal offspring (Calafat et al., 2005; Schonfelder et al., 2002).
- Among women undergoing routine 2nd trimester amniocentesis, about a third of amniotic fluid samples contained detectable levels of hormonally active environmental contaminants including α-HCH, ρ,ρ?-DDE and specific PCB congeners (Foster et al., 2000). Although contaminant concentrations were quite low, these findings show that the fetus is directly exposed to potentially harmful hormonally active toxicants.

Only the United States and Germany have implemented national population biomonitoring to measure and track exposures to environmental contaminant levels in human blood, urine, hair, breast milk and other samples. The Commission for Environmental Cooperation, under the North American Regional Action Plan on Environmental Monitoring and Assessment, plans to implement biomonitoring of persistent toxicants in neonates and infants in Canada, the United States, and Mexico (Commission for Environmental Cooperation, 2002).

For the environmental contaminant and adverse health outcome relationships supported by limited epidemiologic evidence, there are several major health policy and program needs: (1) In the case of proven causal relationships, ongoing interventions are essential to minimize exposure levels in the general population and in high-risk subgroups. (2) For relationships supported by limited evidence, precautionary interventions are warranted to minimize population exposures. (3) Biomonitoring of toxicant exposure is essential to demonstrate the effectiveness of existing interventions and to identify subgroups with exposures exceeding risk-based standards or guidelines. (4) For the many knowledge gaps, strengthened epidemiologic research is needed to build the evidence base.

Many examples of knowledge gaps are documented in this review for relationships supported by limited or inadequate evidence. Moreover, we have adequate toxicologic assessments for only a fraction of the thousands of chemical toxicants in the environment and something approaching adequate epidemiologic evidence for very few of them. The potential anthropogenic sources of environmental chemicals include fossil fuel combustion, manufacturing processes, various uses of commercial products (pesticides, building materials, solvents), human activities (e.g., smoking indoors), waste disposal (hazardous waste disposal sites, incineration), and accidents. One of the major drivers is the vast and rapidly growing number of commercial chemicals—over 70,000 commercial chemicals are registered for use in the United States, and the U,.S. EPA annually receives about 1500 petitions to approve new chemicals or new uses of existing chemicals (U.S. Environmental Protection Agency, 2001). Intervention and tracking programs should target not only the general population but also subgroups, especially those at high risk (e.g., because of poverty, occupation, geographic region or other factors). Considerable time and effort are generally needed to develop sufficient evidence of causal relationships in observational human research studies. Protection of public health requires

precautionary interventions when faced with limited scientific evidence and related uncertainties. Failure to take precautionary measures can have disastrous consequences, e.g., the introduction of tetraethyl lead as a fuel additive during the early 20th century over the objections of public health authorities (Needleman, 1997).

Although this review does not address specific intervention needs, others have identified a broad range of needs, including: (1) explicit recognition of children's vulnerability in environmental legislation; (2) improved developmental and reproductive toxicity testing of commercial chemicals; (3) coordination of chemical toxicity testing; (4) creation of publically accessible databases on toxicity of commercial chemicals; (5) increased capacity for epidemiologic and toxicologic research and biomonitoring of environmental contaminants in children—including infrastructure (personnel, equipment) and major research program funding; (6) increased operational capacity through establishment of a national comprehensive Children's Environmental Health Program to oversee resource allocation, research and biomonitoring initiatives and to ensure that new policies and regulations for hazards address children's health; (7) increased legislative capacity to address children's environmental health through amendments to the Canadian Environmental Protection Act (CEPA), reviews of other relevant federal legislation to identify where an additional margin of safety is needed to protect child health, examination of legislation across government jurisdictions to assess the net impact on total environmental exposures of children and reproductive-age adults (e.g., legislation relating to toxicants in foods, drinking water, air, commercial products) and development of mechanisms to ensure that new research findings are incorporated in a timely fashion into future risk assessments and risk management decisions; (8) strengthened communication and education strategies to assure that clear and effective public health messages reach critical target groups; and (9) assured accountability through annual reports to Parliament including measures taken to protect and improve children's environmental health (Krewski et al., 2007; Tyshenko et al., 2006). Increased investment in environmental interventions promises to be offset not only be reduced health care costs, but also by improved health status and productivity of tomorrow's labor force (Landrigan et al., 2002).

REFERENCES

Abadi-Korek, I., Stark, B., Zaizov, R., and Shaham, J. 2006. Parental occupational exposure and the risk of acute lymphoblastic leukemia in offspring in Israel. *J. Occup. Environ. Med.* 48:165–174 .

Abell, A., Juul, S., and Bonde, J. P. 2000. Time to pregnancy among female greenhouse workers. *Scand. J. Work Environ Health* 26:131–136.

Agency for Toxic Substances and Disease Registry. 1999a. Toxicological profile for cadmium. Located at: http://www.atsdr.cdc.gov/toxprofiles/tp5.html.

Agency for Toxic Substances and Disease Registry. 1999b. Toxicological profile for lead. Located at: http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf.

Agency for Toxic Substances and Disease Registry. 2000a. Toxicological profile for arsenic. Located at: http://www.atsdr.cdc.gov/toxprofiles/tp2.html.

Agency for Toxic Substances and Disease Registry. 2000b. Toxicological profile for manganese. Located at: http://www.atsdr.cdc.gov/toxprofiles/tp151.html.

Agnesi, R., Valentini, F., and Mastrangelo, G. 1997. Risk of spontaneous abortion and maternal exposure to organic solvents in the shoe industry. *Int. Arch. Occup. Environ. Health* 69:311–316.

Ahlborg, G., Jr., Axelsson, G., and Bodin, L. 1996. Shift work, nitrous oxide exposure and subfertility among Swedish midwives. *Int. J. Epidemiol.* 25:783–790.

Ahlborg, G., Jr., and Bodin, L. 1991. Tobacco smoke exposure and pregnancy outcome among working women. A prospective study at prenatal care centers in Orebro County, Sweden. *Am. J. Epidemiol.* 133:338–347.

Ahmad, S. A., Sayed, M. H., Barua, S., Khan, M. H., Faruquee, M. H., Jalil, A., Hadi, S. A., and Talukder, H. K. 2001. Arsenic in drinking water and pregnancy outcomes. *Environ. Health Perspect.* 109:629–631.

Alaluusua, S., Calderara, P., Gerthoux, P. M., Lukinmaa, P. L., Kovero, O., Needham, L., Patterson, D. G. Jr, Tuomisto, J., and Mocarelli, P. 2004. Developmental dental aberrations after the dioxin accident in S.eveso. *Environ. Health Perspect.* 112:1313–1318.

Alaluusua, S., Kiviranta, H., Leppaniemi, A., Holtta, P., Lukinmaa, P. L., Lope, L., Jarvenpaa, A. L., Renlund, M., Toppari, J., Virtanen, H., Kaleva, M., and Vartiainen, T. 2002. Natal and neonatal teeth in relation to environmental toxicants. *Pediatr. Res.* 52:652–655.

Alaluusua, S., Lukinmaa, P. L., Torppa, J., Tuomisto, J., and Vartiainen, T. 1999. Developing teeth as biomarker of dioxin exposure. *Lancet* 353:206.

Alderton, L. E., Spector, L. G., Blair, C. K., Roesler, M., Olshan, A. F., Robison, L. L., and Ross, J. A. 2006. Child and maternal household chemical exposure and the risk of acute leukemia in children with Down's syndrome: A report from the Children's Oncology Group. *Am. J. Epidemiol.* 164:212–221.

Alexander, B. H., Checkoway, H., Van Netten, C., Kaufman, J. D., Vaughan, T. L., Mueller, B. A., and Faustman, E. M. 1996. Paternal occupational lead exposure and pregnancy outcome. *Int. J. Occup. Environ. Health* 2:280–285.

Alexander, F. E., Patheal, S. L., Biondi, A., Brandalise, S., Cabrera, M. E., Chan, L. C., Chen, Z., Cimino, G., Cordoba, J. C., Gu, L. J., Hussein, H., Ishii, E., Kamel, A. M., Labra, S., Magalhaes, I. Q., Mizutani, S., Petridou, E., de Oliveira, M. P., Yuen, P., Wiemels, J. L., and Greaves, M. F. 2001. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res.* 61:2542–2546.

Almqvist, C., Pershagen, G., and Wickman, M. 2005. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. *Clin. Exp. Allergy* 35:612–618.

Altmann, L., Sveinsson, K., Kramer, U., Weishoff-Houben, M., Turfeld, M., Winneke, G., and Wiegand, H. 1998. Visual functions in 6-year-old children in relation to lead and mercury levels. *Neurotoxicol. Teratol.* 20:9–17.

American Academy of Pediatrics Committee on Environmental Health. 2003. *Pediatric environmental health*. Elk Grove Village, IL: American Academy of Pediatrics.

American Cancer Society. 2006. Cancer Facts & Figures 2006. Located at: http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. 1974a. Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 54:587–595.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. R. 1974b. Studies of infants postnatally exposed to methylmercury. *J. Pediatr.* 85:81–84.

Amin-Zaki, L., Majeed, M. A., Clarkson, T. W., and Greenwood, M. R. 1978. Methylmercury poisoning in Iraqi children: Clinical observations over two years. *Br. Med. J.* 1:613–616.

Amin-Zaki, L., Majeed, M. A., Elhassani, S. B., Clarkson, T. W., Greenwood, M. R., and Doherty, R. A. 1979. Prenatal methylmercury poisoning. Clinical observations over five years. *Am. J. Dis. Child.* 133:172–177.

Amin-Zaki, L., Majeed, M. A., Greenwood, M. R., Elhassani, S. B., Clarkson, T. W., and Doherty, R. A. 1981. Methylmercury poisoning in the Iraqi suckling infant: A longitudinal study over five years. *J. Appl. Toxicol.* 1:210–214.

Anderson, H. R., and Cook, D. G. 1997. Passive smoking and sudden infant death syndrome: Review of the epidemiological evidence. *Thorax* 52:1003–1009.

Andrews, K. W., Savitz, D. A., and Hertz-Picciotto, I. 1994. Prenatal lead exposure in relation to gestational age and birth weight: A review of epidemiologic studies. *Am. J. Ind. Med.* 26:13–32.

Annest JL, Pirkle JL, Makuc D, Neese JW, Bayse DD, and Kovar MG. 1983. Chronological trend in blood lead levels between 1976 and 1980. N Engl J Med 308:1373–1377.

Anttila, A., and Sallmen, M. 1995. Effects of parental occupational exposure to lead and other metals on spontaneous abortion. *J. Occup. Environ. Med.* 37:915–921.

Arbuckle, T. E., Lin, Z., and Mery, L. S. 2001. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ. Health Perspect.* 109:851–857.

Arbuckle, T. E., Savitz, D. A., Mery, L. S., and Curtis, K. M. 1999. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology* 10:752–760.

Arbuckle, T. E., and Sever, L. E. 1998. Pesticide exposures and fetal death: A review of the epidemiologic literature. *Crit. Rev. Toxicol.* 28:229–270.

Arbuckle, T. E., Sherman, G. J., Corey, P. N., Walters, D., and Lo, B. 1988. Water nitrates and CNS birth defects: A population-based case-control study. *Arch. Environ. Health* 43:162–167.

Arias, E., and Smith, B. L. 2003. Deaths: Preliminary data for 2001. *Natl. Vital Stat. Rep.* 51:1–45.

Aschengrau, A., Zierler, S., and Cohen, A. 1989. Quality of community drinking water and the occurrence of spontaneous abortion. *Arch. Environ. Health* 44:283–290.

Aschengrau, A., Zierler, S., and Cohen, A. 1993. Quality of community drinking water and the occurrence of late adverse pregnancy outcomes. *Arch. Environ. Health* 48:105–113.

Atuma, S. S., Hansson, L., Johnsson, H., Slorach, S., de Wit, C. A., and Lindstrom, G. 1998. Organochlorine pesticides, polychlorinated biphenyls and dioxins in human milk from Swedish mothers. *Food Addit. Contam.* 15:142–150.

Axmon, A., Rylander, L., Stromberg, U., and Hagmar, L. 2000. Miscarriages and stillbirths in women with a high intake of fish contaminated with persistent organochlorine compounds. *Int. Arch. Occup. Environ. Health* 73:204–208.

Axmon, A., Rylander, L., Stromberg, U., Jonsson, B., Nilsson-Ehle, P., and Hagmar, L. 2004. Polychlorinated biphenyls in serum and time to pregnancy. *Environ. Res.* 96:186–195.

Axtell, C. D., Cox, C., Myers, G. J., Davidson, P. W., Choi, A. L., Cernichiari, E., Sloane-Reeves, J., Shamlaye, C. F., and Clarkson, T. W. 2000. Association between methylmercury exposure from fish consumption and child development at five and a half years of age in the Seychelles Child Development Study: An evaluation of nonlinear relationships. *Environ. Res.* 84:71–80.

Axtell, C. D., Myers, G. J., Davidson, P. W., Choi, A. L., Cernichiari, E., Sloane-Reeves, J., Cox, C., Shamlaye, C., and Clarkson, T. W. 1998. Semiparametric modeling of age at achieving developmental milestones after prenatal exposure to methylmercury in the Seychelles child development study. *Environ. Health Perspect.* 106:559–563.

Baghurst, P. A., McMichael, A. J., Wigg, N. R., Vimpani, G. V., Robertson, E. F., Roberts, R. J., and Tong, S. L. 1992. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. *N. Engl. J. Med.* 327:1279–1284.

Baghurst, P. A., Robertson, E. F., Oldfield, R. K., King, B. M., McMichael, A. J., Vimpani, G. V., and Wigg, N. R. 1991. Lead in the placenta, membranes, and umbilical cord in relation to pregnancy outcome in a lead-smelter community. *Environ. Health Perspect.* 90:315–320.

Baibergenova, A., Kudyakov, R., Zdeb, M., and Carpenter, D. O. 2003. Low birth weight and residential proximity to PCB-contaminated waste sites. *Environ. Health Perspect.* 111:1352–1357.

Baird, D. D., Wilcox, A. J., and Weinberg, C. R. 1986. Use of time to pregnancy to study environmental exposures. *Am. J. Epidemiol.* 124:470–480.

Ballew, C., Khan, L. K., Kaufmann, R., Mokdad, A., Miller, D. T., and Gunter, E. W. 1999. Blood lead concentration and children's anthropometric dimensions in the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. *J. Pediatr.* 134:623–630.

Banks, E. C., Ferretti, L. E., and Shucard, D. W. 1997. Effects of low level lead exposure on cognitive function in children: A review of behavioral, neuropsychological and biological evidence. *Neurotoxicology* 18:237–281.

Bell, E. M., Hertz-Picciotto, I., and Beaumont, J. J. 2001a. A case-control study of pesticides and fetal death due to congenital anomalies. *Epidemiology* 12:148–156.

Bell, E. M., Hertz-Picciotto, I., and Beaumont, J. J. 2001b. Pesticides and fetal death due to congenital anomalies: Implications of an erratum. *Epidemiology* 12:595–596.

Bell, E. M., Hertz-Picciotto, I., and Beaumont, J. J. 2001c. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am. J. Epidemiol.* 154:702–710.

Bellinger, D., Leviton, A., Allred, E., and Rabinowitz, M. 1994. Pre- and postnatal lead exposure and behavior problems in school-aged children. *Environ. Res.* 66:12–30.

Bellinger, D., Leviton, A., Rabinowitz, M., Allred, E., Needleman, H., and Schoenbaum, S. 1991. Weight gain and maturity in fetuses exposed to low levels of lead. *Environ. Res.* 54:151–158.

Bellinger, D., Leviton, A., Waternaux, C., Needleman, H., and Rabinowitz, M. 1988. Low-level lead exposure, social class, and infant development. *Neurotoxicol. Teratol.* 10:497–503.

Bellinger, D., Sloman, J., Leviton, A., Rabinowitz, M., Needleman, H. L., and Waternaux, C. 1991. Low-level lead exposure and children's cognitive function in the preschool years. *Pediatrics* 87:219–227.

Bellinger, D. C. 2004. Lead. *Pediatrics* 113:1016–1022.

Bellinger, D. C. 2005. Teratogen update: Lead and pregnancy. *Birth Defects Res. A Clin. Mol. Teratol.* 73:409–420.

Bellinger, D. C., and Needleman, H. L. 2003. Intellectual impairment and blood lead levels. *N. Engl. J. Med.* 349:500–502.

Bellinger, D. C., Needleman, H. L., Leviton, A., Waternaux, C., Rabinowitz, M. B., and Nichols, M. L. 1984. Early sensory-motor development and prenatal exposure to lead. *Neurobehav. Toxicol. Teratol.* 6:387–402.

Bellinger, D. C., Stiles, K. M., and Needleman, H. L. 1992. Low-level lead exposure, intelligence and academic achievement: A long-term follow-up study. *Pediatrics* 90:855–861.

Berkowitz, G. S., Wetmur, J. G., Birman-Deych, E., Obel, J., Lapinski, R. H., Godbold, J. H., Holzman, I. R., and Wolff, M. S. 2004. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ. Health Perspect.* 112:388–391.

Berkowitz, Z., Price-Green, P., Bove, F. J., and Kaye, W. E. 2006. Lead exposure and birth outcomes in five communities in Shoshone County, Idaho. *Int. J. Hyg. Environ. Health* 209:123–132.

Berlin, C. M., Jr., Kacew, S., Lawrence, R., LaKind, J. S., and Campbell, R. 2002. Criteria for chemical selection for programs on human milk surveillance and research for environmental chemicals. *J. Toxicol. Environ. Health A* 65:1839–1851.

Bernard, A., Carbonnelle, S., de Burbure, C., Michel, O., and Nickmilder, M. 2006. Chlorinated pool attendance, atopy, and the risk of asthma during childhood. *Environ. Health Perspect.* 114:1567–1573.

Bernard, A., Carbonnelle, S., Michel, O., Higuet, S., De Burbure, C., Buchet, J. P., Hermans, C., Dumont, X., and Doyle, I. 2003. Lung hyperpermeability and asthma prevalence in schoolchildren: Unexpected associations with the attendance at indoor chlorinated swimming pools. *Occup. Environ. Med.* 60:385–394.

Bernard, A. M., Vyskocil, A., Roels, H., Kriz, J., Kodl, M., and Lauwerys, R. 1995. Renal effects in children living in the vicinity of a lead smelter. *Environ. Res.* 68:91–95.

Bernard, S. M., and McGeehin, M. A. 2003. Prevalence of blood lead levels 5+ microg/dl among US children 1 to 5 years of age and socioeconomic and demographic factors associated with blood of lead levels 5 to 10 microg/dl, Third National Health and Nutrition Examination Survey, 1988–1994. *Pediatrics* 112:1308–1313.

Berry, M., and Bove, F. 1997. Birth weight reduction associated with residence near a hazardous waste landfill. *Environ. Health Perspect.* 105:856–861.

Bérubé, A. 2006. Toward an economic analysis of the environmental burden of disease among Canadian children. *J. Toxicol. Environ. Health B* 10:131–142.

Bhatia, R., Shiau, R., Petreas, M., Weintraub, J. M., Farhang, L., and Eskenazi, B. 2005. Organochlorine pesticides and male genital anomalies in the child health and development studies. *Environ. Health Perspect.* 113:220–224.

Binkova, B., Bobak, M., Chatterjee, A., Chauhan, A. J., Dejmek, J., Dockery, D. W., Everard, M., Forastiere, F., Gilliland, F., Holgate, S., Johnston, S., Krzyanowski, M., Kuna-Dibbert, B., Maynard, R., Raaschou-Nielsen, O., Samet, J., Schneider, J., Skerrett, P. J., Šrám, R. J., Walters, D., Weiland, S. K., and Winneke, G. 2005. Effects of air pollution on children's health and development: A review of the evidence. World Health Organization, European Centre for Environment and Health, Bonn Office. Located at: http://www.euro.who.int/document/E86575.pdf.

Birnbaum, L. S. 1995. Developmental effects of dioxins. *Environ. Health Perspect.* 103(Suppl. 7):89–94.

Blanck, H. M., Marcus, M., Rubin, C., Tolbert, P. E., Hertzberg, V. S., Henderson, A. K., and Zhang, R. H. 2002. Growth in girls exposed in utero and postnatally to polybrominated biphenyls and polychlorinated biphenyls. *Epidemiology* 13:205–210.

Blanck, H. M., Marcus, M., Tolbert, P. E., Rubin, C., Henderson, A. K., Hertzberg, V. S., Zhang, R. H., and Cameron, L. 2000. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology* 11:641–647.

Blanco Munoz, J., Lacasana, M., Borja Aburto, V. H., Torres Sanchez, L. E., Garcia Garcia, A. M., and Lopez Carrillo, L. 2005. Socioeconomic factors and the risk of anencephaly in a Mexican population: A case-control study. *Public Health Rep.* 120:39–45.

Blatter, B. M., Hermens, R., Bakker, M., Roeleveld, N., Verbeek, A. L., and Zielhuis, G. A. 1997. Paternal occupational exposure around conception and spina bifida in offspring. *Am. J. Ind. Med.* 32:283–291.

Blatter, B. M., Roeleveld, N., Zielhuis, G. A., Gabreels, F. J., and Verbeek, A. L. 1996a. Maternal occupational exposure during pregnancy and the risk of spina bifida. *Occup. Environ. Med.* 53:80–86.

Blatter, B. M., Roeleveld, N., Zielhuis, G. A., Mullaart, R. A., and Gabreels, F. J. 1996b. Spina bifida and parental occupation. *Epidemiology* 7:188–193.

Bobak, M., and Leon, D. A. 1999. Pregnancy outcomes and outdoor air pollution: An ecological study in districts of the Czech Republic 1986–8. *Occup. Environ. Med.* 56:539–543.

Boffetta, P., Tredaniel, J., and Greco, A. 2000. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: A meta-analysis. *Environ. Health Perspect.* 108:73–82.

Bolumar, F., Olsen, J., and Boldsen, J. 1996. Smoking reduces fecundity: A European multicenter study on infertility and subfecundity. The European Study Group on Infertility and Subfecundity. *Am. J. Epidemiol.* 143:578–587.

Bonde, J. P., Joffe, M., Apostoli, P., Dale, A., Kiss, P., Spano, M., Caruso, F., Giwercman, A., Bisanti, L., Porru, S., Vanhoorne, M., Comhaire, F., and Zschiesche, W. 2002. Sperm count and chromatin structure in men exposed to inorganic lead: Lowest adverse effect levels. *Occup. Environ. Med.* 59:234–242.

Borja-Aburto, V. H., Hertz-Picciotto, I., Rojas Lopez, M., Farias, P., Rios, C., and Blanco, J. 1999. Blood lead levels measured prospectively and risk of spontaneous abortion. *Am. J. Epidemiol.* 150:590–597.

Bornehag, C. G., Sundell, J., Weschler, C. J., Sigsgaard, T., Lundgren, B., Hasselgren, M., and Hagerhed-Engman, L. 2004. The association between asthma and allergic symptoms in children and phthalates in house dust: A nested case-control study. *Environ. Health Perspect.* 112:1393–1397.

Borzsonyi, M., Bereczky, A., Rudnai, P., Csanady, M., and Horvath, A. 1992. Epidemiological studies on human subjects exposed to arsenic in drinking water in southeast Hungary (letter to the editor). *Arch. Toxicol.* 66:77–78.

Bound, J. P., Harvey, P. W., Francis, B. J., Awwad, F., and Gatrell, A. C. 1997. Involvement of deprivation and environmental lead in neural tube defects: A matched case-control study. *Arch. Dis. Child.* 76:107–112.

Bove, F., Shim, Y., and Zeitz, P. 2002. Drinking water contaminants and adverse pregnancy outcomes: A review. *Environ. Health Perspect.* 110(Suppl. 1):61–74.

Bove, F. J., Fulcomer, M. C., Klotz, J. B., Esmart, J., Dufficy, E. M., and Savrin, J. E. 1995. Public drinking water contamination and birth outcomes. *Am. J. Epidemiol.* 141:850–862.

Boyle, E., Johnson, H., Kelly, A., and McDonnell, R. 2004. Congenital anomalies and proximity to landfill sites. *Ir. Med. J.* 97:16–18.

Brauer, M., Gehring, U., Brunekreef, B., de Jongste, J., Gerritsen, J., Rovers, M., Wichmann, H. E., Wijga, A., and Heinrich, J. 2006. Traffic-related air pollution and otitis media. *Environ. Health Perspect.* 114:1414–1418.

Brauer, M., Hoek, G., Van Vliet, P., Meliefste, K., Fischer, P. H., Wijga, A., Koopman, L. P., Neijens, H. J., Gerritsen, J., Kerkhof, M., Heinrich, J., Bellander, T., and Brunekreef, B. 2002. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am. J. Respir. Crit. Care Med.* 166:1092–1098.

Brender, J., Suarez, L., Hendricks, K., Baetz, R. A., and Larsen, R. 2002. Parental occupation and neural tube defect-affected pregnancies among Mexican Americans. *J. Occup. Environ. Med.* 44:650–656.

Brender, J. D., Olive, J. M., Felkner, M., Suarez, L., Marckwardt, W., and Hendricks, K. A. 2004. Dietary nitrites and nitrates, nitrosatable drugs, and neural tube defects. *Epidemiology* 15:330–336.

Brender, J. D., and Suarez, L. 1990. Paternal occupation and anencephaly. *Am. J. Epidemiol.* 131:517–521.

Brender, J. D., Suarez, L., Felkner, M., Gilani, Z., Stinchcomb, D., Moody, K., Henry, J., and Hendricks, K. 2006. Maternal exposure to arsenic, cadmium, lead, and mercury and neural tube defects in offspring. *Environ. Res.* 101:132–139.

Briggs, N. C., Levine, R. S., Hall, H. I., Cosby, O., Brann, E. A., and Hennekens, C. H. 2003. Occupational risk factors for selected cancers among African American and White men in the United States. *Am. J. Public Health* 93:1748–1752.

Brouwer, A., Ahlborg, U. G., Van den Berg, M., Birnbaum, L. S., Boersma, E. R., Bosveld, B., Denison, M. S., Gray, L. E., Hagmar, L., Holene, E., Huisman, M., Jacobson, S. W., Jacobson, J. L., Koopman-Esseboom, C., Koppe, J. G., Kulig, B. M., Morse, D. C., Muckle, G., Peterson, R. E., Sauer, P. J. J., Seegal, R. F., Smits-Van Prooije, A. E., Touwen, B. C. L., Weisglas-Kuperus, N., and Winneke, G. 1995. Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. *Eur. J. Pharmacol.* 293:1–40.

Brouwer, A., Ahlborg, U. G., van Leeuwen, F. X., and Feeley, M. M. 1998. Report of the WHO working group on the assessment of health risks for human infants from exposure to PCDDs, PCDFs and PCBs. *Chemosphere* 37:1627–1643.

Brown, R. C. 2006. Review: Windows of exposure to pesticides for increased risk of childhood leukemia. *Toxicol. Environ. Chem.* 88:423–433.

Bruce, N., Perez-Padilla, R., and Albalak, R. 2002. The health effects of indoor air pollution exposure in developing countries (WHO/SDE/OEH/02.05). Geneva: World Health Organization.

Buckley, J. D., Meadows, A. T., Kadin, M. E., Le Beau, M. M., Siegel, S., and Robison, L. L. 2000. Pesticide exposures in children with nonHodgkin lymphoma. *Cancer* 89:2315–2321.

Buckley, J. D., Robison, L. L., Swotinsky, R., Garabrant, D. H., LeBeau, M., Manchester, P., Nesbit, M. E., Odom, L., Peters, J. M., Woods, W. G., et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia: A report from the Childrens Cancer Study Group. *Cancer Res.* 49:4030–4037.

Budtz-Jorgensen, E., Grandjean, P., Keiding, N., White, R. F., and Weihe, P. 2000. Benchmark dose calculations of methylmercury-associated neurobehavioural deficits. *Toxicol. Lett.* 112–113:193–199.

Buffler, P. A., Kwan, M. L., Reynolds, P., and Urayama, K. Y. 2005. Environmental and genetic risk factors for childhood leukemia: Appraising the evidence. *Cancer Invest.* 23:60–75.

Bukowski, J., Somers, G., and Bryanton, J. 2001. Agricultural contamination of groundwater as a possible risk factor for growth restriction or prematurity. *J. Occup. Environ. Med.* 43:377–383.

Bull, N., Riise, T., and Moen, B. E. 1999. Influence of paternal exposure to oil and oil products on time to pregnancy and spontaneous abortions. *Occup. Med*. (*Lond*.) 49:371–376.

Bunin, G. R., Buckley, J. D., Boesel, C. P., Rorke, L. B., and Meadows, A. T. 1994. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: A report from the Children's Cancer Group. *Cancer Epidemiol. Biomarkers Prev*. 3:197–204.

Bunin, G. R., Petrakova, A., Meadows, A. T., Emanuel, B. S., Buckley, J. D., Woods, W. G., and Hammond, G. D. 1990. Occupations of parents of children with retinoblastoma: A report from the Children's Cancer Study Group. *Cancer Res*. 50:7129–7133.

Burns, J. M., Baghurst, P. A., Sawyer, M. G., McMichael, A. J., and Tong, S. L. 1999. Lifetime low-level exposure to environmental lead and children's emotional and behavioral development at ages 11–13 years. The Port Pirie Cohort Study. *Am. J. Epidemiol*. 149:740–749.

Byers, R. K., and Lord, E. E. 1943. Late effects of lead poisoning on mental development. *Am. J. Dis. Child*. 66:471–494.

Caceres Udina, M. J., Alvarez Martinez, J. A., Argente del Castillo, J., Chumilla Valderas, M. A., Fernandez Alvarez, E., Garrido Romera, A., Sanchez Gascon, F., and Garcia-Marcos, L. 2004. Incidence, air pollution and risk factors of acute otitis media in the first year of life: A prospective study. *An. Pediatr*. (*Barc*.) 60:133–138.

Calafat, A. M., Kuklenyik, Z., Reidy, J. A., Caudill, S. P., Ekong, J., and Needham, L. L. 2005. Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environ. Health Perspect*. 113:391–395.

Calderon, J., Navarro, M. E., Jimenez-Capdeville, M. E., Santos-Diaz, M. A., Golden, A., Rodriguez-Leyva, I., Borja-Aburto, V., and Diaz-Barriga, F. 2001. Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ. Res*. 85:69–76.

California Environmental Protection Agency. 2005. Proposed identication of environmental tobacco smoke as a toxic air contaminant. Located at: http://www.arb.ca.gov/toxics/ets/finalreport/finalreport.htm.

Campbell, J. R., Moss, M. E., and Raubertas, R. F. 2000. The association between caries and childhood lead exposure . *Environ. Health Perspect*. 108:1099–1102.

Can, A., Semiz, O., and Cinar, O. 2005. Bisphenol-A induces cell cycle delay and alters centrosome and spindle microtubular organization in oocytes during meiosis. *Mol. Hum. Reprod*. 11:389–396.

Canfield, R. L., Henderson, C. R. Jr, Cory-Slechta, D. A., Cox, C., Jusko, T. A., and Lanphear, B. P. 2003. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. *N. Engl. J. Med*. 348:1517–1526.

Carbone, P., Giordano, F., Nori, F., Mantovani, A., Taruscio, D., Lauria, L., and Figa-Talamanca, I. 2007. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: A population-based case-control study in rural Sicily. *Int. J. Androl*. 30:3–13.

Carpenter, R. G., Irgens, L. M., Blair, P. S., England, P. D., Fleming, P., Huber, J., Jorch, G., and Schreuder, P. 2004. Sudden unexplained infant death in 20 regions in Europe: Case control study. *Lancet* 363:185–191.

Cedergren, M. I., Selbing, A. J., Lofman, O., and Kallen, B. A. 2002. Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects. *Environ. Res*. 89:124–130.

Centers for Disease Control. 1989. *Centers for Disease Control Vietnam Experience Study. Health status of Vietnam veterans. Vol. V. Reproductive outcomes and child health*. Atlanta, GA: Center for Environmental Health and Injury Control, Centers for Disease Control, Public Health Service, U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. 2004. Racial/ethnic trends in fetal mortality—United States, 1990–2000. *Morbid. Mortal. Weekly Rep*. 53:529–532.

Centers for Disease Control and Prevention. 2005a. Metropolitan Atlanta Congenital Defects Program. Located at: http://www.cdc.gov/ncbddd/bd/macdp.htm.

Centers for Disease Control and Prevention. 2005b. Third national report on human exposures to environmental chemicals. Located at: http://www.cdc.gov/exposurereport/3rd/default.htm.

Centers for Disease Control and Prevention. 2006. Lead: Questions and answers. Located at: http://www.cdc.gov/lead/.

Chaix, B., Gustafsson, S., Jerrett, M., Kristersson, H., Lithman, T., Boalt, A., and Merlo, J. 2006. Children's exposure to nitrogen dioxide in Sweden: Investigating environmental injustice in an egalitarian country. *J. Epidemiol. Commun. Health* 60:234–241.

Chang, J. S., Selvin, S., Metayer, C., Crouse, V., Golembesky, A., and Buffler, P. A. 2006. Parental smoking and the risk of childhood leukemia. *Am. J. Epidemiol*. 163:1091–1100.

Chao, W. Y., Hsu, C. C., and Guo, Y. L. 1997. Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. *Arch. Environ. Health* 52:257–262.

Chen, A., Dietrich, K. N., Ware, J. H., Radcliffe, J., and Rogan, W. J. 2005. IQ and blood lead from 2 to 7 years of age: Are the effects in older children the residual of high blood lead concentrations in 2-year-olds? *Environ. Health Perspect*. 113:597–601.

Chen, L., Yang, W., Jennison, B. L., Goodrich, A., and Omaye, S. T. 2002a. Air pollution and birth weight in northern Nevada, 1991–1999. *Inhal. Toxicol*. 14:141–157.

Chen, P. C., Hsieh, G. Y., Wang, J. D., and Cheng, T. J. 2002b. Prolonged time to pregnancy in female workers exposed to ethylene glycol ethers in semiconductor manufacturing. *Epidemiology* 13:191–196.

Chen, P. C., Pan, I. J., and Wang, J. D. 2006. Parental exposure to lead and small for gestational age births. *Am. J. Ind. Med*. 49:417–422.

Chen, Y. C., Yu, M. L., Rogan, W. J., Gladen, B. C., and Hsu, C. C. 1994. A 6-year follow-up of behavior and activity disorders in the Taiwan Yu-cheng children. *Am. J. Public Health* 84:415–421.

Chen, Y. J., and Hsu, C. C. 1994. Effects of prenatal exposure to PCBs on the neurological function of children: a neuropsychological and neurophysiological study. *Dev. Med. Child. Neurol*. 36:312–320.

Chen, Z., Robison, L., Giller, R., Krailo, M., Davis, M., Davies, S., and Shu, X. O. 2006. Environmental exposure to residential pesticides, chemicals, dusts, fumes, and metals, and risk of childhood germ cell tumors. *Int. J. Hyg. Environ. Health* 209:31–40.

Chen, Z., Robison, L., Giller, R., Krailo, M., Davis, M., Gardner, K., Davies, S., and Shu, X. O. 2005a. Risk of childhood germ cell tumors in association with parental smoking and drinking. *Cancer* 103:1064–1071.

Chen, Z., Stewart, P. A., Davies, S., Giller, R., Krailo, M., Davis, M., Robison, L., and Shu, X. O. 2005b. Parental occupational exposure to pesticides and childhood germ-cell tumors. *Am. J. Epidemiol.* 162:858–867.

Chia, S. E., Lee, J., Chia, K. S., and Chan, O. Y. 2004. Low birth weight in relation to parental occupations—A population-based registry in Singapore (1994–1998). *Neurotoxicol. Teratol.* 26:285–290.

Chiodo, L. M., Jacobson, S. W., and Jacobson, J. L. 2004. Neurodevelopmental effects of postnatal lead exposure at very low levels. *Neurotoxicol. Teratol.* 26:359–371.

Cho, S. I., Li, Q., Yang, J., Chen, C., Padungtod, C., Ryan, L., Christiani, D. C., and Xu, X. 1999. Drinking water source and spontaneous abortion: A cross-sectional study in a rural Chinese population. *Int. J. Occup. Environ. Health* 5:164–169.

Clarkson, T. W. 2002. The three modern faces of mercury. *Environ. Health Perspect.* 110(Suppl. 1):11–23.

Clavel, J., Bellec, S., Rebouissou, S., Menegaux, F., Feunteun, J., Bonaiti-Pellie, C., Baruchel, A., Kebaili, K., Lambilliotte, A., Leverger, G., Sommelet, D., Lescoeur, B., Beaune, P., Hemon, D., and Loriot, M. A. 2005. Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur. J. Cancer Prev.* 14:531–540.

Cocco, P., Fadda, D., Ibba, A., Melis, M., Tocco, M. G., Atzeri, S., Avataneo, G., Meloni, M., Monni, F., and Flore, C. 2005. Reproductive outcomes in DDT applicators. *Environ. Res.* 98:120–126.

Cohn, B. A., Cirillo, P. M., Wolff, M. S., Schwingl, P. J., Cohen, R. D., Sholtz, R. I., Ferrara, A., Christianson, R. E., van den Berg, B. J., and Siiteri, P. K. 2003. DDT and DDE exposure in mothers and time to pregnancy in daughters. *Lancet* 361:2205–2206.

Cohn, R. D., Arbes, S. J. Jr, Jaramillo, R., Reid, L. H., and Zeldin, D. C. 2006. National prevalence and exposure risk for cockroach allergen in U.S. households. *Environ. Health Perspect.* 114:522–526.

Colon, I., Caro, D., Bourdony, C. J., and Rosario, O. 2000. Identification of phthalate esters in the serum of young puerto rican girls with premature breast development. *Environ. Health Perspect.* 108:895–900.

Colt, J. S., and Blair, A. 1998. Parental occupational exposures and risk of childhood cancer. *Environ. Health Perspect.* 106(Suppl. 3):909–925.

Commission for Environmental Cooperation. 2002. North American regional action plan on environmental monitoring and assessment. Located at: http://www.cec.org/files/PDF/POLLUTANTS/EMA-NARAP_final-e2.pdf.

Commission for Environmental Cooperation. 2006. Children's health and the environment in North America: A first report on available indicators and measures. Located at: http://www.cec.org/children.

Cook, D. G., and Strachan, D. P. 1999. Health effects of passive smoking–10: Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 54:357–366.

Cooney, G. H., Bell, A., McBride, W., and Carter, C. 1989a. Neurobehavioural consequences of prenatal low level exposures to lead. *Neurotoxicol. Teratol.* 11:95–104.

Cooney, G. H., Bell, A., McBride, W., and Carter, C. 1989b. Low-level exposures to lead: The Sydney lead study. *Dev. Med. Child. Neurol.* 31:640–649.

Cooney, M. A., Daniels, J. L., Ross, J. A., Breslow, N. E., Pollock, B. H., and Olshani, A. F. 2007. Household pesticides and the risk of Wilms tumor. *Environ. Health Perspect.* 115:134–137.

Cordier, S., Bergeret, A., Goujard, J., Ha, M. C., Ayme, S., Bianchi, F., Calzolari, E., De Walle, H. E., Knill-Jones, R., Candela, S., Dale, I., Dananche, B., de Vigan, C., Fevotte, J., Kiel, G., and Mandereau, L. 1997. Congenital malformation and maternal occupational exposure to glycol ethers. *Epidemiology* 8:355–363.

Cordier, S., Chevrier, C., Robert-Gnansia, E., Lorente, C., Brula, P., and Hours, M. 2004. Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. *Occup. Environ. Med.* 61:8–15.

Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P., Gosme-Seguret, S., Josse, D., White, R., and Amiel-Tison, C. 2002. Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. *Environ. Res.* 89:1–11.

Cordier, S., Ha, M. C., Ayme, S., and Goujard, J. 1992. Maternal occupational exposure and congenital malformations. *Scand. J. Work Environ Health* 18:11–17.

Cordier, S., Iglesias, M. J., Le Goaster, C., Guyot, M. M., Mandereau, L., and Hemon, D. 1994. Incidence and risk factors for childhood brain tumors in the Ile de France. *Int. J. Cancer* 59:776–782.

Cordier, S., Lefeuvre, B., Filippini, G., Peris-Bonet, R., Farinotti, M., Lovicu, G., and Mandereau, L. 1997. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors (Italy, France, Spain). *Cancer Causes Control* 8:688–697.

Cordier, S., Mandereau, L., Preston-Martin, S., Little, J., Lubin, F., Mueller, B., Holly, E., Filippini, G., Peris-Bonet, R., McCredie, M., Choi, N. W., and Arsla, A. 2001. Parental occupations and childhood brain tumors: results of an international case-control study. *Cancer Causes Control* 12:865–874.

Correa, A., Gray, R. H., Cohen, R., Rothman, N., Shah, F., Seacat, H., and Corn, M. 1996. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *Am. J. Epidemiol.* 143:707–717.

Correa-Villasenor, A., Ferencz, C., Boughman, J. A., and Neill, C. A. 1991. Total anomalous pulmonary venous return: familial and environmental factors. The Baltimore-Washington Infant Study Group. *Teratology* 44:415–428.

Correa-Villasenor, A., Ferencz, C., Loffredo, C., and Magee, C. 1993. Paternal exposures and cardiovascular malformations. The Baltimore–Washington Infant Study Group. *J. Expos. Anal. Environ. Epidemiol.* 3(Suppl. 1):173–185.

Counter, S. A. 2003. Neurophysiological anomalies in brainstem responses of mercury-exposed children of Andean gold miners. *J. Occup. Environ. Med.* 45:87–95.

Counter, S. A., Buchanan, L. H., Laurell, G., and Ortega, F. 1998. Blood mercury and auditory neuro-sensory responses in children and adults in the Nambija gold mining area of Ecuador. *Neurotoxicology* 19:185–196.

Counter, S. A., Buchanan, L. H., Ortega, F., and Laurell, G. 1997. Normal auditory brainstem and cochlear function in extreme pediatric plumbism. *J. Neurol. Sci.* 152:85–92.

Cox, C., Clarkson, T. W., Marsh, D. O., Amin-Zaki, L., Tikriti, S., and Myers, G. G. 1989. Dose-response analysis of infants prenatally exposed to methyl mercury: An application of a single compartment model to single-strand hair analysis. *Environ. Res.* 49:318–332.

Croen, L. A., Shaw, G. M., Sanbonmatsu, L., Selvin, S., and Buffler, P. A. 1997. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. *Epidemiology* 8:347–354.

Croen, L. A., Todoroff, K., and Shaw, G. M. 2001. Maternal exposure to nitrate from drinking water and diet and risk for neural tube defects. *Am. J. Epidemiol.* 153:325–331.

Crosignani, P., Tittarelli, A., Borgini, A., Codazzi, T., Rovelli, A., Porro, E., Contiero, P., Bianchi, N., Tagliabue, G., Fissi, R., Rossitto, F., and Berrino, F. 2004. Childhood leukemia and road traffic: A population-based case-control study. *Int. J. Cancer* 108:596–599.

Crump, K. S., Kjellstrom, T., Shipp, A. M., Silvers, A., and Stewart, A. 1998. Influence of prenatal mercury exposure upon scholastic and psychological test performance: Benchmark analysis of a New Zealand cohort. Risk Anal 18:701–713.

Curtis, K. M., Savitz, D. A., and Arbuckle, T. E. 1997. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. *Am. J. Epidemiol.* 146:32–41.

Curtis, K. M., Savitz, D. A., Weinberg, C. R., and Arbuckle, T. E. 1999. The effect of pesticide exposure on time to pregnancy. *Epidemiology* 10:112–117.

Dahl, R., White, R. F., Weihe, P., Sorensen, N., Letz, R., Hudnell, H. K., Otto, D. A., and Grandjean, P. 1996. Feasibility and validity of three computer-assisted neurobehavioral tests in 7-year-old children. *Neurotoxicol. Teratol.* 18:413–419.

Dallaire, F., Dewailly, E., Muckle, G., Vezina, C., Jacobson, S. W., Jacobson, J. L., and Ayotte, P. 2004. Acute infections and environmental exposure to organochlorines in Inuit infants from Nunavik. *Environ. Health Perspect.* 112:1359–1365.

Dallaire, F., Dewailly, E., Vezina, C., Muckle, G., Weber, J. P., Bruneau, S., and Ayotte, P. 2006. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. *Environ. Health Perspect.* 114:1301–1305.

Damgaard, I. N., Skakkebaek, N. E., Toppari, J., Virtanen, H. E., Shen, H., Schramm, K. W., Petersen, J. H., Jensen, T. K., and Main, K. M. 2006. Persistent pesticides in human breast milk and cryptorchidism. *Environ. Health Perspect.* 114:1133–1138.

Daniell, W. E., and Vaughan, T. L. 1988. Paternal employment in solvent related occupations and adverse pregnancy outcomes. *Br. J. Ind. Med.* 45:193–197.

Daniels, J. L., Longnecker, M. P., Klebanoff, M. A., Gray, K. A., Brock, J. W., Zhou, H., Chen, Z., and Needham, L. L. 2003. Prenatal exposure to low-level polychlorinated biphenyls in relation to mental and motor development at 8 months. *Am. J. Epidemiol.* 157:485–492.

Daniels, J. L., Longnecker, M. P., Rowland, A. S., and Golding, J. 2004. Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology* 15:394–402.

Daniels, J. L., Olshan, A. F., Teschke, K., Hertz-Picciotto, I., Savitz, D. A., Blatt, J., Bondy, M. L., Neglia, J. P., Pollock, B. H., Cohn, S. L., Look, A. T., Seeger, R. C., and Castleberry, R. P. 2001. Residential pesticide exposure and neuroblastoma. *Epidemiology* 12:20–27.

Darvill, T., Lonky, E., Reihman, J., Stewart, P., and Pagano, J. 2000. Prenatal exposure to PCBs and infant performance on the Fagan test of infant intelligence. *Neurotoxicology* 21:1029–1038.

Davidson, P. W., Myers, G. J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M., and Clarkson, T. W. 1998. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: Outcomes at 66 months of age in the Seychelles Child Development Study. *J. Am. Med. Assoc.* 280:701–707.

Davidson, P. W., Myers, G. J., Cox, C., Shamlaye, C. F., Marsh, D. O., Tanner, M. A., Berlin, M., SloaneReeves, J., Cernichiari, E., Choisy, O. and others. 1995. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: Outcomes at 19 and 29 months. *Neurotoxicology* 16:677–688.

Davidson, P. W., Myers, G. J., and Weiss, B. 2004. Mercury exposure and child development outcomes. *Pediatrics* 113:1023–1029.

Davidson, P. W., Palumbo, D., Myers, G. J., Cox, C., Shamlaye, C. F., Sloane-Reeves, J., Cernichiari, E., Wilding, G. E., and Clarkson, T. W. 2000. Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet. *Environ. Res.* 84:1–11.

Davis, J. R., Brownson, R. C., Garcia, R., Bentz, B. J., and Turner, A. 1993. Family pesticide use and childhood brain cancer. *Arch. Environ. Contam. Toxicol.* 24:87–92.

Dawson, E. B., Evans, D. R., Harris, W. A., and Van Hook, J. W. 1999. Amniotic fluid B12, calcium, and lead levels associated with neural tube defects. *Am. J. Perinatol.* 16:373–378.

de Burbure, C., Buchet, J. P., Bernard, A., Leroyer, A., Nisse, C., Haguenoer, J. M., Bergamaschi, E., and Mutti, A. 2003. Biomarkers of renal effects in children and adults with low environmental exposure to heavy metals. *J. Toxicol. Environ. Health A* 66:783–798.

de Burbure, C., Buchet, J. P., Leroyer, A., Nisse, C., Haguenoer, J. M., Mutti, A., Smerhovsky, Z., Cikrt, M., Trzcinka-Ochocka, M., Razniewska, G., Jakubowski, M., and Bernard, A. 2006. Renal and neurologic effects of cadmium, lead, mercury, and arsenic in children: Evidence of early effects and multiple interactions at environmental exposure levels. *Environ. Health Perspect.* 114:584–590.

de Cock, J., Westveer, K., Heederik, D., te Velde, E., and van Kooij, R. 1994. Time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands. *Occup. Environ. Med.* 51:693–699.

De Roos, A. J., Olshan, A. F., Teschke, K., Poole, C., Savitz, D. A., Blatt, J., Bondy, M. L., and Pollock, B. H. 2001. Parental occupational exposures to chemicals and incidence of neuroblastoma in offspring. *Am. J. Epidemiol.* 154:106–114.

Debes, F., Budtz-Jorgensen, E., Weihe, P., White, R. F., and Grandjean, P. 2006. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicol. Teratol.* 28: 363–375.

Dejin-Karlsson, E., and Ostergren, P. O. 2003. Psychosocial factors, lifestyle, and fetal growth: The added value of both pre- and post-natal assessments. *Eur. J. Public Health* 13:210–217.

Dejmek, J., Jelinek, R., Solansky', I., Benes, I., and Sram, R. J. 2000. Fecundability and parental exposure to ambient sulfur dioxide. *Environ. Health Perspect.* 108:647–654.

Dejmek, J., Solansk, y. I, Podrazilova, K., and Sram, R. J. 2002. The exposure of nonsmoking and smoking mothers to environmental tobacco smoke during different gestational phases and fetal growth. *Environ. Health Perspect.* 110:601–606.

Del Corno, G., Montesarchio, E., and Fara, G. M. 1985. Problems in the assessment of human exposure to tetrachlorodibenzodioxin (TCDD): The marker chloracne. *Eur. J. Epidemiol.* 1:139–144.

Den Hond, E., Roels, H. A., Hoppenbrouwers, K., Nawrot, T., Thijs, L., Vandermeulen, C., Winneke, G., Vanderschueren, D., and Staessen, J. A. 2002. Sexual maturation in relation to polychlorinated aromatic hydrocarbons: Sharpe and Skakkebaek's hypothesis revisited. *Environ. Health Perspect.* 110:771–776.

DeSesso, J. M., Jacobson, C. F., Scialli, A. R., Farr, C. H., and Holson, J. F. 1998. An assessment of the developmental toxicity of inorganic arsenic. *Reprod. Toxicol.* 12:385–433.

Dewailly, E., Ayotte, P., Bruneau, S., Gingras, S., Belles-Isles, M., and Roy, R. 2000. Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environ. Health Perspect.* 108:205–211.

Dietert, R. R., Etzel, R. A., Chen, D., Halonen, M., Holladay, S. D., Jarabek, A. M., Landreth, K., Peden, D. B., Pinkerton, K., Smialowicz, R. J., and Zoetis, T. 2000. Workshop to identify critical windows of exposure for children's health: Immune and respiratory systems work group summary. *Environ. Health Perspect.* 108(Suppl. 3):483–490.

Dietrich, K. N., Ris, M. D., Succop, P. A., Berger, O. G., and Bornschein, R. L. 2001. Early exposure to lead and juvenile delinquency. *Neurotoxicol. Teratol.* 23:511–518.

Dietrich, K. N., Succop, P. A., Berger, O. G., and Keith, R. W. 1992. Lead exposure and the central auditory processing abilities and cognitive development of urban children: The Cincinnati Lead Study Cohort at age 5 years. *Neurotoxicol. Teratol.* 14:51–56.

Dietrich, K. N., Succop, P. A., Bornschein, R. L., Krafft, K. M., Berger, O., Hammond, P. B., and Buncher, C. R. 1990. Lead exposure and neurobehavioral development in later infancy. *Environ. Health Perspect.* 89:13–19.

DiFranza, J. R., Aligne, C. A., and Weitzman, M. 2004. Prenatal and postnatal environmental tobacco smoke exposure and children's health. *Pediatrics* 113:1007–1015.

Dimich-Ward, H., Hertzman, C., Teschke, K., Hershler, R., Marion, S. A., Ostry, A., and Kelly, S. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. *Scand. J. Work Environ Health* 22:267–273.

Dodds, L., King, W., Allen, A. C., Armson, B. A., Fell, D. B., and Nimrod, C. 2004. Trihalomethanes in public water supplies and risk of stillbirth. *Epidemiology* 15:179–186.

Dodds, L., King, W., Woolcott, C., and Pole, J. 1999. Trihalomethanes in public water supplies and adverse birth outcomes. *Epidemiology* 10:233–237.

Dodds, L., and King, W. D. 2001. Relation between trihalomethane compounds and birth defects. *Occup. Environ. Med.* 58:443–446.

Dodds, L., and Seviour, R. 2001. Congenital anomalies and other birth outcomes among infants born to women living near a hazardous waste site in Sydney, Nova Scotia. *Can. J. Public Health* 92:331–334.

Dolk, H., Pattenden, S., Vrijheid, M., Thakrar, B., and Armstrong, B. 2000. Perinatal and infant mortality and low birth weight among residents near cokeworks in Great Britain. *Arch. Environ. Health* 55:26–30.

Dolk, H., and Vrijheid, M. 2003. The impact of environmental pollution on congenital anomalies. *Br. Med. Bull.* 68:25–45.

Dolk, H., Vrijheid, M., Armstrong, B., Abramsky, L., Bianchi, F., Garne, E., Nelen, V., Robert, E., Scott, J. E., Stone, D., and Tenconi, R. 1998. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. *Lancet* 352:423–427.

Dorsch, M. M., Scragg, R. K., McMichael, A. J., Baghurst, P. A., and Dyer, K. F. 1984. Congenital malformations and maternal drinking water supply in rural South Australia: A case-control study. *Am. J. Epidemiol.* 119:473–486.

Doyle, P., Roman, E., Beral, V., and Brookes, M. 1997. Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. *Occup. Environ. Med.* 54:848–853.

Dugandzic, R., Dodds, L., Stieb, D., and Smith-Doiron, M. 2006. The association between low level exposures to ambient air pollution and term low birth weight: A retrospective cohort study. *Environ. Health* 5:1–8.

Dulout, F. N., Grillo, C. A., Seoane, A. I., Maderna, C. R., Nilsson, R., Vahter, M., Darroudi, F., and Natarajan, A. T. 1996. Chromosomal aberrations in peripheral blood lymphocytes from native Andean women and children from northwestern Argentina exposed to arsenic in drinking water. *Mutat. Res.* 370:151–158.

Dummer, T. J., Dickinson, H. O., and Parker, L. 2003a. Adverse pregnancy outcomes around incinerators and crematoriums in Cumbria, north west England, 1956–93. *J. Epidemiol. Commun. Health* 57:456–461.

Dummer, T. J., Dickinson, H. O., and Parker, L. 2003b. Prevalence of adverse pregnancy outcomes around hazardous industrial sites in Cumbria, north-west England, 1950–93. *Paediatr. Perinat. Epidemiol.* 17:250–255.

Efird, J. T., Holly, E. A., Preston-Martin, S., Mueller, B. A., Lubin, F., Filippini, G., Peris-Bonet, R., McCredie, M., Cordier, S., Arslan, A., and Bracci, P. M. 2003. Farm-related exposures and childhood brain tumours in seven countries: Results from the SEARCH International Brain Tumour Study. *Paediatr. Perinat. Epidemiol.* 17:201–211.

Eiben, B., Bartels, I., Bahr-Porsch, S., Borgmann, S., Gatz, G., Gellert, G., Goebel, R., Hammans, W., Hentemann, M., Osmers, R., and et, a. l. 1990. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. *Am. J. Hum. Genet.* 47:656–663.

Elghany, N. A., Stopford, W., Bunn, W. B., and Fleming, L. E. 1997. Occupational exposure to inorganic mercury vapour and reproductive outcomes. *Occup. Med.* 47:333–336.

Elliott, P., Briggs, D., Morris, S., de Hoogh, C., Hurt, C., Jensen, T. K., Maitland, I., Richardson, S., Wakefield, J., and Jarup, L. 2001. Risk of adverse birth outcomes in populations living near landfill sites. *Br. Med. J.* 323:363–368.

Elliott, R. C., Jones, J. R., McElvenny, D. M., Pennington, M. J., Northage, C., Clegg, T. A., Clarke, S. D., Hodgson, J. T., and Osman, J. 1999. Spontaneous abortion in the British semiconductor industry. *Am. J. Ind. Med.* 36:557–572.

Ellish, N. J., Saboda, K., O'Connor, J., Nasca, P. C., Stanek, E. J., and Boyle, C. 1996. A prospective study of early pregnancy loss. *Hum. Reprod.* 11:406–412.

Elwood, J. M., and Coldman, A. J. 1981. Water composition in the etiology of anencephalus. *Am. J. Epidemiol.* 113:681–690.
Emory, E., Ansari, Z., Pattillo, R., Archibold, E., and Chevalier, J. 2003. Maternal blood lead effects on infant intelligence at age 7 months. *Am. J. Obstet. Gynecol.* 188:S26–S32.
Engel, L. S., O'Meara, E. S., and Schwartz, S. M. 2000. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980–1993. *Scand. J. Work Environ. Health* 26:193–198.
Erickson, J. D., Mulinare, J., McClain, P. W., Fitch, T. G., James, L. M., McClearn, A. B., and Adams, M. J. Jr. 1984. Vietnam veterans' risks for fathering babies with birth defects. *J. Am. Med. Assoc.* 252:903–912.
Ernhart, C. B., Morrow-Tlucak, M., and Wolf, A. W. 1988. Low level lead exposure and intelligence in the preschool years. *Sci. Total Environ.* 71:453–459.
Ernhart, C. B., Morrow-Tlucak, M., Wolf, A. W., Super, D., and Drotar, D. 1989. Low level lead exposure in the prenatal and early preschool periods: Intelligence prior to school entry. *Neurotoxicol. Teratol.* 11:161–170.
Eskenazi, B., and Bergmann, J. J. 1995. Passive and active maternal smoking during pregnancy, as measured by serum cotinine, and post-natal smoke exposure. I. Effects on physical growth at age 5 years. *Am. J. Epidemiol.* 142:S10–S18.
Eskenazi, B., Marks, A. R., Bradman, A., Fenster, L., Johnson, C., Barr, D. B., and Jewell, N. P. 2006. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. *Pediatrics* 118:233–241.
Eskenazi, B., Mocarelli, P., Warner, M., Chee, W. Y., Gerthoux, P. M., Samuels, S., Needham, L. L., and Patterson, D. G. Jr. 2003. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. *Environ. Health Perspect.* 111:947–953.
European Environment Agency and the WHO Regional Office for Europe (Copenhagen). 2002. Children's health and environment: A review of evidence (Environmental Issue Report No 29). Located at: http://reports.eea.eu.int/environmental_issue_report_2002_29/en.
Fabia, J., and Thuy, T. D. 1974. Occupation of father at time of birth of children dying of malignant diseases. *Br. J. Prev. Soc. Med.* 28:98–100.
Factor-Litvak, P., Graziano, J. H., Kline, J. K., Popovac, D., Mehmeti, A., Ahmedi, G., Shrout, P., Murphy, M. J., Gashi, E., Haxhiu, R. and others. 1991. A prospective study of birthweight and length of gestation in a population surrounding a lead smelter in Kosovo, Yugoslavia. *Int. J. Epidemiol.* 20:722–728.
Factor-Litvak, P., Wasserman, G., Kline, J. K., and Graziano, J. 1999. The Yugoslavia Prospective Study of environmental lead exposure. *Environ. Health Perspect.* 107:9–15.
Falcon, M., Vinas, P., and Luna, A. 2003. Placental lead and outcome of pregnancy. *Toxicology* 185:59–66.
Fan, A. M., and Steinberg, V. E. 1996. Health implications of nitrate and nitrite in drinking water: An update on methemoglobinemia occurrence and reproductive and developmental toxicity. *Regul. Toxicol. Pharmacol.* 23:35–43.
Faustman, E. M., Silbernagel, S. M., Fenske, R. A., Burbacher, T. M., and Ponce, R. A. 2000. Mechanisms underlying children's susceptibility to environmental toxicants. *Environ. Health Perspect.* 108(Suppl. 1):13–21.
Feingold, L., Savitz, D. A., and John, E. M. 1992. Use of a job-exposure matrix to evaluate parental occupation and childhood cancer. *Cancer Causes Control* 3:161–169.
Fell, J. M., Reynolds, A. P., Meadows, N., Khan, K., Long, S. G., Quaghebeur, G., Taylor, W. J., and Milla, P. J. 1996. Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 347:1218–1221.
Fels, L. M., Wunsch, M., Baranowski, J., Norska-Borowka, I., Price, R. G., Taylor, S. A., Patel, S., De Broe, M., Elsevier, M. M., Lauwerys, R., Roels, H., Bernard, A., Mutti, A., Gelpi, E., Rosello, J., and Stolte, H. 1998. Adverse effects of chronic low level lead exposure on kidney function—A risk group study in children. *Nephrol. Dial. Transplant*. 13:2248–2256.
Fenske, R. A., Lu, C., Curl, C. L., Shirai, J. H., and Kissel, J. C. 2005. Biologic monitoring to characterize organophosphorus pesticide exposure among children and workers: An analysis of recent studies in Washington State. *Environ. Health Perspect.* 113:1651–1657.
Fenster, L., Eskenazi, B., Anderson, M., Bradman, A., Harley, K., Hernandez, H., Hubbard, A., and Barr, D. B. 2006. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ. Health Perspect.* 114:597–602.
Feychting, M., Plato, N., Nise, G., and Ahlbom, A. 2001. Paternal occupational exposures and childhood cancer. *Environ. Health Perspect.* 109:193–196.
Feychting, M., Svensson, D., and Ahlbom, A. 1998. Exposure to motor vehicle exhaust and childhood cancer. *Scand. J. Work Environ. Health* 24:8–11.
Figa-Talamanca, I., Petrelli, G., Tropeano, R., Papa, G., and Boccia, G. 2000. Fertility of male workers of the Italian mint. *Reprod. Toxicol.* 14:325–330.
Filippini, G., Maisonneuve, P., McCredie, M., Peris-Bonet, R., Modan, B., Preston-Martin, S., Mueller, B. A., Holly, E. A., Cordier, S., Choi, N. W., Little, J., Arslan, A., and Boyle, P. 2002. Relation of childhood brain tumors to exposure of parents and children to tobacco smoke: The SEARCH international case-control study. Surveillance of Environmental Aspects Related to Cancer in Humans. *Int. J. Cancer* 100:206–213.
Fleming, L. E., Bean, J. A., Rudolph, M., and Hamilton, K. 1999. Cancer incidence in a cohort of licensed pesticide applicators in Florida. *J. Occup. Environ. Med.* 41:279–88.
Flores-Luevano, S., Farias, P., Hernandez, M., Romano-Riquer, P., Weber, J. P., Dewailly, E., Cuevas-Alpuche, J., and Romieu, I. 2003. DDT/DDE concentrations and risk of hypospadias. Pilot case-control study. *Salud Publica Mex.* 45:431–438.
Flower, K. B., Hoppin, J. A., Lynch, C. F., Blair, A., Knott, C., Shore, D. L., and Sandler, D. P. 2004. Cancer risk and parental pesticide application in children of agricultural health study participants. *Environ. Health Perspect.* 112:631–635.
Ford, A. M., Bennett, C. A., Price, C. M., Bruin, M. C., Van Wering, E. R., and Greaves, M. 1998. Fetal origins of the TEL-AML1 fusion gene in identical twins with leukemia. *Proc. Natl. Acad. Sci. USA* 95:4584–4588.

Foster, P. M. 2006. Disruption of reproductive development in male rat offspring following in utero exposure to phthalate esters. *Int. J. Androl.* 29:140–147; discussion 181–185.

Foster, W., Chan, S., Platt, L., and Hughes, C. 2000. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. J Clin Endocrinol Metab 85:2954–2957.

Freedman, D. M., Stewart, P., Kleinerman, R. A., Wacholder, S., Hatch, E. E., Tarone, R. E., Robison, L. L., and Linet, M. S. 2001. Household solvent exposures and childhood acute lymphoblastic leukemia. *Am. J. Public Health* 91:564–567.

Gale, K. B., Ford, A. M., Repp, R., Borkhardt, A., Keller, C., Eden, O. B., and Greaves, M. F. 1997. Backtracking leukemia to birth: Identification of clonotypic gene fusion sequences in neonatal blood spots. *Proc. Natl. Acad. Sci. USA* 94:13950–13954.

Gallagher, M. D., Nuckols, J. R., Stallones, L., and Savitz, D. A. 1998. Exposure to trihalomethanes and adverse pregnancy outcomes. *Epidemiology* 9:484–489.

Garcia-Rodriguez, J., Garcia-Martin, M., Nogueras-Ocana, M., de Dios Luna-del-Castillo, J., Espigares Garcia, M., Olea, N., and Lardelli-Claret, P. 1996. Exposure to pesticides and cryptorchidism: Geographical evidence of a possible association. *Environ. Health Perspect.* 104:1090–1095.

Gardner, M. J., Snee, M. P., Hall, A. J., Powell, C. A., Downes, S., and Terrell, J. D. 1990. Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br. Med. J.* 300:423–429.

Garry, V. F. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the red river valley of Minnesota, USA. *Environ. Health Perspect.* 110 Suppl 3:441–449.

Garry, V. F., Harkins, M., Lyubimov, A., Erickson, L., and Long, L. 2002. Reproductive outcomes in the women of the Red River Valley of the north. I. The spouses of pesticide applicators: Pregnancy loss, age at menarche, and exposures to pesticides. *J. Toxicol. Environ. Health A* 65:769–786.

Garry, V. F., Schreinemachers, D., Harkins, M. E., and Griffith, J. 1996. Pesticide appliers, biocides, and birth defects in rural Minnesota. *Environ. Health Perspect.* 104:394–399.

Gehring, U., Cyrys, J., Sedlmeir, G., Brunekreef, B., Bellander, T., Fischer, P., Bauer, C. P., Reinhardt, D., Wichmann, H. E., and Heinrich, J. 2002. Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur. Respir. J.* 19:690–698.

Gemmel, A., Tavares, M., Alperin, S., Soncini, J., Daniel, D., Dunn, J., Crawford, S., Braveman, N., Clarkson, T. W., McKinlay, S., and Bellinger, D. C. 2002. Blood lead level and dental caries in school-age children. *Environ. Health Perspect.* 110:A625–A630.

George, L., Granath, F., Johansson, A. L., Anneren, G., and Cnattingius, S. 2006. Environmental tobacco smoke and risk of spontaneous abortion. *Epidemiology* 17:500–505.

Geschwind, S. A., Stolwijk, J. A., Bracken, M., Fitzgerald, E., Stark, A., Olsen, C., and Melius, J. 1992. Risk of congenital malformations associated with proximity to hazardous waste sites. *Am. J. Epidemiol.* 135:1197–1207.

Gilboa, S. M., Mendola, P., Olshan, A. F., Langlois, P. H., Savitz, D. A., Loomis, D., Herring, A. H., and Fixler, D. E. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. *Am. J. Epidemiol.* 162:238–252.

Gilbreath, S., and Kass, P. H. 2006a. Fetal and neonatal deaths and congenital anomalies associated with open dumpsites in Alaska Native villages. *Int. J. Circumpolar Health* 65:133–147.

Gilbreath, S., and Kass, P. H. 2006b. Adverse birth outcomes associated with open dumpsites in Alaska Native Villages. *Am. J. Epidemiol.* 164:518–528.

Gladen, B. C., Klebanoff, M. A., Hediger, M. L., Katz, S. H., Barr, D. B., Davis, M. D., and Longnecker, M. P. 2004. Prenatal DDT exposure in relation to anthropometric and pubertal measures in adolescent males. *Environ. Health Perspect.* 112:1761–1767.

Gladen, B. C., Ragan, N. B., and Rogan, W. J. 2000. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J. Pediatr.* 136:490–496.

Gladen, B. C., and Rogan, W. J. 1991. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. *J. Pediatr.* 119:58–63.

Gladen, B. C., Rogan, W. J., Hardy, P., Thullen, J., Tingelstad, J., and Tully, M. 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. *J. Pediatr.* 113:991–995.

Gladen, B. C., Shkiryak-Nyzhnyk, Z. A., Chyslovska, N., Zadorozhnaja, T. D., and Little, R. E. 2003. Persistent organochlorine compounds and birth weight. *Ann. Epidemiol.* 13:151–157.

Glinianaia, S. V., Rankin, J., Bell, R., Pless-Mulloli, T., and Howel, D. 2004a. Particulate air pollution and fetal health: A systematic review of the epidemiologic evidence. *Epidemiology* 15:36–45.

Glinianaia, S. V., Rankin, J., Bell, R., Pless-Mulloli, T., and Howel, D. 2004b. Does particulate air pollution contribute to infant death? A systematic review. *Environ. Health Perspect.* 112:1365–1371.

Gocmen, A., Peters, H. A., Cripps, D. J., Bryan, G. T., and Morris, C. R. 1989. Hexachlorobenzene episode in Turkey. *Biomed. Environ. Sci.* 2:36–43.

Goel, P., Radotra, A., Singh, I., Aggarwal, A., and Dua, D. 2004. Effects of passive smoking on outcome in pregnancy. *J. Postgrad. Med.* 50:12–16.

Gold, E., Gordis, L., Tonascia, J., and Szklo, M. 1979. Risk factors for brain tumors in children. *Am. J. Epidemiol.* 109:309–319.

Goldberg, M. S., Goulet, L., Riberdy, H., and Bonvalot, Y. 1995. Low birth weight and preterm births among infants born to women living near a municipal solid waste landfill site in Montreal, Quebec. *Environ. Res.* 69:37–50.

Golding, J., Pembrey, M., and Jones, R. 2001. ALSPAC—The Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr. Perinat. Epidemiol.* 15:74–87.

Golub, M. S., Macintosh, M. S., and Baumrind, N. 1998. Developmental and reproductive toxicity of inorganic arsenic: Animal studies and human concerns. *J. Toxicol. Environ. Health B* 1:199–241.

Gomaa, A., Hu, H., Bellinger, D., Schwartz, J., Tsaih, S. W., Gonzalez-Cossio, T., Schnaas, L., Peterson, K., Aro, A., and Hernandez-Avila, M. 2002. Maternal bone lead as an independent risk factor for fetal neurotoxicity: A prospective study. *Pediatrics* 110:110–118.

Gonzalez-Cossio, T., Peterson, K. E., Sanin, L. H., Fishbein, E., Palazuelos, E., Aro, A., Hernandez-Avila, M., and Hu, H. 1997. Decrease in birth weight in relation to maternal bone lead burden. *Pediatrics* 100:856–862.

Gotelli, C. A., Astolfi, E., Cox, C., Cernichiari, E., and Clarkson, T. W. 1985. Early biochemical effects of an organic mercury fungicide on infants: "Dose makes the poison." *Science* 227:638–640.

Gouveia, N., Bremner, S. A., and Novaes, H. M. 2004. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. *J. Epidemiol. Commun. Health* 58:11–17.

Goyer, R. A. 1990. Lead toxicity: From overt to subclinical to subtle health effects. *Environ. Health Perspect.* 86:177–181.

Grandjean, P., Bjerve, K. S., Weihe, P., and Steuerwald, U. 2001. Birthweight in a fishing community: significance of essential fatty acids and marine food contaminants. *Int. J. Epidemiol.* 30:1272–1278.

Grandjean, P., Budtz-Jorgensen, E., Steuerwald, U., Heinzow, B., Needham, L. L., Jorgensen, P. J., and Weihe, P. 2003. Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. *FASEB J.* 17:699–701.

Grandjean, P., Budtz-Jorgensen, E., White, R. F., Jorgensen, P. J., Weihe, P., Debes, F., and Keiding, N. 1999. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. *Am. J. Epidemiol.* 150:301–305.

Grandjean, P., Weihe, P., Burse, V. W., Needham, L. L., Storr-Hansen, E., Heinzow, B., Debes, F., Murata, K., Simonsen, H., Ellefsen, P., Budtz-Jorgensen, E., Keiding, N., and White, R. F. 2001. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol. Teratol.* 23:305–317.

Grandjean, P., Weihe, P., and White, R. F. 1995. Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicology* 16:27–33.

Grandjean, P., Weihe, P., White, R. F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R., and Jorgensen, P. J. 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol. Teratol.* 19:417–428.

Grandjean, P., White, R. F., Nielsen, A., Cleary, D., and de Oliveira Santos, E. C. 1999. Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ. Health Perspect.* 107:587–591.

Grandjean, P., White, R. F., Sullivan, K., Debes, F., Murata, K., Otto, D. A., and Weihe, P. 2001. Impact of contrast sensitivity performance on visually presented neurobehavioral tests in mercury-exposed children. *Neurotoxicol. Teratol.* 23:141–146.

Grandjean, P., White, R. F., Weihe, P., and Jorgensen, P. J. 2003. Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood. *Ambul. Pediatr.* 3:18–23.

Graves, C. G., Matanoski, G. M., and Tardiff, R. G. 2001. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products: A critical review. *Regul. Toxicol. Pharmacol.* 34:103–124.

Gray, K. A., Klebanoff, M. A., Brock, J. W., Zhou, H., Darden, R., Needham, L., and Longnecker, M. P. 2005. In utero exposure to background levels of polychlorinated biphenyls and cognitive functioning among school-age children. *Am. J. Epidemiol.* 162:17–26.

Gray, L. E., Ostby, J., Furr, J., Wolf, C. J., Lambright, C., Parks, L., Veeramachaneni, D. N., Wilson, V., Price, M., Hotchkiss, A., Orlando, E., and Guillette, L. 2001. Effects of environmental antiandrogens on reproductive development in experimental animals. *Hum. Reprod. Update* 7:248–264.

Greene, T., and Ernhart, C. B. 1991. Prenatal and preschool age lead exposure: Relationship with size. *Neurotoxicol. Teratol.* 13:417–427.

Gresie-Brusin, D. F., Kielkowski, D., Baker, A., Channa, K., and Rees, D. 2006. Occupational exposure to ethylene oxide during pregnancy and association with adverse reproductive outcomes. *Int. Arch. Occup. Environ. Health* [Epub Ahead of Print] .

Guo, Y. L., Chen, Y. C., Yu, M. L., and Hsu, C. C. 1994. Early development of Yu-Cheng children born seven to twelve years after the Taiwan PCB outbreak. *Chemosphere* 29:2395–404.

Guo, Y. L., Yu, M. L., Hsu, C. C., Rogan, W. J. 1999. Chlorance, goiter, arthritis, and anemia after pslychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. *Environ. Health Perspect. 107*:715–719.

Guo, Y. L., Lambert, G. H., and Hsu, C. C. 1995. Growth abnormalities in the population exposed in utero and early postnatally to polychlorinated biphenyls and dibenzofurans. *Environ. Health Perspect.* 103(Suppl. 6):117–122.

Guo, Y. L., Lambert, G. H., Hsu, C. C., and Hsu, M. M. 2004. Yucheng: Health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. *Int. Arch. Occup. Environ. Health* 77:153–158.

Guo, Y. L., Lin, C. J., Yao, W. J., Ryan, J. J., and Hsu, C. C. 1994. Musculoskeletal changes in children prenatally exposed to polychlorinated biphenyls and related compounds (Yu-Cheng children). *J. Toxicol. Environ. Health* 41:83–93.

Ha, E., Cho, S. I., Chen, D., Chen, C., Ryan, L., Smith, T. J., Xu, X., and Christiani, D. C. 2002. Parental exposure to organic solvents and reduced birth weight. *Arch. Environ. Health* 57:207–214.

Halfon, N., and Newacheck, P. W. 1999. Prevalence and impact of parent-reported disabling mental health conditions among U.S. children. *J. Am. Acad. Child Adolesc. Psychiatry* 38:600–609.

Hamajima, N., Hirose, K., Tajima, K., Rohan, T., Calle, E. E., Heath, C. W. Jr, Coates, R. J., Liff, J. M., Talamini, R., Chantarakul, N., Koetsawang, S., Rachawat, D., Morabia, A., Schuman, L., Stewart, W., Szklo, M., Bain, C., Schofield, F., Siskind, V., Band, P., Coldman, A. J., Gallagher, R. P., Hislop, T. G., Yang, P., Kolonel, L. M., Nomura, A. M., Hu, J., Johnson, K. C., Mao, Y., De Sanjose, S., Lee, N., Marchbanks, P., Ory, H. W., Peterson, H. B., Wilson, H. G., Wingo, P. A., Ebeling, K., Kunde, D., Nishan, P., Hopper, J. L., Colditz, G., Gajalanski, V., Martin, N., Pardthaisong, T., Silpisornkosol, S., Theetranont, C., Boosiri, B., Chutivongse, S., Jimakorn, P., Virutamasen, P., Wongsrichanalai, C., Ewertz, M., Adami, H. O., Bergkvist, L., Magnusson, C., Persson, I., Chang-Claude, J., Paul, C., Skegg, D. C., Spears, G. F., Boyle, P., Evstifeeva, T., Daling, J. R., Hutchinson, W. B., Malone, K., Noonan, E. A., Stanford, J. L., Thomas, D. B., Weiss, N. S., White, E., Andrieu, N., Bremond, A., Clavel, F., Gairard, B., Lansac, J., Piana, L., Renaud, R., Izquierdo, A., Viladiu, P., Cuevas, H. R., Ontiveros, P., Palet, A., Salazar, S. B., Aristizabel, N., Cuadros, A., Tryggvadottir, L., Tulinius, H., Bachelot, A., Le, M. G., Peto, J., Franceschi, S., Lubin, F., Modan, B., Ron, E., Wax, Y., Friedman, G. D., Hiatt, R. A., Levi, F., Bishop, T., Kosmelj, K., Primic-Zakelj, M., Ravnihar, B., Stare, J., Beeson, W. L., Fraser, G., Bullbrook, R. D., Cuzick, J., Duffy, S. W., Fentiman, I. S., Hayward, J. L., Wang, D. Y., McMichael, A. J., McPherson, K., Hanson, R. L., Leske, M. C., Mahoney, M. C., Nasca, P. C.,

Varma, A. O., Weinstein, A. L., Moller, T. R., Olsson, H., Ranstam, J., Goldbohm, R. A., van den Brandt, P. A., Apelo, R. A., Baens, J., de la Cruz, J. R., Javier, B., Lacaya, L. B., Ngelangel, C. A., La Vecchia, C., Negri, E., Marubini, E., Ferraroni, M., Gerber, M., Richardson, S., Segala, C., Gatei, D., Kenya, P., Kungu, A., Mati, J. G., Brinton, L. A., Hoover, R., Schairer, C., Spirtas, R., Lee, H. P., Rookus, M. A., van Leeuwen, F. E., Schoenberg, J. A., McCredie, M., Gammon, M. D., Clarke, E. A., Jones, L., Neil, A., Vessey, M., Yeates, D., Appleby, P., Banks, E., Beral, V., Bull, D., Crossley, B., Goodill, A., Green, J., Hermon, C., Key, T., Langston, N., Lewis, C., Reeves, G., Collins, R., Doll, R., Peto, R., Mabuchi, K., Preston, D., Hannaford, P., Kay, C., Rosero-Bixby, L., Gao, Y. T., Jin, F., Yuan, J. M., Wei, H. Y., Yun, T., Zhiheng, C., Berry, G., Cooper Booth, J., Jelihovsky, T., MacLennan, R., Shearman, R., Wang, Q. S., Baines, C. J., Miller, A. B., Wall, C., Lund, E., Stalsberg, H., Shu, X. O., Zheng, W., Katsouyanni, K., Trichopoulou, A., Trichopoulos, D., Dabancens, A., Martinez, L., Molina, R., Salas, O., Alexander, F. E., Anderson, K., Folsom, A. R., Hulka, B. S., Bernstein, L., Enger, S., Haile, R. W., Paganini-Hill, A., Pike, M. C., Ross, R. K., Ursin, G., Yu, M. C., Longnecker, M. P., Newcomb, P., Bergkvist, L., Kalache, A., Farley, T. M., Holck, S., and Meirik, O. 2002. Alcohol, tobacco and breast cancer—Collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer* 87:1234–45.

Hanke, W., Sobala, W., and Kalinka, J. 2004. Environmental tobacco smoke exposure among pregnant women: Impact on fetal biometry at 20–24 weeks of gestation and newborn child's birth weight. *Int. Arch. Occup. Environ. Health* 77:47–52.

Hansen, C., Neller, A., Williams, G., and Simpson, R. 2006. Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. *BJOG* 113:935–941.

Hansen, E. S., Hasle, H., and Lander, F. 1992. A cohort study on cancer incidence among Danish gardeners. *Am. J. Ind. Med.* 21:651–660.

Hansen, O. N., Trillingsgaard, A., Beese, I., Lyngbye, T., and Grandjean, P. 1989. A neuropsychological study of children with elevated dentine lead level: assessment of the effect of lead in different socio-economic groups. *Neurotoxicol. Teratol.* 11:205–213.

Harada M. 1977. Congenital Minimata disease. In *Minimata disease: Methylmercury poisoning in Minimata and Niigata, Japan*, eds. R. Tsubaki and K. Irukayama, pp. 209–239. New York: Elsevier Scientific.

Harada, M. 1978. Congenital Minamata disease: Intrauterine methylmercury poisoning. *Teratology* 18:285–288.

Harada, M. 1995. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit. Rev. Toxicol.* 25:1–24.

Harada, M., Akagi, H., Tsuda, T., Kizaki, T., and Ohno, H. 1999. Methylmercury level in umbilical cords from patients with congenital Minamata disease. *Sci. Total Environ.* 234:59–62.

Hardell, L., Bavel, B., Lindstrom, G., Eriksson, M., and Carlberg, M. 2006. In utero exposure to persistent organic pollutants in relation to testicular cancer risk. *Int. J. Androl.* 29:228–234.

Hardell, L., van Bavel, B., Lindstrom, G., Carlberg, M., Dreifaldt, A. C., Wijkstrom, H., Starkhammar, H., Eriksson, M., Hallquist, A., and Kolmert, T. 2003. Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. *Environ. Health Perspect.* 111:930–934.

Harrison, R. M., Leung, P. L., Somervaille, L., Smith, R., and Gilman, E. 1999. Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. *Occup. Environ. Med.* 56:774–780.

Harvey, P. G., Hamlin, M. W., Kumar, R., Morgan, G., and Spurgeon, A. 1988. Relationships between blood lead, behavior, psychometric and neuropsychological test performance in young children. *Br. J. Dev. Psychol.* 6:145–156.

Hassan, M. A., and Killick, S. R. 2004. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil. Steril.* 81:384–392.

He, P., Liu, D. H., and Zhang, G. Q. 1994. Effects of high-level-manganese sewage irrigation on children's neurobehavior. *Chung Hua Yu Fang I Hsueh Tsa Chih* 28:216–218.

Heacock, H., Hertzman, C., Demers, P. A., Gallagher, R., Hogg, R. S., Teschke, K., Hershler, R., Bajdik, C. D., Dimich-Ward, H., Marion, S. A., Ostry, A., and Kelly, S. 2000. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. *Environ. Health Perspect.* 108:499–503.

Health Canada. 2003. *Canadian perinatal health report, 2003*. Ottawa: Minister of Public Works and Government Services Canada.

Heinrich, J., Hoelscher, B., Frye, C., Meyer, I., Pitz, M., Cyrys, J., Wjst, M., Neas, L., and Wichmann, H. E. 2002. Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology* 13:394–401.

Hemminki, K., Kyyronen, P., and Lindbohm, M. L. 1985. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J. Epidemiol. Commun. Health* 39:141–147.

Herrstrom, P., Schutz, A., Raihle, G., Holthuis, N., Hogstedt, B., and Rastam, L. 1995. Dental amalgam, low-dose exposure to mercury, and urinary proteins in young Swedish men. *Arch. Environ. Health* 50:103–107.

Hertz-Picciotto, I. 2000 . The evidence that lead increases the risk for spontaneous abortion. *Am. J. Ind. Med.* 38:300–309.

Hertz-Picciotto, I., Charles, M. J., James, R. A., Keller, J. A., Willman, E., and Teplin, S. 2005. In utero polychlorinated biphenyl exposures in relation to fetal and early childhood growth. *Epidemiology* 16:648–656.

Hery, M., Hecht, G., Gerber, J. M., Gendre, J. C., Hubert, G., and Rebuffaud, J. 1995. Exposure to chloramines in the atmosphere of indoor swimming pools. *Ann. Occup. Hyg.* 39:427–439.

Hewitt, J. B., and Tellier, L. 1998. Risk of adverse outcomes in pregnant women exposed to solvents. *J. Obstet. Gynecol. Neonatal Nurs.* 27:521–531.

Hinckley, A. F., Bachand, A. M., and Reif, J. S. 2005. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environ. Health Perspect.* 113:1808–1813.

Hing, E., Cherry, D. K., and Woodwell, D. A. 2006. National Ambulatory Medical Care Survey: 2004 summary. *Adv. Data* :1–33.

Hjollund, N. H., Bonde, J. P., Jensen, T. K., Henriksen, T. B., Andersson, A. M., Kolstad, H. A., Ernst, E., Giwercman, A., Skakkebaek, N. E., and Olsen, J. 2000. Male-mediated spontaneous abortion among spouses of stainless steel welders. *Scand. J. Work Environ. Health* 26:187–192.

Hjollund, N. H., Bonde, J. P., Jensen, T. K., Henriksen, T. B., Kolstad, H. A., Ernst, E., Giwercman, A., Pritzl, G., Skakkebaek, N. E., and Olsen, J. 1998. A follow-up study of male exposure to welding and time to pregnancy. *Reprod. Toxicol.* 12:29–37.

Hoar Zahm, S., Blair, A., Holmes, F. F., Boysen, C. D., and Robel, R. J. 1988. A case-referent study of soft-tissue sarcoma and Hodgkin's disease. Farming and insecticide use. *Scand. J. Work Environ. Health* 14:224–230.

Holly, E. A., Aston, D. A., Ahn, D. K., and Kristiansen, J. J. 1992. Ewing's bone sarcoma, paternal occupational exposure, and other factors. *Am. J. Epidemiol.* 135:122–129.

Holly, E. A., Bracci, P. M., Mueller, B. A., and Preston-Martin, S. 1998. Farm and animal exposures and pediatric brain tumors: Results from the United States West Coast Childhood Brain Tumor Study. *Cancer Epidemiol. Biomarkers Prev.* 7:797–802.

Hong, Y. C., Lee, K. H., Son, B. K., Ha, E. H., Moon, H. S., and Ha, M. 2003. Effects of the GSTM1 and GSTT1 polymorphisms on the relationship between maternal exposure to environmental tobacco smoke and neonatal birth weight. *J. Occup. Environ. Med.* 45:492–498.

Hopenhayn, C., Ferreccio, C., Browning, S. R., Huang, B., Peralta, C., Gibb, H., and Hertz-Picciotto, I. 2003. Arsenic exposure from drinking water and birth weight. *Epidemiology* 14:593–602.

Hopenhayn-Rich, C., Browning, S. R., Hertz-Picciotto, I., Ferreccio, C., Peralta, C., and Gibb, H. 2000. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environ. Health Perspect.* 108:667–673.

Hoppin, J. A., Tolbert, P. E., Flanders, W. D., Zhang, R. H., Daniels, D. S., Ragsdale, B. D., and Brann, E. A. 1999 . Occupational risk factors for sarcoma subtypes. *Epidemiology* 10:300–306.

Hosie, S., Loff, S., Witt, K., Niessen, K., and Waag, K. L. 2000. Is there a correlation between organochlorine compounds and undescended testes? *Eur. J. Pediatr. Surg.* 10:304–309.

Howe, G. R., Burch, J. D., Chiarelli, A. M., Risch, H. A., and Choi, B. C. 1989. An exploratory case-control study of brain tumors in children. *Cancer Res.* 49:4349–4352.

Hruba, D., and Kachlik, P. 2000. Influence of maternal active and passive smoking during pregnancy on birthweight in newborns. *Cent. Eur. J. Public Health* 8:249–252.

Hsu, M. M., Mak, C. P., and Hsu, C. C. 1995. Follow-up of skin manifestations in Yu-Cheng children. *Br. J. Dermatol.* 132:427–32.

Hu, H. 1991. Knowledge of diagnosis and reproductive history among survivors of childhood plumbism. *Am. J. Public Health* 81:1070–1072.

Hu, H., Tellez-Rojo, M. M., Bellinger, D., Smith, D., Ettinger, A. S., Lamadrid-Figueroa, H., Schwartz, J., Schnaas, L., Mercado-Garcia, A., and Hernandez-Avila, M. 2006. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. *Environ. Health Perspect.* 114 :1730–1735.

Huel, G., Boudene, C., and Ibrahim, M. A. 1981. Cadmium and lead content of maternal and newborn hair: relationship to parity, birth weight, and hypertension. *Arch. Environ. Health* 36:221–227.

Huisman, M., Koopman-Esseboom, C., Fidler, V., Hadders-Algra, M., van der Paauw, C. G., Tuinstra, L. G., Weisglas-Kuperus, N., Sauer, P. J., Touwen, B. C., and Boersma, E. R. 1995a. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum. Dev.* 41:111–127.

Huisman, M., Koopman-Esseboom, C., Lanting, C. I., van der Paauw, C. G., Tuinstra, L. G., Fidler, V., Weisglas-Kuperus, N., Sauer, P. J., Boersma, E. R., and Touwen, B. C. 1995b. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. *Early Hum. Dev.* 43:165–176.

Hull, M. G., North, K., Taylor, H., Farrow, A., and Ford, W. C. 2000. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. *Fertil. Steril.* 74:725–733.

Hum, L., Kreiger, N., and Finkelstein, M. M. 1998. The relationship between parental occupation and bone cancer risk in offspring. *Int. J. Epidemiol.* 27:766–771.

Hunt, P. A., Koehler, K. E., Susiarjo, M., Hodges, C. A., Ilagan, A., Voigt, R. C., Thomas, S., Thomas, B. F., and Hassold, T. J. 2003. Bisphenol A exposure causes meiotic aneuploidy in the female mouse. *Curr. Biol.* 13:546–553.

Huynh, M., Woodruff, T. J., Parker, J. D., and Schoendorf, K. C. 2006. Relationships between air pollution and preterm birth in California. *Paediatr. Perinat. Epidemiol.* 20:454–461.

Hwang, B. F., and Jaakkola, J. J. 2003. Water chlorination and birth defects: A systematic review and meta-analysis. *Arch. Environ. Health* 58:83–91.

Hwang, B. F., Magnus, P., and Jaakkola, J. J. 2002. Risk of specific birth defects in relation to chlorination and the amount of natural organic matter in the water supply. *Am. J. Epidemiol.* 156:374–382.

Idrovo, A. J., Sanin, L. H., Cole, D., Chavarro, J., Caceres, H., Narvaez, J., and Restrepo, M. 2005. Time to first pregnancy among women working in agricultural production. *Int. Arch. Occup. Environ. Health* 78:493–500.

Ihrig, M. M., Shalat, S. L., and Baynes, C. 1998. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. *Epidemiology* 9:290–294.

Infante-Rivard, C., Amre, D., and Sinnett, D. 2002. GSTT1 and CYP2E1 polymorphisms and trihalomethanes in drinking water: Effect on childhood leukemia. *Environ. Health Perspect.* 110:591–593.

Infante-Rivard, C., Krajinovic, M., Labuda, D., and Sinnett, D. 2000. Parental smoking, CYP1A1 genetic polymorphisms and childhood leukemia (Quebec, Canada). *Cancer Causes Control* 11:547–553.

Infante-Rivard, C., Labuda, D., Krajinovic, M., and Sinnett, D. 1999. Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology* 10:481–487.

Infante-Rivard, C., Mur, P., Armstrong, B., Alvarez-Dardet, C., and Bolumar, F. 1991. Acute lymphoblastic leukaemia among Spanish children and mothers' occupation: A case-control study. *J. Epidemiol. Commun. Health* 45:11–15.

Infante-Rivard, C., Olson, E., Jacques, L., and Ayotte, P. 2001. Drinking water contaminants and childhood leukemia. *Epidemiology* 12:13–19.

Infante-Rivard, C., Siemiatycki, J., Lakhani, R., and Nadon, L. 2005. Maternal exposure to occupational solvents and childhood leukemia. *Environ. Health Perspect.* 113:787–792.

Infante-Rivard, C., and Sinnett, D. 1999. Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia. *Lancet* 354:1819.

Infante-Rivard, C., and Weichenthal, S. 2006. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *J. Toxicol. Environ. Health B* 10:81–99.

International Agency for Research on Cancer. 1989. *IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 46. Diesel and gasoline engine exhausts and some nitroarenes*. Lyon, France.

International Clearinghouse for Birth Defect Monitoring Systems. 2000. *Annual report 2000*. Rome: International Centre for Birth Defects.

Irgens, A., Kruger, K., Skorve, A. H., and Irgens, L. M. 1998. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *Am. J. Ind. Med.* 34:431–437.

Irgens, A., Kruger, K., Skorve, A. H., and Irgens, L. M. 2000. Birth defects and paternal occupational exposure. Hypotheses tested in a record linkage based dataset. *Acta Obstet. Gynecol. Scand.* 79:465–470.

Jaakkola, J. J., and Jaakkola, M. S. 2002. Effects of environmental tobacco smoke on the respiratory health of children. *Scand. J. Work Environ. Health* 28(Suppl. 2):71–83.

Jaakkola, J. J., Jaakkola, N., and Zahlsen, K. 2001a. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. *Environ. Health Perspect.* 109:557–561.

Jaakkola, J. J., Magnus, P., Skrondal, A., Hwang, B. F., Becher, G., and Dybing, E. 2001b. Foetal growth and duration of gestation relative to water chlorination. *Occup. Environ. Med.* 58:437–442.

Jackson, L. W., Correa-Villasenor, A., Lees, P. S., Dominici, F., Stewart, P. A., Breysse, P. N., and Matanoski, G. 2004. Parental lead exposure and total anomalous pulmonary venous return. *Birth Defects Res. A Clin. Mol. Teratol.* 70:185–193.

Jacobson, J. L., and Jacobson, S. W. 1996a. Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): The Michigan and North Carolina cohort studies. *Toxicol. Ind. Health* 12:435–445.

Jacobson, J. L., and Jacobson, S. W. 1996b. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N. Engl. J. Med.* 335:783–789.

Jacobson, J. L., and Jacobson, S. W. 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. *J. Pediatr.* 143:780–788.

Jacobson, J. L., Jacobson, S. W., and Humphrey, H. E. 1990a. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J. Pediatr.* 116:38–45.

Jacobson, J. L., Jacobson, S. W., and Humphrey, H. E. 1990b. Effects of exposure to PCBs and related compounds on growth and activity in children. *Neurotoxicol. Teratol.* 12:319–326.

Jacobson, S. W., Fein, G. G., Jacobson, J. L., Schwartz, P. M., and Dowler, J. K. 1985. The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev.* 56:853–860.

Jan, J., and Vrbic, V. 2000. Polychlorinated biphenyls cause developmental enamel defects in children. *Caries Res.* 34:469–473.

Jarrell, J., Gocmen, A., Foster, W., Brant, R., Chan, S., and Sevcik, M. 1998. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s. *Reprod. Toxicol.* 12:469–476.

Jarup, L., Briggs, D., de Hoogh, C., Morris, S., Hurt, C., Lewin, A., Maitland, I., Richardson, S., Wakefield, J., and Elliott, P. 2002. Cancer risks in populations living near landfill sites in Great Britain. *Br. J. Cancer* 86:1732–1736.

Jedrychowski, W., Bendkowska, I., Flak, E., Penar, A., Jacek, R., Kaim, I., Spengler, J. D., Camann, D., and Perera, F. P. 2004. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: An epidemiologic prospective cohort study in Poland. *Environ. Health Perspect.* 112:1398–1402.

Jedrychowski, W., Jankowski, J., Flak, E., Skarupa, A., Mroz, E., Sochacka-Tatara, E., Lisowska-Miszczyk, I., Szpanowska-Wohn, A., Rauh, V., Skolicki, Z., Kaim, I., and Perera, F. 2006. Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: Epidemiologic cohort study in Poland. *Ann. Epidemiol.* 16:439–447.

Jelliffe-Pawlowski, L. L., Miles, S. Q., Courtney, J. G., Materna, B., and Charlton, V. 2006. Effect of magnitude and timing of maternal pregnancy blood lead (Pb) levels on birth outcomes. *J. Perinatol.* 26:154–162.

Joffe, M., Bisanti, L., Apostoli, P., Kiss, P., Dale, A., Roeleveld, N., Lindbohm, M. L., Sallmen, M., Vanhoorne, M., and Bonde, J. P. 2003. Time to pregnancy and occupational lead exposure. *Occup. Environ. Med.* 60:752–758.

Joffe, M., Key, J., Best, N., Keiding, N., Scheike, T., and Jensen, T. K. 2005. Studying time to pregnancy by use of a retrospective design. *Am. J. Epidemiol.* 162:115–124.

Johnson, B. L., and DeRosa, C. T. 1995. Chemical mixtures released from hazardous waste sites: implications for health risk assessment. *Toxicology* 105:145–156.

Johnson, C. C., Annegers, J. F., Frankowski, R. F., Spitz, M. R., and Buffler, P. A. 1987. Childhood nervous system tumors—An evaluation of the association with paternal occupational exposure to hydrocarbons. *Am. J. Epidemiol.* 126:605–613.

Johnson, C. C., Feingold, M., and Tilley, B. 1990. A meta-analysis of exposure to phenoxy acid herbicides and chlorophenols in relation to risk of soft tissue sarcoma. *Int. Arch. Occup. Environ. Health* 62:513–20.

Kafourou, A., Touloumi, G., Makropoulos, V., Loutradi, A., Papanagiotou, A., and Hatzakis, A. 1997. Effects of lead on the somatic growth of children. *Arch. Environ. Health* 52:377–383.

Kaiser, R., Romieu, I., Medina, S., Schwartz, J., Krzyzanowski, M., and Kunzli, N. 2004. Air pollution attributable postneonatal infant mortality in U.S. metropolitan areas: A risk assessment study. *Environ. Health* 3:1–6.

Kallen, B. A., and Robert, E. 2000. Drinking water chlorination and delivery outcome-a registry-based study in Sweden. *Reprod. Toxicol.* 14:303–309.

Karmaus, W., Asakevich, S., Indurkhya, A., Witten, J., and Kruse, H. 2002. Childhood growth and exposure to dichlorodiphenyl dichloroethene and polychlorinated biphenyls. *J. Pediatr.* 140:33–39.

Karmaus, W., Davis, S., Chen, Q., Kuehr, J., and Kruse, H. 2003. Atopic manifestations, breast-feeding protection and the adverse effect of DDE. *Paediatr. Perinat. Epidemiol.* 17:212–220.

Karmaus, W., Kuehr, J., and Kruse, H. 2001. Infections and atopic disorders in childhood and organochlorine exposure. *Arch. Environ. Health* 56:485–492.

Karmaus, W., and Wolf, N. 1995. Reduced birthweight and length in the offspring of females exposed to PCDFs, PCP, and lindane. *Environ. Health Perspect.* 103:1120–1125.

Karmaus, W., and Zhu, X. 2004. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: A cohort study. *Environ. Health* 3:1–9.

Karpati, A. M., Perrin, M. C., Matte, T., Leighton, J., Schwartz, J., and Barr, R. G. 2004. Pesticide spraying for West Nile virus control and emergency department asthma visits in New York City, 2000. *Environ. Health Perspect.* 112:1183–1187.

Kasim, K., Levallois, P., Abdous, B., Auger, P., and Johnson, K. C. 2005. Environmental tobacco smoke and risk of adult leukemia. *Epidemiology* 16:672–680.

keOliveira, L. M., Stein, N., Sanseverino, M. T., Vargas, V. M., Fachel, J. M., and Schuler, L. 2002. Reproductive outcomes in an area adjacent to a petrochemical plant in southern Brazil. *Rev. Saude Publica* 36:81–87.

Kerr, M. A., Nasca, P. C., Mundt, K. A., Michalek, A. M., Baptiste, M. S., and Mahoney, M. C. 2000. Parental occupational exposures and risk of neuroblastoma: A case-control study (United States). *Cancer Causes Control* 11:635–643.

Khanjani, N., and Sim, M. R. 2006. Reproductive outcomes of maternal contamination with cyclodiene insecticides, hexachlorobenzene and beta-benzene hexachloride. *Sci. Total Environ.* 368:557–564.

Khanjani, N., and Sim, M. R. 2007. Maternal contamination with PCBs and reproductive outcomes in an Australian population. *J. Expos. Sci. Environ. Epidemiol.* 17:191–195.

Kharrazi, M., DeLorenze, G. N., Kaufman, F. L., Eskenazi, B., Bernert, J. T., Jr., Graham, S., Pearl, M., and Pirkle, J. 2004. Environmental tobacco smoke and pregnancy outcome. *Epidemiology* 15:660–670.

Kharrazi, M., Von Behren, J., Smith, M., Lomas, T., Armstrong, M., Broadwin, R., Blake, E., McLaughlin, B., Worstell, G., and Goldman, L. 1997. A community-based study of adverse pregnancy outcomes near a large hazardous waste landfill in California. *Toxicol. Ind. Health* 13:299–310.

Khattak, S., K-Moghtader, G., McMartin, K., Barrera, M., Kennedy, D., and Koren, G. 1999. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *J. Am. Med. Assoc.* 281:1106–1109.

King, W. D., Dodds, L., and Allen, A. C. 2000. Relation between stillbirth and specific chlorination by-products in public water supplies. *Environ. Health Perspect.* 108:883–886.

Kogevinas, M., Becher, H., Benn, T., Bertazzi, P. A., Boffetta, P., Bueno-de-Mesquita, H. B., Coggon, D., Colin, D., Flesch-Janys, D., Fingerhut, M., Green, L., Kauppinen, T., Littorin, M., Lynge, E., Mathews, J. D., Neuberger, M., Pearce, N., and Saracci, R. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study . *Am. J. Epidemiol.* 145:1061–1075.

Koller, K., Brown, T., Spurgeon, A., and Levy, L. 2004. Recent developments in low-level lead exposure and intellectual impairment in children. *Environ. Health Perspect.* 112:987–994.

Kolstad, H. A., Bisanti, L., Roeleveld, N., Baldi, R., Bonde, J. P., and Joffe, M. 2000. Time to pregnancy among male workers of the reinforced plastics industry in Denmark, Italy and The Netherlands. ASCLEPIOS. *Scand. J. Work Environ. Health* 26:353–358.

Komaki, H., Maisawa, S., Sugai, K., Kobayashi, Y., and Hashimoto, T. 1999. Tremor and seizures associated with chronic manganese intoxication. *Brain Dev.* 21:122–124.

Komulainen, H. 2004. Experimental cancer studies of chlorinated by-products. *Toxicology* 198:239–248.

Koopman-Esseboom, C., Weisglas-Kuperus, N., de Ridder, M. A., Van der Paauw, C. G., Tuinstra, L. G., and Sauer, P. J. 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 97:700–706.

Korrick, S. A., Chen, C., Damokosh, A. I., Ni, J., Liu, X., Cho, S. I., Altshul, L., Ryan, L., and Xu, X. 2001. Association of DDT with spontaneous abortion: A case-control study. *Ann. Epidemiol.* 11:491–496.

Kramer, M. D., Lynch, C. F., Isacson, P., and Hanson, J. W. 1992. The association of waterborne chloroform with intrauterine growth retardation. *Epidemiology* 3:407–413.

Krewski, D., Hogan, V., Turner, M. C., Zeman, P., McDowell, I., Edwards, N., and Losos, J. 2007. An integrated framework for risk management and population health. *Hum. Ecol. Risk Assessment 13:*1288–1312.

Kristensen, P., Andersen, A., Irgens, L. M., Bye, A. S., and Sundheim, L. 1996a. Cancer in offspring of parents engaged in agricultural activities in Norway: Incidence and risk factors in the farm environment. *Int. J. Cancer* 65:39–50.

Kristensen, P., Andersen, A., Irgens, L. M., Bye, A. S., and Vagstad, N. 1996b. Testicular cancer and parental use of fertilizers in agriculture. *Cancer Epidemiol. Biomarkers Prev.* 5:3–9.

Kristensen, P., Irgens, L. M., Andersen, A., Bye, A. S., and Sundheim, L. 1997a. Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967–1991. *Am. J. Epidemiol.* 146:329–338.

Kristensen, P., Irgens, L. M., Andersen, A., Bye, A. S., and Sundheim, L. 1997b. Birth defects among offspring of Norwegian farmers, 1967–1991. *Epidemiology* 8:537–544.

Kristensen, P., Irgens, L. M., Daltveit, A. K., and Andersen, A. 1993. Perinatal outcome among children of men exposed to lead and organic solvents in the printing industry. *Am. J. Epidemiol.* 137:134–144.

Kuhnert, B. R., Kuhnert, P. M., Debanne, S., and Williams, T. G. 1987. The relationship between cadmium, zinc, and birth weight in pregnant women who smoke. *Am. J. Obstet. Gynecol.* 157:1247–1251.

Kuijten, R. R., Bunin, G. R., Nass, C. C., and Meadows, A. T. 1992. Parental occupation and childhood astrocytoma: results of a case-control study. *Cancer Res.* 52:782–786.

Lacasana, M., Vazquez-Grameix, H., Borja-Aburto, V. H., Blanco-Munoz, J., Romieu, I., Aguilar-Garduno, C., and Garcia, A. M. 2006. Maternal and paternal occupational exposure to agricultural work and the risk of anencephaly. *Occup. Environ. Med.* 63:649–656.

Lai, T. J., Guo, Y. L., Guo, N. W., and Hsu, C. C. 2001. Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: A longitudinal study in Taiwan. *Br. J. Psychiatry Suppl.* 40:S49–S52.

Lai, T. J., Guo, Y. L., Yu, M. L., Ko, H. C., and Hsu, C. C. 1994. Cognitive development in Yucheng children. Chemosphere 29:2405–2411.

Lamb, M. R., Taylor, S., Liu, X., Wolff, M. S., Borrell, L., Matte, T. D., Susser, E. S., and Factor-Litvak, P. 2006. Prenatal exposure to polychlorinated biphenyls and postnatal growth: A structural analysis. *Environ. Health Perspect.* 114:779–785.

Lan, S. J., Yen, Y. Y., Ko, Y. C., and Chen, E. R. 1989. Growth and development of permanent teeth germ of transplacental Yu-Cheng babies in Taiwan. *Bull. Environ. Contam. Toxicol.* 42:931–934.

Landgren, O. 1996. Environmental pollution and delivery outcome in southern Sweden: A study with central registries. *Acta Paediatr.* 85:1361–1364.

Landrigan, P. J. 1999. Risk assessment for children and other sensitive populations. *Ann. NY Acad. Sci.* 895:1–9.

Landrigan, P. J., Schechter, C. B., Lipton, J. M., Fahs, M. C., and Schwartz, J. 2002. Environmental pollutants and disease in American children: Estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ. Health Perspect.* 110:721–728.

Landrigan, P. J., Whitworth, R. H., Baloh, R. W., Staehling, N. W., Barthel, W. F., and Rosenblum, B. F. 1975. Neuropsychological dysfunction in children with chronic low-level lead absorption. *Lancet* 29:708–712.

Langholz, B., Ebi, K. L., Thomas, D. C., Peters, J. M., and London, S. J. 2002. Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. *Ann. Epidemiol.* 12:482–487.

Lanphear, B. P., Dietrich, K., Auinger, P., and Cox, C. 2000. Cognitive deficits associated with blood lead concentrations <10 microg/dl in US children and adolescents. *Public Health Rep.* 115:521–529.

Lanphear, B. P., Hornung, R., Khoury, J., Yolton, K., Baghurst, P., Bellinger, D. C., Canfield, R. L., Dietrich, K. N., Bornschein, R., Greene, T., Rothenberg, S. J., Needleman, H. L., Schnaas, L., Wasserman, G., Graziano, J., and Roberts, R. 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ. Health Perspect.* 113:894–899.

Lansdown, R., Yule, W., Urbanowicz, M. A., and Hunter, J. 1986. The relationship between blood-lead concentrations, intelligence, attainment and behaviour in a school population: The second London study. *Int. Arch. Occupational and Environ. Health* 57:225–235.

Lanting, C. I., Fidler, V., Huisman, M., and Boersma, E. R. 1998a. Determinants of polychlorinated biphenyl levels in plasma from 42-month- old children. *Arch. Environ. Contam. Toxicol.* 35:135–139 .

Lanting, C. I., Patandin, S., Fidler, V., Weisglas-Kuperus, N., Sauer, P. J., Boersma, E. R., and Touwen, B. C. 1998b. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. *Early Hum. Dev.* 50: 283–92.

Larsen, S. B., Joffe, M., and Bonde, J. P. 1998. Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. *Occup. Environ. Med.* 55:278–283.

Laslo-Baker, D., Barrera, M., Knittel-Keren, D., Kozer, E., Wolpin, J., Khattak, S., Hackman, R., Rovet, J., and Koren, G. 2004. Child neurodevelopmental outcome and maternal occupational exposure to solvents. *Arch. Pediatr. Adolesc. Med.* 158:956–961.

Laumon, B., Martin, J. L., Collet, P., Bertucat, I., Verney, M. P., and Robert, E. 1996. Exposure to organic solvents during pregnancy and oral clefts: A case-control study. *Reprod. Toxicol.* 10:15–19.

Law, D. C., Klebanoff, M. A., Brock, J. W., Dunson, D. B., and Longnecker, M. P. 2005. Maternal serum levels of polychlorinated biphenyls and 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) and time to pregnancy. *Am. J. Epidemiol.* 162:523–532.

Lawson, C. C., Schnorr, T. M., Whelan, E. A., Deddens, J. A., Dankovic, D. A., Piacitelli, L. A., Sweeney, M. H., and Connally, L. B. 2004. Paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-P-dioxin and birth outcomes of offspring: birth weight, preterm delivery, and birth defects. *Environ. Health Perspect.* 112:1403–1408.

Lee, B. E., Ha, E. H., Park, H. S., Kim, Y. J., Hong, Y. C., Kim, H., and Lee, J. T. 2003. Exposure to air pollution during different gestational phases contributes to risks of low birth weight. *Hum. Reprod.* 18:638–643.

Leem, J. H., Kaplan, B. M., Shim, Y. K., Pohl, H. R., Gotway, C. A., Bullard, S. M., Rogers, J. F., Smith, M. M., and Tylenda, C. A. 2006. Exposures to air pollutants during pregnancy and preterm delivery. *Environ. Health Perspect.* 114:905–910.

Leiss, J. K., and Savitz, D. A. 1995. Home pesticide use and childhood cancer: A case-control study. *Am. J. Public Health* 85:249–252.

Levario-Carrillo, M., Amato, D., Ostrosky-Wegman, P., Gonzalez-Horta, C., Corona, Y., and Sanin, L. H. 2004. Relation between pesticide exposure and intrauterine growth retardation. *Chemosphere* 55:1421–1427.

Leviton, A., Bellinger, D., Allred, E. N., Rabinowitz, M., Needleman, H., and Schoenbaum, S. 1993. Pre- and postnatal low-level lead exposure and children's dysfunction in school. *Environ. Res.* 60:30–43.

Li, J. S., Peat, J. K., Xuan, W., and Berry, G. 1999. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. *Pediatr. Pulmonol.* 27:5–13.

Li, Y. F., Langholz, B., Salam, M. T., and Gilliland, F. D. 2005. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 127:1232–1241.

Lidsky, T. I., and Schneider, J. S. 2003. Lead neurotoxicity in children: Basic mechanisms and clinical correlates. *Brain* 126:5–19.

Lin, M., Chen, Y., Villeneuve, P. J., Burnett, R. T., Lemyre, L., Hertzman, C., McGrail, K. M., and Krewski, D. 2004. Gaseous air pollutants and asthma hospitalization of children with low household income in Vancouver, British Columbia, Canada. *Am. J. Epidemiol.* 159:294–303.

Lin, M. C., Chiu, H. F., Yu, H. S., Tsai, S. S., Cheng, B. H., Wu, T. N., Sung, F. C., and Yang, C. Y. 2001a. Increased risk of preterm delivery in areas with air pollution from a petroleum refinery plant in Taiwan. *J. Toxicol. Environ. Health A* 64:637–644.

Lin, M. C., Yu, H. S., Tsai, S. S., Cheng, B. H., Hsu, T. Y., Wu, T. N., and Yang, C. Y. 2001b. Adverse pregnancy outcome in a petrochemical polluted area in Taiwan. *J. Toxicol. Environ. Health A* 63:565–574.

Lin, S., Hwang, S. A., Marshall, E. G., and Marion, D. 1998. Does paternal occupational lead exposure increase the risks of low birth weight or prematurity? *Am. J. Epidemiol.* 148:173–181.

Lin, S., Marshall, E. G., and Davidson, G. K. 1994. Potential parental exposure to pesticides and limb reduction defects. *Scand. J. Work Environ. Health* 20:166–179.

Lindbohm, M. L., Hemminki, K., Bonhomme, M. G., Anttila, A., Rantala, K., Heikkila, P., and Rosenberg, M. J. 1991a. Effects of paternal occupational exposure on spontaneous abortions. *Am. J. Public Health* 81:1029–1033.

Lindbohm, M. L., Sallmen, M., Anttila, A., Taskinen, H., and Hemminki, K. 1991b. Paternal occupational lead exposure and spontaneous abortion. *Scand. J. Work Environ. Health* 17:95–103.

Lindbohm, M. L., Sallmen, M., and Taskinen, H. 2002. Effects of exposure to environmental tobacco smoke on reproductive health. *Scand. J. Work Environ. Health* 28 Suppl 2:84–96.

Linet, M. S., Ries, L. A., Smith, M. A., Tarone, R. E., and Devesa, S. S. 1999. Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. *JNCI* 91:1051–1058.

Liu, S., Krewski, D., Shi, Y., Chen, Y., and Burnett, R. T. 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ. Health Perspect.* 111:1773–1778.

Loffredo, C. A., Silbergeld, E. K., Ferencz, C., and Zhang, J. 2001. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. *Am. J. Epidemiol.* 153:529–536.

Loghman-Adham, M. 1997. Renal effects of environmental and occupational lead exposure. *Environ. Health Perspect.* 105:928–939.

Logman, J. F., de Vries, L. E., Hemels, M. E., Khattak, S., and Einarson, T. R. 2005. Paternal organic solvent exposure and adverse pregnancy outcomes: A meta-analysis. *Am. J. Ind. Med.* 47:37–44.

Loiacono, N. J., Graziano, J. H., Kline, J. K., Popovac, D., Ahmedi, X., Gashi, E., Mehmeti, A., and Rajovic, B. 1992. Placental cadmium and birthweight in women living near a lead smelter. *Arch. Environ. Health* 47:250–255.

Longnecker, M. P., Hoffman, H. J., Klebanoff, M. A., Brock, J. W., Zhou, H., Needham, L., Adera, T., Guo, X., and Gray, K. A. 2004. In utero exposure to polychlorinated biphenyls and sensorineural hearing loss in 8-year-old children. *Neurotoxicol. Teratol.* 26:629–637.

Longnecker, M. P., Klebanoff, M. A., Brock, J. W., and Guo, X. 2005. Maternal levels of polychlorinated biphenyls in relation to preterm and small-for-gestational-age birth. *Epidemiology* 16:641–647.

Longnecker, M. P., Klebanoff, M. A., Brock, J. W., Zhou, H., Gray, K. A., Needham, L. L., and Wilcox, A. J. 2002 . Maternal serum level of 1,1-dichloro–2,2-bis(p-chlorophenyl)ethylene and risk of cryptorchidism, hypospadias, and polythelia among male offspring. *Am. J. Epidemiol.* 155:313–322.

Longnecker, M. P., Klebanoff, M. A., Dunson, D. B., Guo, X., Chen, Z., Zhou, H., and Brock, J. W. 2005. Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies. *Environ. Res.* 97:127–133.

Longnecker, M. P., Klebanoff, M. A., Zhou, H., and Brock, J. W. 2001. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet* 358:110–114.

Longnecker, M. P., Rogan, W. J., and Lucier, G. 1997. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annu. Rev. Public Health* 18:211–244.

Longnecker, M. P., Wolff, M. S., Gladen, B. C., Brock, J. W., Grandjean, P., Jacobson, J. L., Korrick, S. A., Rogan, W. J., Weisglas-Kuperus, N., Hertz-Picciotto, I., Ayotte, P., Stewart, P., Winneke, G., Charles, M. J., Jacobson, S. W., Dewailly, E., Boersma, E. R., Altshul, L. M., Heinzow, B., Pagano, J. J., and Jensen, A. A. 2003. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. *Environ. Health Perspect.* 111:65–70.

Lorente, C., Cordier, S., Bergeret, A., De Walle, H. E., Goujard, J., Ayme, S., Knill-Jones, R., Calzolari, E., and Bianchi, F. 2000. Maternal occupational risk factors for oral clefts. Occupational Exposure and Congenital Malformation Working Group. *Scand. J. Work Environ. Health* 26:137–145.

Lowengart, R. A., Peters, J. M., Cicioni, C., Buckley, J., Bernstein, L., Preston-Martin, S., and Rappaport, E. 1987 . Childhood leukemia and parents' occupational and home exposures. *JNCI* 79:39–46.

Luderer, U., Bushley, A., Stover, B. D., Bremner, W. J., Faustman, E. M., Takaro, T. K., Checkoway, H., and Brodkin, C. A. 2004. Effects of occupational solvent exposure on reproductive hormone concentrations and fecundability in men. *Am. J. Ind. Med.* 46:614–626.

Lund, K. E., and Helgason, A. R. 2005. Environmental tobacco smoke in Norwegian homes, 1995 and 2001: changes in children's exposure and parents attitudes and health risk awareness. *Eur. J. Public Health* 15:123–127.

Lynge, E. 1998. Cancer incidence in Danish phenoxy herbicide workers, 1947–1993. *Environ. Health Perspect.* 106(Suppl. 2):683–688.

Ma, S. K., Wan, T. S., and Chan, L. C. 1999. Cytogenetics and molecular genetics of childhood leukemia. *Hematol. Oncol.* 17:91–105.

Ma, X., Buffler, P. A., Gunier, R. B., Dahl, G., Smith, M. T., Reinier, K., and Reynolds, P. 2002. Critical windows of exposure to household pesticides and risk of childhood leukemia. *Environ. Health Perspect.* 110:955–960.

Magnani, C., Pastore, G., Luzzatto, L., and Terracini, B. 1990. Parental occupation and other environmental factors in the etiology of leukemias and nonHodgkin's lymphomas in childhood: A case-control study. *Tumori* 76:413–419.

Magnus, P., Jaakkola, J. J., Skrondal, A., Alexander, J., Becher, G., Krogh, T., and Dybing, E. 1999. Water chlorination and birth defects. *Epidemiology* 10:513–517.

Maia, A. T., Koechling, J., Corbett, R., Metzler, M., Wiemels, J. L., and Greaves, M. 2004. Protracted postnatal natural histories in childhood leukemia. *Genes Chromosomes Cancer* 39:335–340.

Maisonet, M., Correa, A., Misra, D., and Jaakkola, J. J. 2004. A review of the literature on the effects of ambient air pollution on fetal growth. *Environ. Res.* 95:106–115.

Malik, S., Schecter, A., Caughy, M., and Fixler, D. E. 2004. Effect of proximity to hazardous waste sites on the development of congenital heart disease. *Arch. Environ. Health* 59:177–181.

Maroziene, L., and Grazuleviciene, R. 2002. Maternal exposure to low-level air pollution and pregnancy outcomes: A population-based study. *Environ. Health* 1:1–7.

Marrett, L. D., Frood, J., Nishri, D., and Ugnat, A. M. 2002. Cancer incidence in young adults in Canada: Preliminary results of a cancer surveillance project. *Chron. Dis. Can.* 23:58–64.

Marsh, D. O., Clarkson, T. W., Cox, C., Myers, G. J., Amin-Zaki, L., and Al-Tikriti, S. 1987. Fetal methylmercury poisoning. Relationship between concentration in single strands of maternal hair and child effects. *Arch. Neurol.* 44:1017–1022.

Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., Tikriti, S., and Majeed, M. A. 1980. Fetal methylmercury poisoning: Clinical and toxicological data on 29 cases. *Ann. Neurol*. 7:348–353.

Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., Tikriti, S., Majeed, M. A., and Dabbagh, A. R. 1981. Dose-response relationship for human fetal exposure to methylmercury. *Clin. Toxicol*. 18:1311–1318.

Marsh, D. O., Turner, M. D., Smith, J. C., Allen, P., and Richdale, N. 1995. Fetal methylmercury study in a Peruvian fish-eating population. *Neurotoxicology* 16:717–726.

Marshall, E. G., Gensburg, L. J., Deres, D. A., Geary, N. S., and Cayo, M. R. 1997. Maternal residential exposure to hazardous wastes and risk of central nervous system and musculoskeletal birth defects. *Arch. Environ. Health* 52:416–425 .

Massachusetts Department of Public Health. 1997. Woburn childhood leukemia follow-up study.Volume 1. Analyses. Located at: http://www.mass.gov/Eeohhs2/docs/dph/environmental/investigations/woburn_cancer_leukemia_follow_up_study_1997.pdf.

Massachusetts Department of Public Health. 1998. Final report of the Woburn Environment and Birth Study. Located at: http://www.mass.gov/Eeohhs2/docs/dph/environmental/investigations/woburn_summary_environment_birth_study.pdf.

Masuda, Y. 2001. Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. *Chemosphere* 43:925–930.

Matsubara, F., Kida, M., Tamakoshi, A., Wakai, K., Kawamura, T., and Ohno, Y. 2000. Maternal active and passive smoking and fetal growth: A prospective study in Nagoya, Japan. *J. Epidemiol*. 10:335–343.

McConnell, R., Berhane, K., Gilliland, F., London, S. J., Islam, T., Gauderman, W. J., Avol, E., Margolis, H. G., and Peters, J. M. 2002. Asthma in exercising children exposed to ozone: A cohort study. *Lancet* 359:386–391.

McConnell, R., Berhane, K., Yao, L., Jerrett, M., Lurmann, F., Gilliland, F., Kunzli, N., Gauderman, J., Avol, E., Thomas, D., and Peters, J. 2006. Traffic, susceptibility, and childhood asthma. *Environ. Health Perspect.* 114:766–772.

McCredie, M., Maisonneuve, P., and Boyle, P. 1994a. Antenatal risk factors for malignant brain tumours in New South Wales children. *Int. J. Cancer* 56:6–10.

McCredie, M., Maisonneuve, P., and Boyle, P. 1994b. Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int. J. Cancer* 56:11–15.

McDonald, A. D., McDonald, J. C., Armstrong, B., Cherry, N. M., Cote, R., Lavoie, J., Nolin, A. D., and Robert, D. 1988. Fetal death and work in pregnancy. *Br. J. Ind. Med.* 45:148–157.

McGready, R., Hamilton, K. A., Simpson, J. A., Cho, T., Luxemburger, C., Edwards, R., Looareesuwan, S., White, N. J., Nosten, F., and Lindsay, S. W. 2001. Safety of the insect repellent *N,N*-diethyl-*m*-toluamide (DEET) in pregnancy. *Am. J. Trop. Med. Hyg*. 65:285–289.

McKee, R. H. 2004. Phthalate exposure and early thelarche. *Environ. Health Perspect.* 112:A541–A543.

McKinney, P. A., Fear, N. T., and Stockton, D. 2003. Parental occupation at periconception: Findings from the United Kingdom Childhood Cancer Study. *Occup. Environ. Med.* 60: 901–909.

McMartin, K. I., Chu, M., Kopecky, E., Einarson, T. R., and Koren, G. 1998. Pregnancy outcome following maternal organic solvent exposure: A meta-analysis of epidemiologic studies. *Am. J. Ind. Med.* 34:288–292.

McMichael, A. J., Vimpani, G. V., Robertson, E. F., Baghurst, P. A., and Clark, P. D. 1986. The Port Pirie cohort study: Maternal blood lead and pregnancy outcome. *J. Epidemiol. Commun. Health* 40:18–25.

Meinert, R., Kaatsch, P., Kaletsch, U., Krummenauer, F., Miesner, A., and Michaelis, J. 1996. Childhood leukaemia and exposure to pesticides: Results of a case- control study in northern Germany. *Eur. J. Cancer* 32A:1943–1948.

Meinert, R., Schuz, J., Kaletsch, U., Kaatsch, P., and Michaelis, J. 2000. Leukemia and nonHodgkin's lymphoma in childhood and exposure to pesticides: Results of a register-based case-control study in Germany. *Am. J. Epidemiol.* 151:639–646.

Meironyte, D., Noren, K., and Bergman, A. 1999. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972–1997. *J. Toxicol. Environ. Health A* 58:329–341.

Mendell, M. J. 2007. Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: A review. *Indoor Air* 17:259–277.

Mendelsohn, A. L., Dreyer, B. P., Fierman, A. H., Rosen, C. M., Legano, L. A., Kruger, H. A., Lim, S. W., and Courtlandt, C. D. 1998. Low-level lead exposure and behavior in early childhood. *Pediatrics* 101:1–7.

Mendola, P., Selevan, S. G., Gutter, S., and Rice, D. 2002. Environmental factors associated with a spectrum of neurodevelopmental deficits. *Ment. Retard. Dev. Disabil. Res. Rev*. 8:188–197.

Menegaux, F., Baruchel, A., Bertrand, Y., Lescoeur, B., Leverger, G., Nelken, B., Sommelet, D., Hemon, D., and Clavel, J. 2006. Household exposure to pesticides and risk of childhood acute leukaemia. *Occup. Environ. Med.* 63:131–134.

Menegaux, F., Steffen, C., Bellec, S., Baruchel, A., Lescoeur, B., Leverger, G., Nelken, B., Philippe, N., Sommelet, D., Hemon, D., and Clavel, J. 2005. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect. Prev*. 29:487–493.

Mes, J., Arnold, D. L., and Bryce, F. 1995. The elimination and estimated half-lives of specific polychlorinated biphenyl congeners from the blood of female monkeys after discontinuation of daily dosing with Aroclor 1254. *Chemosphere* 30:789–800.

Meyer, K. J., Reif, J. S., Rao Veeramachaneni, D. N., Luben, T. J., Mosley, B. S., and Nuckols, J. R. 2006. Agricultural pesticide use and hypospadias in eastern Arkansas. *Environ. Health Perspect*. 114:1589–1595.

Michalek, J. E., Rahe, A. J., and Boyle, C. A. 1998. Paternal dioxin, preterm birth, intrauterine growth retardation, and infant death. *Epidemiology* 9:161–167.

Millar, W. J., and Hill, G. B. 1998. Childhood asthma. *Health Rep*. 10:9–21.

Modigh, C. M., Bodin, S. L., Lillienberg, L., Dahlman-Hoglund, A., Akesson, B., and Axelsson, G. 2002. Time to pregnancy among partners of men exposed to di(2-ethylhexyl)phthalate. *Scand. J. Work Environ. Health* 28:418–428.

Mol, N. M., Sorensen, N., Weihe, P., Andersson, A. M., Jorgensen, N., Skakkebaek, N. E., Keiding, N., and Grandjean, P. 2002. Spermaturia and serum hormone concentrations at the age of puberty in boys prenatally exposed to polychlorinated biphenyls. *Eur. J. Endocrinol*. 146:357–363.

Moller, H. 1997. Work in agriculture, childhood residence, nitrate exposure, and testicular cancer risk: A case-control study in Denmark. *Cancer Epidemiol. Biomarkers Prev*. 6:141–144.

Moore, L. E., Gold, L., Stewart, P. A., Gridley, G., Prince, J. R., and Zahm, S. H. 2005. Parental occupational exposures and Ewing's sarcoma. *Int. J. Cancer* 114:472–478.

Moore, L. E., Lu, M., and Smith, A. H. 2002. Childhood cancer INCIDENCE and arsenic exposure in drinking water in Nevada. *Arch. Environ. Health* 57:201–206.

Mori, H., Colman, S. M., Xiao, Z., Ford, A. M., Healy, L. E., Donaldson, C., Hows, J. M., Navarrete, C., and Greaves, M. 2002. Chromosome translocations and covert leukemic clones are generated during normal fetal development. *Proc. Natl. Acad. Sci. USA* 99:8242–8247.

Morris, S. E., Thomson, A. O., Jarup, L., de Hoogh, C., Briggs, D. J., and Elliott, P. 2003. No excess risk of adverse birth outcomes in populations living near special waste landfill sites in Scotland. *Scott. Med. J*. 48:105–107.

Morrissey, R. E., George, J. D., Price, C. J., Tyl, R. W., Marr, M. C., and Kimmel, C. A. 1987. The developmental toxicity of bisphenol A in rats and mice. *Fundam. Appl. Toxicol*. 8:571–582.

Moss, M. E., Lanphear, B. P., and Auinger, P. 1999. Association of dental caries and blood lead levels. *J. Am. Med. Assoc.* 281:2294–2298.

Moya, J., Bearer, C. F., and Etzel, R. A. 2004. Children's behavior and physiology and how it affects exposure to environmental contaminants. *Pediatrics* 113:996–1006.

Mueller, B. A., Newton, K., Holly, E. A., and Preston-Martin, S. 2001. Residential water source and the risk of childhood brain tumors. *Environ. Health Perspect.* 109:551–556.

Mueller, B. A., Nielsen, S. S., Preston-Martin, S., Holly, E. A., Cordier, S., Filippini, G., Peris-Bonet, R., and Choi, N. W. 2004. Household water source and the risk of childhood brain tumours: results of the SEARCH International Brain Tumor Study. *Int. J. Epidemiol.* 33:1209–1216.

Munger, R., Isacson, P., Hu, S., Burns, T., Hanson, J., Lynch, C. F., Cherryholmes, K., Van Dorpe, P., and Hausler, W. J. 1997. Intrauterine growth retardation in Iowa communities with herbicide- contaminated drinking water supplies. *Environ. Health Perspect.* 105:308–314.

Murata, K., Budtz-Jorgensen, E., and Grandjean, P. 2002. Benchmark dose calculations for methylmercury-associated delays on evoked potential latencies in two cohorts of children. *Risk Anal*. 22:465–474.

Murata, K., Weihe, P., Araki, S., Budtz-Jorgensen, E., and Grandjean, P. 1999. Evoked potentials in Faroese children prenatally exposed to methylmercury. *Neurotoxicol. Teratol.* 21:471–472.

Murata, K., Weihe, P., Budtz-Jorgensen, E., Jorgensen, P. J., and Grandjean, P. 2004. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J. Pediatr.* 144:177–183.

Murray, C. S., Woodcock, A., Smillie, F. I., Cain, G., Kissen, P., and Custovic, A. 2004. Tobacco smoke exposure, wheeze, and atopy. *Pediatr. Pulmonol*. 37:492–498.

Myers, G. J., and Davidson, P. W. 2000. Does methylmercury have a role in causing developmental disabilities in children? *Environ. Health Perspect.* 108(Suppl. 3):413–420.

Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C., Cernichiari, E., and Clarkson, T. W. 2000. Twenty-seven years studying the human neurotoxicity of methylmercury exposure. *Environ. Res.* 83:275–285.

Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Palumbo, D., Cernichiari, E., Sloane-Reeves, J., Wilding, G. E., Kost, J., Huang, L. S., and Clarkson, T. W. 2003. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet* 361:1686–1692.

Myers, G. J., Davidson, P. W., Palumbo, D., Shamlaye, C., Cox, C., Cernichiari, E., and Clarkson, T. W. 2000. Secondary analysis from the Seychelles Child Development Study: The child behavior checklist. *Environ. Res.* 84:12–19.

Myers, G. J., Davidson, P. W., and Shamlaye, C. F. 1998. A review of methylmercury and child development. *Neurotoxicology* 19:313–328.

Myers, G. J., Davidson, P. W., Shamlaye, C. F., Axtell, C. D., Cernichiari, E., Choisy, O., Choi, A., Cox, C., and Clarkson, T. W. 1997. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study. *Neurotoxicology* 18:819–829.

Myers, G. J., Marsh, D. O., Davidson, P. W., Cox, C., Shamlaye, C. F., Tanner, M., Choi, A., Cernichiari, E., Choisy, O., and Clarkson, T. W. 1995. Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months. *Neurotoxicology* 16:653–664.

National Academy of Sciences. 1993. Pesticides in the diets of infants and children. Located at: http://fermat.nap.edu/catalog/2126.html.

National Academy of Sciences. 2000a. Clearing the air. Asthma and indoor air exposures. Located at: http://fermat.nap.edu/catalog/9610.html.

National Academy of Sciences. 2000b. *Scientific frontiers in developmental toxicology and risk assessment*. Washington, DC: National Academy Press.

National Academy of Sciences. 2000c. Toxicological effects of methylmercury. Located at: http://fermat.nap.edu/catalog/9899.html.

National Academy of Sciences. 2003. Veterans and Agent Orange. Update 2002. Located at: http://www.nap.edu/catalog/10603.html.

National Institute of Child Health and Human Development . 2002. The National Children's Study. Located at: http://nationalchildrensstudy.gov/index.cfm.

Needleman, H. L. 1997. Clamped in a straitjacket: The insertion of lead into gasoline. *Environ. Res.* 74:95–103.

Needleman, H. L., and Gatsonis, C. A. 1990. Low-level lead exposure and the IQ of children. A meta-analysis of modern studies. *J. Am. Med. Assoc.* 263:673–678.

Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., and Barrett, P. 1979. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *N. Engl. J. Med.* 300:689–695.

Needleman, H. L., McFarland, C., Ness, R. B., Fienberg, S. E., and Tobin, M. J. 2002. Bone lead levels in adjudicated delinquents. A case control study. *Neurotoxicol. Teratol.* 24:711–717.

Needleman, H. L., Riess, J. A., Tobin, M. J., Biesecker, G. E., and Greenhouse, J. B. 1996. Bone lead levels and delinquent behavior. *J. Am. Med. Assoc.* 275:363–369.

Needleman, H. L., Schell, A., Bellinger, D., Leviton, A., and Allred, E. N. 1990. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report . *N. Engl. J. Med.* 322:83–88.

Neri, M., Ugolini, D., Bonassi, S., Fucic, A., Holland, N., Knudsen, L. E., Sram, R. J., Ceppi, M., Bocchini, V., and Merlo, D. F. 2006. Children's exposure to environmental pollutants and biomarkers of genetic damage II. Results of a comprehensive literature search and meta-analysis. *Mutat. Res.* 612:14–39.

Newland, M. C. 2002. Neurobehavioral toxicity of methylmercury and PCBs. Effects-profiles and sensitive populations. *Environ. Toxicol. Pharmacol.* 12:119–128.

Nickmilder, M., and Bernard, A. 2007. Ecological association between childhood asthma and availability of indoor chlorinated swimming pools in Europe. *Occup. Environ. Med.* 64:37–46.

Nielsen, S. S., Mueller, B. A., De Roos, A. J., Viernes, H. M., Farin, F. M., and Checkoway, H. 2005. Risk of brain tumors in children and susceptibility to organophosphorus insecticides: The potential role of paraoxonase (PON1). *Environ. Health Perspect.* 113:909–913.

Nieuwenhuijsen, M. J., Northstone, K., and Golding, J. 2002. Swimming and birth weight. *Epidemiology* 13:725–728.

Nieuwenhuijsen, M. J., Toledano, M. B., Eaton, N. E., Fawell, J., and Elliott, P. 2000. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: A review. *Occup. Environ. Med.* 57:73–85.

Nishijo, M., Nakagawa, H., Honda, R., Tanebe, K., Saito, S., Teranishi, H., and Tawara, K. 2002. Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. *Occup. Environ. Med.* 59:394–396.

Nishijo, M., Tawara, K., Honda, R., Nakagawa, H., Tanebe, K., and Saito, S. 2004. Relationship between newborn size and mother's blood cadmium levels, Toyama, Japan. *Arch. Environ. Health* 59:22–25.

Noonan, C. W., Sarasua, S. M., Campagna, D., Kathman, S. J., Lybarger, J. A., and Mueller, P. W. 2002. Effects of exposure to low levels of environmental cadmium on renal biomarkers. *Environ. Health Perspect.* 110:151–155.

Nordlinder, R., and Jarvholm, B. 1997. Environmental exposure to gasoline and leukemia in children and young adults—An ecology study. *Int. Arch. Occup. Environ. Health* 70:57–60.

Nurminen, T., Rantala, K., Kurppa, K., and Holmberg, P. C. 1995. Agricultural work during pregnancy and selected structural malformations in Finland. *Epidemiology* 6:23–30.

O'sullivan, B. C., Lafleur, J., Fridal, K., Hormozdi, S., Schwartz, S., Belt, M., and Finkel, M. 2005. The effect of pesticide spraying on the rate and severity of ED asthma. *Am. J. Emerg. Med.* 23:463–7.

Odland, J. O., Nieboer, E., Romanova, N., and Thomassen, Y. 2004. Elements in placenta and pregnancy outcome in arctic and subarctic areas. *Int. J. Circumpolar Health* 63:169–187.

Oken, E., Wright, R. O., Kleinman, K. P., Bellinger, D., Amarasiriwardena, C. J., Hu, H., Rich-Edwards, J. W., and Gillman, M. W. 2005. Maternal fish consumption, hair mercury, and infant cognition in a U.S. cohort. *Environ. Health Perspect.* 113:1376–1380.

Olsen, J., Hemminki, K., Ahlborg, G., Bjerkedal, T., Kyyronen, P., Taskinen, H., Lindbohm, M. L., Heinonen, O. P., Brandt, L., Kolstad, H., and et, a. l. 1990. Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia. *Scand. J. Work Environ. Health* 16:163–168.

Olshan, A. F., De Roos, A. J., Teschke, K., Neglia, J. P., Stram, D. O., Pollock, B. H., and Castleberry, R. P. 1999. Neuroblastoma and parental occupation. *Cancer Causes Control* 10:539–549.

Olshan, A. F., and van Wijngaarden, E. 2003. Paternal occupation and childhood cancer. *Adv. Exp. Med. Biol.* 518:147–161.

Orr, M., Bove, F., Kaye, W., and Stone, M. 2002. Elevated birth defects in racial or ethnic minority children of women living near hazardous waste sites. *Int. J. Hyg. Environ. Health* 205:19–27.

Osman, K., Akesson, A., Berglund, M., Bremme, K., Schutz, A., Ask, K., and Vahter, M. 2000. Toxic and essential elements in placentas of Swedish women. *Clin. Biochem.* 33:131–138.

Osman, K., Pawlas, K., Schutz, A., Gazdzik, M., Sokal, J. A., and Vahter, M. 1999. Lead exposure and hearing effects in children in Katowice, Poland. *Environ. Res.* 80:1–8.

Otto, D. A., and Fox, D. A. 1993. Auditory and visual dysfunction following lead exposure. *Neurotoxicology* 14:191–207.

Pahwa, P., McDuffie, H. H., Dosman, J. A., Robson, D., McLaughlin, J. R., Spinelli, J. J., and Fincham, S. 2003. Exposure to animals and selected risk factors among Canadian farm residents with Hodgkin's disease, multiple myeloma, or soft tissue sarcoma. *J. Occup. Environ. Med.* 45:857–868.

Pang, D., McNally, R., and Birch, J. M. 2003. Parental smoking and childhood cancer: Results from the United Kingdom Childhood Cancer Study. *Br. J. Cancer* 88:373–381.

Pastore, L. M., Hertz-Picciotto, I., and Beaumont, J. J. 1997. Risk of stillbirth from occupational and residential exposures. *Occup. Environ. Med.* 54:511–518.

Patandin, S., Koopman-Esseboom, C., de Ridder, M. A., Weisglas-Kuperus, N., and Sauer, P. J. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr. Res.* 44:538–545.

Patandin, S., Lanting, C. I., Mulder, P. G., Boersma, E. R., Sauer, P. J., and Weisglas-Kuperus, N. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J. Pediatr.* 134:33–41.

Pearce, M. S., and Parker, L. 2000. Paternal employment in agriculture and childhood kidney cancer. *Pediatr. Hematol. Oncol.* 17:223–230.

Pearson, R. L., Wachtel, H., and Ebi, K. L. 2000. Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. *J. Air Waste Manage. Assoc.* 50:175–180.

Pereira, L. A., Loomis, D., Conceicao, G. M., Braga, A. L., Arcas, R. M., Kishi, H. S., Singer, J. M., Bohm, G. M., and Saldiva, P. H. 1998. Association between air pollution and intrauterine mortality in Sao Paulo, Brazil. *Environ. Health Perspect.* 106:325–329.

Perera, F. P., Illman, S. M., Kinney, P. L., Whyatt, R. M., Kelvin, E. A., Shepard, P., Evans, D., Fullilove, M., Ford, J., Miller, R. L., Meyer, I. H., and Rauh, V. A. 2002. The challenge of preventing environmentally related disease in young children: Community-based research in New York City. *Environ. Health Perspect.* 110:197–204.

Perera, F. P., Rauh, V., Whyatt, R. M., Tsai, W. Y., Bernert, J. T., Tu, Y. H., Andrews, H., Ramirez, J., Qu, L., and Tang, D. 2004. Molecular evidence of an interaction between prenatal environmental exposures and birth outcomes in a multiethnic population. *Environ. Health Perspect.* 112:626–630.

Perera, F. P., Rauh, V., Whyatt, R. M., Tsai, W. Y., Tang, D., Diaz, D., Hoepner, L., Barr, D., Tu, Y. H., Camann, D., and Kinney, P. 2006. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environ. Health Perspect.* 114:1287–1292.

Pesatori, A. C., Consonni, D., Tironi, A., Zocchetti, C., Fini, A., and Bertazzi, P. A. 1993. Cancer in a young population in a dioxin-contaminated area. *Int. J. Epidemiol.* 22:1010–1013.

Petrelli, G., Fig`a-Talamanca, I., Lauria, L., and Mantovani, A. 2003. Spontaneous abortion in spouses of greenhouse workers exposed to pesticides. *Environ. Health Prev. Med.* 8:77–81.

Petrelli, G., and Figa-Talamanca, I. 2001. Reduction in fertility in male greenhouse workers exposed to pesticides. *Eur. J. Epidemiol.* 17:675–677.

Petrelli, G., Figa-Talamanca, I., Tropeano, R., Tangucci, M., Cini, C., Aquilani, S., Gasperini, L., and Meli, P. 2000. Reproductive male-mediated risk: Spontaneous abortion among wives of pesticide applicators. *Eur. J. Epidemiol.* 16:391–393.

Petridou, E., and Dessypris, N. 2000. Maternal pesticide exposure and childhood leukemia. *Epidemiology* 11:230.

Pichini, S., Garcia-Algar, O., Munoz, L., Vall, O., Pacifici, R., Figueroa, C., Pascual, J. A., Diaz, D., and Sunyer, J. 2003. Assessment of chronic exposure to cigarette smoke and its change during pregnancy by segmental analysis of maternal hair nicotine. *J. Expos. Anal. Environ. Epidemiol.* 13:144–151.

Pierik, F. H., Burdorf, A., Deddens, J. A., Juttmann, R. E., and Weber, R. F. 2004. Maternal and paternal risk factors for cryptorchidism and hypospadias: A case-control study in newborn boys. *Environ. Health Perspect.* 112:1570–1576.

Pinkerton, K. E., and Joad, J. P. 2000. The mammalian respiratory system and critical windows of exposure for children's health. *Environ. Health Perspect.* 108(Suppl. 3):457–462.

Pirkle, J. L., Bernert, J. T., Caudill, S. P., Sosnoff, C. S., and Pechacek, T. F. 2006. Trends in the exposure of nonsmokers in the U.S. population to secondhand smoke: 1988–2002. *Environ. Health Perspect.* 114:853–858.

Plenge-Bonig, A., and Karmaus, W. 1999. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. *Occup. Environ. Med.* 56:443–448.

Pocock, S. J., Smith, M., and Baghurst, P. 1994. Environmental lead and children's intelligence: A systematic review of the epidemiological evidence. *Br. Med. J.* 309:1189–1197.

Pogoda, J. M., and Preston-Martin, S. 1997. Household pesticides and risk of pediatric brain tumors. *Environ. Health Perspect.* 105:1214–1220.

Public Health Agency of Canada. 2005. Preterm birth. Located at: http://www.phac-aspc.gc.ca/rhs-ssg/factshts/pterm_e.html.

Raaschou-Nielsen, O., Hertel, O., Thomsen, B. L., and Olsen, J. H. 2001. Air pollution from traffic at the residence of children with cancer. *Am. J. Epidemiol.* 153:433–443.

Raaschou-Nielsen, O., and Reynolds, P. 2006. Air pollution and childhood cancer: A review of the epidemiological literature. *Int. J. Cancer* 118:2920–2929.

Rais-Bahrami, K., Nunez, S., Revenis, M. E., Luban, N. L., and Short, B. L. 2004. Follow-up study of adolescents exposed to di(2-ethylhexyl) phthalate (DEHP) as neonates on extracorporeal membrane oxygenation (ECMO) support. *Environ. Health Perspect.* 112:1339–1340.

Regidor, E., Ronda, E., Garcia, A. M., and Dominguez, V. 2004. Paternal exposure to agricultural pesticides and cause specific fetal death. *Occup. Environ. Med.* 61:334–339.

Restrepo, M., Munoz, N., Day, N., Parra, J. E., Hernandez, C., Blettner, M., and Giraldo, A. 1990a. Birth defects among children born to a population occupationally exposed to pesticides in Colombia. *Scand. J. Work Environ. Health* 16:239–246.

Restrepo, M., Munoz, N., Day, N. E., Parra, J. E., de Romero, L., and Nguyen-Dinh, X. 1990b. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. *Scand. J. Work Environ. Health* 16:232–238.

Reynolds, P., Von Behren, J., Gunier, R., Goldberg, D. E., and Hertz, A. 2005a. Agricultural pesticides and lymphoproliferative childhood cancer in California. *Scand. J. Work Environ. Health* 31(Suppl. 1):46–54; discussion 5–7.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Harnly, M., and Hertz, A. 2005b. Agricultural pesticide use and childhood cancer in California. *Epidemiology* 16:93–100.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., and Hertz, A. 2004. Residential exposure to traffic in California and childhood cancer. *Epidemiology* 15:6–12.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Hertz, A., and Harnly, M. E. 2002a. Childhood cancer and agricultural pesticide use: an ecologic study in california. *Environ. Health Perspect.* 110:319–324.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Hertz, A., and Smith, D. 2002b. Traffic patterns and childhood cancer incidence rates in California, United States. *Cancer Causes Control* 13:665–673.

Reynolds, P., Von Behren, J., Gunier, R. B., Goldberg, D. E., Hertz, A., and Smith, D. F. 2003. Childhood cancer incidence rates and hazardous air pollutants in California: an exploratory analysis. *Environ. Health Perspect.* 111:663–668.

Ribas-Fito, N., Cardo, E., Sala, M., Eulalia de Muga, M., Mazon, C., Verdu, A., Kogevinas, M., Grimalt, J. O., and Sunyer, J. 2003. Breastfeeding, exposure to organochlorine compounds, and neurodevelopment in infants. *Pediatrics* 111:e580–e585.

Ribas-Fito, N., Sala, M., Cardo, E., Mazon, C., De Muga, M. E., Verdu, A., Marco, E., Grimalt, J. O., and Sunyer, J. 2002. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. *Pediatr. Res.* 52:163–167.

Ribas-Fito, N., Sala, M., Kogevinas, M., and Sunyer, J. 2001. Polychlorinated biphenyls (PCBs) and neurological development in children: A systematic review. *J. Epidemiol. Commun. Health* 55:537–546.

Ris, M. D., Dietrich, K. N., Succop, P. A., Berger, O. G., and Bornschein, R. L. 2004. Early exposure to lead and neuropsychological outcome in adolescence. *J. Int. Neuropsychol. Soc.* 10:261–270.

Ritter, W. F. 1990. Pesticide contamination of ground water in the United States—A review. J. *Environ. Sci. Health* 25:1–29.

Ritz, B., Yu, F., Fruin, S., Chapa, G., Shaw, G. M., and Harris, J. A. 2002. Ambient air pollution and risk of birth defects in Southern California. *Am. J. Epidemiol.* 155:17–25.

Roan, C. C., Matanoski, G. E., McIlnay, C. Q., Olds, K. L., Pylant, F., Trout, J. R., Wheeler, P., and Morgan, D. P. 1984. Spontaneous abortions, stillbirths, and birth defects in families of agricultural pilots. *Arch. Environ. Health* 39:56–60.

Robin, L. F., Less, P. S., Winget, M., Steinhoff, M., Moulton, L. H., Santosham, M., and Correa, A. 1996. Wood-burning stoves and lower respiratory illnesses in Navajo children. *Pediatr. Infect. Dis. J.* 15:859–865.

Rodvall, Y., Dich, J., and Wiklund, K. 2003. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. *Occup. Environ. Med.* 60:798–801.

Rogan, W. J., and Gladen, B. C. 1991. PCBs, DDE, and child development at 18 and 24 months. *Ann. Epidemiol.* 1:407–413.

Rogan, W. J., Gladen, B. C., Hung, K. L., Koong, S. L., Shih, L. Y., Taylor, J. S., Wu, Y. C., Yang, D., Ragan, N. B., and Hsu, C. C. 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 241:334–336.

Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tingelstad, J., and Tully, M. 1987. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: Effects on growth, morbidity, and duration of lactation. *Am. J. Public Health* 77:1294–1297.

Rogan, W. J., Gladen, B. C., McKinney, J. D., Carreras, N., Hardy, P., Thullen, J., Tinglestad, J., and Tully, M. 1986. Neonatal effects of transplacental exposure to PCBs and DDE. *J. Pediatr.* 109:335–341.

Romieu, I., Samet, J. M., Smith, K. R., and Bruce, N. 2002. Outdoor air pollution and acute respiratory infections among children in developing countries. *J. Occup. Environ. Med.* 44:640–649.

Rothenberg, S. J., Poblano, A., and Garza-Morales, S. 1994. Prenatal and perinatal low level lead exposure alters brainstem auditory evoked responses in infants. Neurotoxicology 15:695–699.

Rothenberg, S. J., Poblano, A., and Schnaas, L. 2000. Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. *Neurotoxicol. Teratol.* 22:503–510.

Rothenberg, S. J., and Rothenberg, J. C. 2005. Testing the dose-response specification in epidemiology: Public health and policy consequences for lead. *Environ. Health Perspect.* 113:1190–1195.

Rowland, A. S., Baird, D. D., Shore, D. L., Darden, B., and Wilcox, A. J. 1996. Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. *Epidemiology* 7:363–368.

Ruckart, P. Z., Kakolewski, K., Bove, F. J., and Kaye, W. E. 2004. Long-term neurobehavioral health effects of methyl parathion exposure in children in Mississippi and Ohio. *Environ. Health Perspect.* 112:46–51.

Rull, R. P., Ritz, B., and Shaw, G. M. 2006. Neural tube defects and maternal residential proximity to agricultural pesticide applications. *Am. J. Epidemiol.* 163:743–753.

Rumchev, K., Spickett, J., Bulsara, M., Phillips, M., and Stick, S. 2004. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax* 59:746–751.

Rupa, D. S., Reddy, P. P., and Reddi, O. S. 1991. Reproductive performance in population exposed to pesticides in cotton fields in India. *Environ. Res.* 55:123–128.

Rylander, L., Stromberg, U., Dyremark, E., Ostman, C., Nilsson-Ehle, P., and Hagmar, L. 1998. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. *Am. J. Epidemiol.* 147:493–502.

Rylander, L., Stromberg, U., and Hagmar, L. 2000. Lowered birth weight among infants born to women with a high intake of fish contaminated with persistent organochlorine compounds. *Chemosphere* 40:1255–1262.

Rylander, L., Stromberg, U., and Hagmar, L. 2007. Weight and height at 4 and 7 years of age in children born to mothers with a high intake of fish contaminated with persistent organochlorine pollutants. *Chemosphere* 67:498–504.

Sagiv, S. K., Mendola, P., Loomis, D., Herring, A. H., Neas, L. M., Savitz, D. A., and Poole, C. 2005. A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997–2001. *Environ. Health Perspect.* 113:602–606.

Saint-Amour, D., Roy, M. S., Bastien, C., Ayotte, P., Dewailly, E., Despres, C., Gingras, S., and Muckle, G. 2006. Alterations of visual evoked potentials in preschool Inuit children exposed to methylmercury and polychlorinated biphenyls from a marine diet. *Neurotoxicology* 27:567–78.

Salam, M. T., Li, Y. F., Langholz, B., and Gilliland, F. D. 2004. Early-life environmental risk factors for asthma: findings from the Children's Health Study. *Environ. Health Perspect.* 112:760–765.

Salameh, P. R., Baldi, I., Brochard, P., Raherison, C., Abi Saleh, B., and Salamon, R. 2003. Respiratory symptoms in children and exposure to pesticides. *Eur. Respir. J.* 22:507–12.

Salazar-Garcia, F., Gallardo-Diaz, E., Ceron-Mireles, P., Loomis, D., and Borja-Aburto, V. H. 2004. Reproductive effects of occupational DDT exposure among male malaria control workers. *Environ. Health Perspect.* 112:542–547.

Sallmen, M., Baird, D. D., Hoppin, J. A., Blair, A., and Sandler, D. P. 2006. Fertility and exposure to solvents among families in the Agricultural Health Study. *Occup. Environ. Med.* 63:469–75.

Sallmen, M., Liesivuori, J., Taskinen, H., Lindbohm, M. L., Anttila, A., Aalto, L., and Hemminki, K. 2003. Time to pregnancy among the wives of Finnish greenhouse workers. *Scand. J. Work Environ. Health* 29:85–93.

Sallmen, M., Lindbohm, M. L., Anttila, A., Kyyronen, P., Taskinen, H., Nykyri, E., and Hemminki, K. 1998. Time to pregnancy among the wives of men exposed to organic solvents. *Occup. Environ. Med.* 55:24–30.

Salpietro, C. D., Gangemi, S., Minciullo, P. L., Briuglia, S., Merlino, M. V., Stelitano, A., Cristani, M., Trombetta, D., and Saija, A. 2002. Cadmium concentration in maternal and cord blood and infant birth weight: a study on healthy nonsmoking women. *J. Perinat. Med.* 30:395–399.

Savitz, D. A., Arbuckle, T., Kaczor, D., and Curtis, K. M. 1997a. Male pesticide exposure and pregnancy outcome. *Am. J. Epidemiol.* 146: 1025–1036.

Savitz, D. A., Brett, K. M., Dole, N., and Tse, C. K. 1997b. Male and female occupation in relation to miscarriage and preterm delivery in central North Carolina. *Ann. Epidemiol.* 7:509–516.

Savitz, D. A., and Feingold, L. 1989. Association of childhood cancer with residential traffic density. *Scand. J. Work Environ. Health* 15:360–363.

Savitz, D. A., Whelan, E. A., and Kleckner, R. C. 1989a. Effect of parents' occupational exposures on risk of stillbirth, preterm delivery, and small-for-gestational-age infants. *Am. J. Epidemiol.* 129:1201–1218.

Savitz, D. A., Whelan, E. A., and Kleckner, R. C. 1989b. Self-reported exposure to pesticides and radiation related to pregnancy outcome—Results from National Natality and Fetal Mortality Surveys. *Public Health Rep.* 104:473–477 .

Schantz, S. L. 1996. Developmental neurotoxicity of PCBs in humans: what do we know and where do we go from here? *Neurotoxicol. Teratol.* 18:217–27.

Schantz, S. L., Widholm, J. J., and Rice, D. C. 2003. Effects of PCB exposure on neuropsychological function in children. *Environ. Health Perspect.* 111:357–376.

Scheele, J., Teufel, M., and Niessen, K. H. 1992. Chlorinated hydrocarbons in the bone marrow of children: studies on their association with leukaemia. *Eur. J. Pediatr.* 151: 802–805.

Schenker, M. B., Gold, E. B., Beaumont, J. J., Eskenazi, B., Hammond, S. K., Lasley, B. L., McCurdy, S. A., Samuels, S. J., Saiki, C. L., and Swan, S. H. 1995. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *Am. J. Ind. Med.* 28:639–659.

Schnaas, L., Rothenberg, S. J., Flores, M. F., Martinez, S., Hernandez, C., Osorio, E., Velasco, S. R., and Perroni, E. 2006. Reduced intellectual development in children with prenatal lead exposure. *Environ. Health Perspect.* 114:791–797.

Schnaas, L., Rothenberg, S. J., Perroni, E., Martinez, S., Hernandez, C., and Hernandez, R. M. 2000. Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. *Neurotoxicol. Teratol.* 22:805–810.

Schneider, D., Freeman, N. C., and McGarvey, P. 2004. Asthma and respiratory dysfunction among urban, primarily Hispanic school children. *Arch. Environ. Health* 59:4–13.

Schnorr, T. M., Lawson, C. C., Whelan, E. A., Dankovic, D. A., Deddens, J. A., Piacitelli, L. A., Reefhuis, J., Sweeney, M. H., Connally, L. B., and Fingerhut, M. A. 2001. Spontaneous abortion, sex ratio, and paternal occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Environ. Health Perspect.* 109:1127–1132.

Schonfelder, G., Wittfoht, W., Hopp, H., Talsness, C. E., Paul, M., and Chahoud, I. 2002. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. *Environ. Health Perspect.* 110:A703–707.

Schreinemachers, D. M. 2003. Birth malformations and other adverse perinatal outcomes in four U.S. Wheat-producing states. *Environ. Health Perspect.* 111:1259–1264.

Schuz, J., Kaletsch, U., Kaatsch, P., Meinert, R., and Michaelis, J. 2001. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med. Pediatr.* Oncol 36:274–282.

Schuz, J., Kaletsch, U., Meinert, R., Kaatsch, P., and Michaelis, J. 2000. Risk of childhood leukemia and parental self-reported occupational exposure to chemicals, dusts, and fumes: results from pooled analyses of German population-based case-control studies. *Cancer Epidemiol. Biomarkers Prev.* 9:835–838.

Schuz, J., Kaletsch, U., Meinert, R., Kaatsch, P., and Michaelis, J. 2001. High-birth weight and other risk factors for Wilms tumour: Results of a population-based case-control study. *Eur. J. Pediatr.* 160:333–338.

Schwartz, D. A., and LoGerfo, J. P. 1988. Congenital limb reduction defects in the agricultural setting. *Am. J. Public Health* 78:654–658.

Schwartz, J. 1993. Beyond LOEL's, p values, and vote counting: Methods for looking at the shapes and strengths of associations. *Neurotoxicology* 14:237–246.

Schwartz, J. 1994. Low-level lead exposure and children's IQ: A meta-analysis and search for a threshold. *Environ. Res.* 65:42–55.

Schwartz, J. 2004. Air pollution and children's health. *Pediatrics* 113:1037–1043.

Schwartz, J., Angle, C., and Pitcher, H. 1986. Relationship between childhood blood lead levels and stature. *Pediatrics* 77:281–288.

Schwartz, J., and Otto, D. 1987. Blood lead, hearing thresholds, and neurobehavioral development in children and youth. *Arch. Environ. Health* 42:153–160.

Schwartz, J., and Otto, D. 1991. Lead and minor hearing impairment. *Arch. Environ. Health* 46:300–305.

Seidler, A., Raum, E., Arabin, B., Hellenbrand, W., Walter, U., and Schwartz, F. W. 1999. Maternal occupational exposure to chemical substances and the risk of infants small-for-gestational-age. *Am. J. Ind. Med.* 36:213–222.

Selevan, S. G., Kimmel, C. A., and Mendola, P. 2000. Identifying critical windows of exposure for children's health. *Environ. Health Perspect.* 108 Suppl 3:451–455.

Selevan, S. G., Rice, D. C., Hogan, K. A., Euling, S. Y., Pfahles-Hutchens, A., and Bethel, J. 2003. Blood lead concentration and delayed puberty in girls. *N. Engl. J. Med.* 348:1527–1536.

Sever, L. E., Arbuckle, T. E., and Sweeney, A. 1997. Reproductive and developmental effects of occupational pesticide exposure: The epidemiologic evidence. *Occup. Med.* 12:305–325.

Shapiro, G. G., and Stout, J. W. 2002. Childhood asthma in the United States: Urban issues. *Pediatr. Pulmonol.* 33:47–55.

Sharpe, C. R., Franco, E. L., de Camargo, B., Lopes, L. F., Barreto, J. H., Johnsson, R. R., and Mauad, M. A. 1995. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. *Am. J. Epidemiol.* 141:210–217.

Shaw, G. M., Nelson, V., Iovannisci, D. M., Finnell, R. H., and Lammer, E. J. 2003a. Maternal occupational chemical exposures and biotransformation genotypes as risk factors for selected congenital anomalies. *Am. J. Epidemiol.* 157:475–484.

Shaw, G. M., Ranatunga, D., Quach, T., Neri, E., Correa, A., and Neutra, R. R. 2003b. Trihalomethane exposures from municipal water supplies and selected congenital malformations. *Epidemiology* 14:191–199.

Shaw, G. M., Wasserman, C. R., O'Malley, C. D., Nelson, V., and Jackson, R. J. 1999. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 10:60–66.

Shen, X. M., Yan, C. H., Guo, D., Wu, S. M., Li, R. Q., Huang, H., Ao, L. M., Zhou, J. D., Hong, Z. Y., Xu, J. D., Jin, X. M., and Tang, J. M. 1998. Low-level prenatal lead exposure and neurobehavioral development of children in the first year of life: A prospective study in Shanghai. *Environ. Res.* 79:1–8.

Shi, L., and Chia, S. E. 2001. A review of studies on maternal occupational exposures and birth defects, and the limitations associated with these studies. *Occup. Med.* 51:230–244.

Shiau, C. Y., Wang, J. D., and Chen, P. C. 2004. Decreased fecundity among male lead workers. *Occup. Environ. Med.* 61:915–923.

Shima, M., and Adachi, M. 2000. Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren. *Int. J. Epidemiol.* 29:862–870.

Shima, M., Nitta, Y., and Adachi, M. 2003. Traffic-related air pollution and respiratory symptoms in children living along trunk roads in Chiba Prefecture, Japan. *J. Epidemiol.* 13:108–119.

Shima, M., Nitta, Y., Ando, M., and Adachi, M. 2002. Effects of air pollution on the prevalence and incidence of asthma in children. *Arch. Environ. Health* 57:529–535.

Shu, X. O., Gao, Y. T., Brinton, L. A., Linet, M. S., Tu, J. T., Zheng, W., and Fraumeni, J. F. 1988. A population-based case-control study of childhood leukemia in Shanghai. *Cancer* 62:635–644.

Shu, X. O., Nesbit, M. E., Buckley, J. D., Krailo, M. D., and Robinson, L. L. 1995. An exploratory analysis of risk factors for childhood malignant germ- cell tumors: Report from the Childrens Cancer Group (Canada, United States). *Cancer Causes Control* 6:187–198.

Shu, X. O., Perentesis, J. P., Wen, W., Buckley, J. D., Boyle, E., Ross, J. A., and Robison, L. L. 2004. Parental exposure to medications and hydrocarbons and ras mutations in children with acute lymphoblastic leukemia: A report from the Children's Oncology Group. *Cancer Epidemiol. Biomarkers Prev.* 13:1230–1235.

Shu, X. O., Stewart, P., Wen, W. Q., Han, D., Potter, J. D., Buckley, J. D., Heineman, E., and Robison, L. L. 1999. Parental occupational exposure to hydrocarbons and risk of acute lymphocytic leukemia in offspring. *Cancer Epidemiol. Biomarkers Prev.* 8:783–791.

Shukla, R., Bornschein, R. L., Dietrich, K. N., Buncher, C. R., Berger, O. G., Hammond, P. B., and Succop, P. A. 1989. Fetal and infant lead exposure: Effects on growth in stature. *Pediatrics* 84:604–612.

Shukla, R., Dietrich, K. N., Bornschein, R. L., Berger, O., and Hammond, P. B. 1991. Lead exposure and growth in the early preschool child: A follow-up report from the Cincinnati Lead Study. *Pediatrics* 88:886–892.

Silva, P. A., Hughes, P., Williams, S., and Faed, J. M. 1988. Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. *J. Child Psychol. Psychiatry* 29:43–52.

Small, C. M., Cheslack-Postava, K., Terrell, M., Blanck, H. M., Tolbert, P., Rubin, C., Henderson, A., and Marcus, M. 2007. Risk of spontaneous abortion among women exposed to polybrominated biphenyls. *Environ. Res.* [Epub Ahead of Print] .

Smith, A. H., Marshall, G., Yuan, Y., Ferreccio, C., Liaw, J., von Ehrenstein, O., Steinmaus, C., Bates, M. N., and Selvin, S. 2006. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *Environ. Health Perspect.* 114:1293–1296.

Sonnenfeld, N., Hertz-Picciotto, I., and Kaye, W. E. 2001. Tetrachloroethylene in drinking water and birth outcomes at the US Marine Corps Base at Camp Lejeune, North Carolina. *Am. J. Epidemiol.* 154:902–908.

Sosniak, W. A., Kaye, W. E., and Gomez, T. M. 1994. Data linkage to explore the risk of low birthweight associated with maternal proximity to hazardous waste sites from the National Priorities List. *Arch. Environ. Health* 49:251–255.

Spinelli, A., Figa-Talamanca, I., and Osborn, J. 1997. Time to pregnancy and occupation in a group of Italian women. *Int. J. Epidemiol.* 26:601–609.

Staessen, J. A., Nawrot, T., Hond, E. D., Thijs, L., Fagard, R., Hoppenbrouwers, K., Koppen, G., Nelen, V., Schoeters, G., Vanderschueren, D., Van Hecke, E., Verschaeve, L., Vlietinck, R., and Roels, H. A. 2001. Renal function, cytogenetic measurements, and sexual development in adolescents in relation to environmental pollutants: A feasibility study of biomarkers. Lancet 357:1660–1669.

Steffen, C., Auclerc, M. F., Auvrignon, A., Baruchel, A., Kebaili, K., Lambilliotte, A., Leverger, G., Sommelet, D., Vilmer, E., Hemon, D., and Clavel, J. 2004. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; A case-control study. *Occup. Environ. Med.* 61:773–778.

Steliarova-Foucher, E., Stiller, C., Kaatsch, P., Berrino, F., Coebergh, J. W., Lacour, B., and Parkin, M. 2004. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): An epidemiological study. *Lancet* 364:2097–2105.

Steuerwald, U., Weihe, P., Jorgensen, P. J., Bjerve, K., Brock, J., Heinzow, B., Budtz-Jorgensen, E., and Grandjean, P. 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *J. Pediatr.* 136:599–605.

Stewart, P., Reihman, J., Lonky, E., Darvill, T., and Pagano, J. 2000. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. *Neurotoxicol. Teratol.* 22:21–29.

Stewart, P. W., Reihman, J., Lonky, E. I., Darvill, T. J., and Pagano, J. 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol. Teratol.* 25:11–22.

Steyn, K., de Wet, T., Saloojee, Y., Nel, H., and Yach, D. 2006. The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: The Birth To Ten Study. *Paediatr. Perinat. Epidemiol.* 20:90–99.

Stiles, K. M., and Bellinger, D. C. 1993. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. *Neurotoxicol. Teratol.* 15:27–35.

Stockbauer, J. W., Hoffman, R. E., Schramm, W. F., and Edmonds, L. D. 1988. Reproductive outcomes of mothers with potential exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Am. J. Epidemiol.* 128:410–419.

Stokes, L., Letz, R., Gerr, F., Kolczak, M., McNeill, F. E., Chettle, D. R., and Kaye, W. E. 1998. Neurotoxicity in young adults 20 years after childhood exposure to lead: The Bunker Hill experience. *Occup. Environ. Med.* 55:507–516.

Storgaard, L., Bonde, J. P., and Olsen, J. 2006. Male reproductive disorders in humans and prenatal indicators of estrogen exposure. A review of published epidemiological studies. *Reprod. Toxicol.* 21:4–15.

Strachan, D. P., and Cook, D. G. 1998a. Parental smoking, middle ear disease and adenotonsillectomy in children. *Thorax* 53:50–56.

Strachan, D. P., and Cook, D. G. 1998b. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 53:204–212.

Suarez, L., Gilani, Z., Felkner, M., Brender, J., Henry, J., and Hendricks, K. 2005. Exposure to polychlorinated biphenyls and risk of neural-tube defects in a Mexican American population. *Int. J. Occup. Environ. Health* 11:233–237.

Sugiura-Ogasawara, M., Ozaki, Y., Sonta, S., Makino, T., and Suzumori, K. 2003. PCBs, hexachlorobenzene and DDE are not associated with recurrent miscarriage. *Am. J. Reprod. Immunol.* 50:485–489.

Sugiura-Ogasawara, M., Ozaki, Y., Sonta, S., Makino, T., and Suzumori, K. 2005. Exposure to bisphenol A is associated with recurrent miscarriage. *Hum. Reprod.* 20:2325–2329.

Suh, H. H., Bahadori, T., Vallarino, J., and Spengler, J. D. 2000. Criteria air pollutants and toxic air pollutants. *Environ. Health Perspect.* 108(Suppl. 4):625–633.

Sunyer, J., Torrent, M., Munoz-Ortiz, L., Ribas-Fito, N., Carrizo, D., Grimalt, J., Anto, J. M., and Cullinan, P. 2005. Prenatal dichlorodiphenyldichloroethylene (DDE) and asthma in children. *Environ. Health Perspect.* 113:1787–90.

Swan, S. H., Beaumont, J. J., Hammond, S. K., VonBehren, J., Green, R. S., Hallock, M. F., Woskie, S. R., Hines, C. J., and Schenker, M. B. 1995. Historical cohort study of spontaneous abortion among fabrication workers in the Semiconductor Health Study: Agent-level analysis. *Am. J. Ind. Med.* 28:751–769.

Swan, S. H., Main, K. M., Liu, F., Stewart, S. L., Kruse, R. L., Calafat, A. M., Mao, C. S., Redmon, J. B., Ternand, C. L., Sullivan, S., and Teague, J. L. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ. Health Perspect.* 113:1056–1061.

Sweeney, M. H., and Mocarelli, P. 2000. Human health effects after exposure to 2,3,7,8-TCDD. *Food Addit. Contam.* 17:303–316.

Taha, T. E., and Gray, R. H. 1993. Agricultural pesticide exposure and perinatal mortality in central Sudan. Bull World Health Organ 71:317–321.

Tajimi, M., Uehara, R., Watanabe, M., Oki, I., Ojima, T., and Nakamura, Y. 2005. Relationship of PCDD/F and Co-PCB concentrations in breast milk with infant birthweights in Tokyo, Japan. *Chemosphere* 61:383–388.

Takser, L., Mergler, D., Hellier, G., Sahuquillo, J., and Huel, G. 2003. Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology* 24:667–674.

Tango, T., Fujita, T., Tanihata, T., Minowa, M., Doi, Y., Kato, N., Kunikane, S., Uchiyama, I., Tanaka, M., and Uehata, T. 2004. Risk of adverse reproductive outcomes associated with proximity to municipal solid waste incinerators with high dioxin emission levels in Japan. *J. Epidemiol.* 14:83–93.

Taskinen, H., Anttila, A., Lindbohm, M. L., Sallmen, M., and Hemminki, K. 1989. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work Environ. Health* 15:345–352.

Taskinen, H., Kyyronen, P., Hemminki, K., Hoikkala, M., Lajunen, K., and Lindbohm, M. L. 1994. Laboratory work and pregnancy outcome. *J. Occup. Med.* 36:311–319.

Taskinen, H. K., Kyyronen, P., Sallmen, M., Virtanen, S. V., Liukkonen, T. A., Huida, O., Lindbohm, M. L., and Anttila, A. 1999. Reduced fertility among female wood workers exposed to formaldehyde. *Am. J. Ind. Med.* 36:206–212.

Taub, J. W., and Ge, Y. 2004. The prenatal origin of childhood acute lymphoblastic leukemia. *Leuk. Lymphoma* 45:19–25.

Taylor, P. R., Stelma, J. M., and Lawrence, C. E. 1989. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. *Am. J. Epidemiol.* 129:395–406.

Tellez-Rojo, M. M., Bellinger, D. C., Arroyo-Quiroz, C., Lamadrid-Figueroa, H., Mercado-Garcia, A., Schnaas-Arrieta, L., Wright, R. O., Hernandez-Avila, M., and Hu, H. 2006. Longitudinal associations between blood lead concentrations lower than 10 microg/dl and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* 118:323–330.

Thacker, S. B., Hoffman, D. A., Smith, J., Steinberg, K., and Zack, M. 1992. Effect of low-level body burdens of lead on the mental development of children: Limitations of meta-analysis in a review of longitudinal data. *Arch. Environ. Health* 47:336–346.

Thatcher, R. W., Lester, M. L., McAlaster, R., and Horst, R. 1982. Effects of low levels of cadmium and lead on cognitive functioning in children. *Arch. Environ. Health* 37:159–166.

Thomas, D. C., Petitti, D. B., Goldhaber, M., Swan, S. H., Rappaport, E. B., and Hertz-Picciotto, I. 1992. Reproductive outcomes in relation to malathion spraying in the San Francisco Bay Area, 1981–1982. *Epidemiology* 3:32–39.

Thonneau, P., Abell, A., Larsen, S. B., Bonde, J. P., Joffe, M., Clavert, A., Ducot, B., Multigner, L., and Danscher, G. 1999. Effects of pesticide exposure on time to pregnancy: results of a multicenter study in France and Denmark. ASCLEPIOS Study Group. *Am. J. Epidemiol.* 150:157–163.

Thorpe, N., and Shirmohammadi, A. 2005. Herbicides and nitrates in groundwater of Maryland and childhood cancers: A geographic information systems approach. *J. Environ. Sci. Health C Environ. Carcinogen. Ecotoxicol. Rev.* 23:261–278.

Tikkanen, J., and Heinonen, O. P. 1991. Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring. *Teratology* 43:591–600.

Tikkanen, J., and Heinonen, O. P. 1992a. Occupational risk factors for congenital heart disease. *Int. Arch. Occup. Environ. Health* 64:59–64.

Tikkanen, J., and Heinonen, O. P. 1992b. Risk factors for conal malformations of the heart. *Eur. J. Epidemiol.* 8:48–57.

Tilson, H. A., and Kodavanti, P. R. 1997. Neurochemical effects of polychlorinated biphenyls: An overview and identification of research needs. *Neurotoxicology* 18:727–743.

Toft, G., Hagmar, L., Giwercman, A., and Bonde, J. P. 2004. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. *Reprod. Toxicol.* 19:5–26.

Toledano, M. B., Nieuwenhuijsen, M. J., Best, N., Whitaker, H., Hambly, P., de Hoogh, C., Fawell, J., Jarup, L., and Elliott, P. 2005. Relation of trihalomethane concentrations in public water supplies to stillbirth and birth weight in three water regions in England. *Environ. Health Perspect.* 113:225–232.

Tong, S., Baghurst, P., McMichael, A., Sawyer, M., and Mudge, J. 1996. Lifetime exposure to environmental lead and children's intelligence at 11–13 years: The Port Pirie cohort study. *Br. Med. J.* 312:1569–1575.

Tong, S., Baghurst, P. A., Sawyer, M. G., Burns, J., and McMichael, A. J. 1998. Declining blood lead levels and changes in cognitive function during childhood: The Port Pirie Cohort Study. *J. Am. Med. Assoc.* 280:1915–1919.

Tong, S., and Colditz, P. 2004. Air pollution and sudden infant death syndrome: A literature review. *Paediatr. Perinat. Epidemiol.* 18:327–335.

Torchio, P., Lepore, A. R., Corrao, G., Comba, P., Settimi, L., Belli, S., Magnani, C., and di Orio, F. 1994. Mortality study on a cohort of Italian licensed pesticide users. *Sci. Total Environ.* 149:183–191.

Torres-Arreola, L., Berkowitz, G., Torres-Sanchez, L., Lopez-Cervantes, M., Cebrian, M. E., Uribe, M., and Lopez-Carrillo, L. 2003. Preterm birth in relation to maternal organochlorine serum levels. *Ann. Epidemiol.* 13:158–162.

Torres-Sanchez, L. E., Berkowitz, G., Lopez-Carrillo, L., Torres-Arreola, L., Rios, C., and Lopez-Cervantes, M. 1999. Intrauterine lead exposure and preterm birth. *Environ. Res.* 81:297–301.

Tryphonas, H. 1998. The impact of PCBs and dioxins on children's health: Immunological considerations. *Can. J. Public Health* 89 Suppl 1:S49–57.

Tsai, J., Kaye, W. E., and Bove, F. J. 2006. Wilms' tumor and exposures to residential and occupational hazardous chemicals. *Int. J. Hyg. Environ. Health* 209:57–64.

Tsai, S. S., Yu, H. S., Chang, C. C., Chuang, H. Y., and Yang, C. Y. 2004. Increased risk of preterm delivery in women residing near thermal power plants in Taiwan. *Arch. Environ. Health* 59:478–483.

Tsai, S. S., Yu, H. S., Liu, C. C., and Yang, C. Y. 2003. Increased incidence of preterm delivery in mothers residing in an industrialized area in Taiwan. *J. Toxicol. Environ. Health A* 66:987–994.

Tyshenko, M., Benidickson, J., Turner, M. C., Craig, L., Armstrong, V., Harrison, J., and Krewski, D. 2006. Regulatory and nonregulatory strategies for improving children's environmental health in Canada. *J. Toxicol. Environ. Health B* 10:143–156.

U.S. Department of Health and Human Services. 2001. Women and smoking: a report of the Surgeon General. Located at: http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2001/00_pdfs/chp3.pdf.

U.S. Department of Health and Human Services . 2003. Child Health USA 2003. Rockville, Maryland: U.S. Department of Health and Human Services.

U.S. Department of Health and Human Services. 2004. The health consequences of smoking: a report of the Surgeon General. Located at: http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/index.htm.

U.S. Department of Health and Human Services. 2006. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Located at: http://www.surgeongeneral.gov/library/secondhandsmoke/.

U.S. Department of Health EaW. 1964. *Smoking and health. Report of the advisory committee to the Surgeon General of the Public Health Service*. Washington, DC: Public Health Service, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103.

U.S. Environmental Protection Agency. 2001. Chemical testing and information home page. Located at: http://www.epa.gov/opptintr/chemtest/index.htm.

United Nations Environment Programme. 2002. Global mercury assessment. Located at: http://www.chem.unep.ch/mercury/Report/final-report-download.htm.

Valery, P. C., McWhirter, W., Sleigh, A., Williams, G., and Bain, C. 2002. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: A national case-control study. *Cancer Causes Control* 13:263–270.

van Steensel-Moll, H. A., Valkenburg, H. A., and van Zanen, G. E. 1985. Childhood leukemia and parental occupation. A register-based case- control study. *Am. J. Epidemiol.* 121:216–224.

van Wijngaarden, E., Beck, C., Shamlaye, C. F., Cernichiari, E., Davidson, P. W., Myers, G. J., and Clarkson, T. W. 2006. Benchmark concentrations for methyl mercury obtained from the 9-year follow-up of the Seychelles Child Development Study. Neurotoxicology 27:702–709.

van Wijngaarden, E., Stewart, P. A., Olshan, A. F., Savitz, D. A., and Bunin, G. R. 2003. Parental occupational exposure to pesticides and childhood brain cancer. *Am. J. Epidemiol.* 157:989–997.

Vartiainen, T., Jaakkola, J. J., Saarikoski, S., and Tuomisto, J. 1998 . Birth weight and sex of children and the correlation to the body burden of PCDDs/PCDFs and PCBs of the mother. *Environ. Health Perspect.* 106:61–66.

Vasiliu, O., Muttineni, J., and Karmaus, W. 2004. In utero exposure to organochlorines and age at menarche. *Hum. Reprod.* 19:1506–12.

Venners, S. A., Korrick, S., Xu, X., Chen, C., Guang, W., Huang, A., Altshul, L., Perry, M., Fu, L., and Wang, X. 2005. Preconception serum DDT and pregnancy loss: A prospective study using a biomarker of pregnancy. *Am. J. Epidemiol.* 162:709–716.

Verberk, M. M., Willems, T. E., Verplanke, A. J., and De Wolff, F. A. 1996. Environmental lead and renal effects in children. *Arch. Environ. Health* 51:83–87.

Villeneuve, P. J., Johnson, K. C., Mao, Y., and Hanley, A. J. 2004. Environmental tobacco smoke and the risk of pancreatic cancer: Findings from a Canadian population-based case-control study. *Can. J. Public Health* 95:32–37.

Vinceti, M., Rovesti, S., Bergomi, M., Calzolari, E., Candela, S., Campagna, A., Milan, M., and Vivoli, G. 2001. Risk of birth defects in a population exposed to environmental lead pollution. *Sci. Total Environ.* 278: 23–30.

Vineis, P., Terracini, B., Ciccone, G., Cignetti, A., Colombo, E., Donna, A., Maffi, L., Pisa, R., Ricci, P., Zanini, E., and et, a. l. 1987. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders. A population-based case-referent study. *Scand. J. Work Environ. Health* 13:9–17.

Vivoli, G., Fantuzzi, G., Bergomi, M., Tonelli, E., Gatto, M. R., Zanetti, F., and Del Dot, M. 1993. Relationship between low lead exposure and somatic growth in adolescents. *J. Expos. Anal. Environ. Epidemiol.* 3 Suppl 1:201–209.

Vreugdenhil, H. J., Lanting, C. I., Mulder, P. G., Boersma, E. R., and Weisglas-Kuperus, N. 2002. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. *J. Pediatr.* 140:48–56.

Vreugdenhil, H. J., Mulder, P. G., Emmen, H. H., and Weisglas-Kuperus, N. 2004a. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. *Neuropsychology* 18:185–193.

Vreugdenhil, H. J., Van Zanten, G. A., Brocaar, M. P., Mulder, P. G., and Weisglas-Kuperus, N. 2004b. Prenatal exposure to polychlorinated biphenyls and breastfeeding: opposing effects on auditory P300 latencies in 9-year-old Dutch children. *Dev. Med. Child. Neurol.* 46:398–405.

Vrijheid, M. 2000. Health effects of residence near hazardous waste landfill sites: a review of epidemiologic literature. *Environ. Health Perspect.* 108(Suppl. 1):101–112.

Vrijheid, M., Armstrong, B., Dolk, H., van Tongeren, M., and Botting, B. 2003. Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. *Occup. Environ. Med.* 60:543–550.

Vrijheid, M., Dolk, H., Armstrong, B., Abramsky, L., Bianchi, F., Fazarinc, I., Garne, E., Ide, R., Nelen, V., Robert, E., Scott, J. E., Stone, D., and Tenconi, R. 2002a. Chromosomal congenital anomalies and residence near hazardous waste landfill sites. *Lancet* 359:320–322.

Vrijheid, M., Dolk, H., Armstrong, B., Boschi, G., Busby, A., Jorgensen, T., and Pointer, P. 2002b. Hazard potential ranking of hazardous waste landfill sites and risk of congenital anomalies. *Occup. Environ. Med.* 59:768–776.

Walkowiak, J., Altmann, L., Kramer, U., Sveinsson, K., Turfeld, M., Weishoff-Houben, M., and Winneke, G. 1998. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. *Neurotoxicol. Teratol.* 20:511–521.

Walkowiak, J., Wiener, J. A., Fastabend, A., Heinzow, B., Kramer, U., Schmidt, E., Steingruber, H. J., Wundram, S., and Winneke, G. 2001. Environmental exposure to polychlorinated biphenyls and quality of the home environment: Effects on psychodevelopment in early childhood. *Lancet* 358:1602–1607.

Wang, S. L., Chen, T. T., Hsu, J. F., Hsu, C. C., Chang, L. W., Ryan, J. J., Guo, Y. L., and Lambert, G. H. 2003a. Neonatal and childhood teeth in relation to perinatal exposure to polychlorinated biphenyls and dibenzofurans: observations of the Yucheng children in Taiwan. *Environ. Res.* 93:131–137.

Wang, X., Chen, C., Wang, L., Chen, D., Guang, W., and French, J. 2003b . Conception, early pregnancy loss, and time to clinical pregnancy: A population-based prospective study. *Fertil. Steril.* 79:577–584.

Wasserman, G., Graziano, J. H., Factor-Litvak, P., Popovac, D., Morina, N., Musabegovic, A., Vrenezi, N., Capuni-Paracka, S., Lekic, V., Preteni-Redjepi, E. and others. 1992. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. *J. Pediatr.* 121:695–703.

Wasserman, G. A., Factor-Litvak, P., Liu, X., Todd, A. C., Kline, J. K., Slavkovich, V., Popovac, D., and Graziano, J. H. 2003. The relationship between blood lead, bone lead and child intelligence. *Neuropsychol. Dev. Cogn. Sect. C Child Neuropsychol.* 9:22–34.

Wasserman, G. A., Liu, X., Lolacono, N. J., Factor-Litvak, P., Kline, J. K., Popovac, D., Morina, N., Musabegovic, A., Vrenezi, N., Capuni-Paracka, S., Lekic, V., Preteni-Redjepi, E., Hadzialjevic, S., Slavkovich, V., and Graziano, J. H. 1997. Lead exposure and intelligence in 7-year-old children: The Yugoslavia Prospective Study. *Environ. Health Perspect.* 105:956–962.

Wasserman, G. A., Liu, X., Popovac, D., Factor-Litvak, P., Kline, J., Waternaux, C., LoIacono, N., and Graziano, J. H. 2000a. The Yugoslavia Prospective Lead Study: Contributions of prenatal and postnatal lead exposure to early intelligence. *Neurotoxicol. Teratol.* 22:811–818.

Wasserman, G. A., Musabegovic, A., Liu, X., Kline, J., Factor-Litvak, P., and Graziano, J. H. 2000b. Lead exposure and motor functioning in 4(1/2)-year-old children: The Yugoslavia prospective study. *J. Pediatr.* 137:555–561.

Wasserman, G. A., Staghezza-Jaramillo, B., Shrout, P., Popovac, D., and Graziano, J. 1998. The effect of lead exposure on behavior problems in preschool children. *Am. J. Public Health* 88:481–486.

Weidner, I. S., Moller, H., Jensen, T. K., and Skakkebaek, N. E. 1998. Cryptorchidism and hypospadias in sons of gardeners and farmers. *Environ. Health Perspect.* 106:793–796.

Weihe, P., Hansen, J. C., Murata, K., Debes, F., Jorgensen, P., Steuerwald, U., White, R. F., and Grandjean, P. 2002. Neurobehavioral performance of Inuit children with increased prenatal exposure to methylmercury. *Int. J. Circumpolar Health* 61:41–49.

Weisglas-Kuperus, N., Patandin, S., Berbers, G. A., Sas, T. C., Mulder, P. G., Sauer, P. J., and Hooijkaas, H. 2000. Immunologic effects of background exposure to polychlorinated biphenyls and dioxins in Dutch preschool children. *Environ. Health Perspect.* 108:1203–1207.

Weisglas-Kuperus, N., Vreugdenhil, H. J., and Mulder, P. G. 2004. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. *Toxicol. Lett.* 149:281–285.

Weisskopf, M. G., Anderson, H. A., Hanrahan, L. P., Kanarek, M. S., Falk, C. M., Steenport, D. M., and Draheim, L. A. 2005. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. *Environ. Res.* 97:149–162.

Wennborg, H., Bodin, L., Vainio, H., and Axelsson, G. 2000. Pregnancy outcome of personnel in Swedish biomedical research laboratories. *J. Occup. Environ. Med.* 42:438–446.

Wennborg, H., Bodin, L., Vainio, H., and Axelsson, G. 2001. Solvent use and time to pregnancy among female personnel in biomedical laboratories in Sweden. *Occup. Environ. Med.* 58:225–231.

Weselak, M., Arbuckle, T. E., and Foster, W. 2006. Pesticide exposures and developmental outcomes: the epidemiological evidence. *J. Toxicol. Environ. Health B* 10:41–80.

Weselak, M., Arbuckle, T. E., Wigle, D. T., and Krewski, D. 2007. In utero pesticide exposure and childhood morbidity. *Environ. Res.* 103:79–86.

Whyatt, R. M., Rauh, V., Barr, D. B., Camann, D. E., Andrews, H. F., Garfinkel, R., Hoepner, L. A., Diaz, D., Dietrich, J., Reyes, A., Tang, D., Kinney, P. L., and Perera, F. P. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ. Health Perspect.* 112:1125–1132.

Wigg, N. R., Vimpani, G. V., McMichael, A. J., Baghurst, P. A., Robertson, E. F., and Roberts, R. J. 1988. Port Pirie Cohort study: Childhood blood lead and neuropsychological development at age two years. *J. Epidemiol. Commun. Health* 42:213–219.

Wigle, D. T. 2003. *Child health and the environment*. New York: Oxford University Press.

Wigle, D. T. 2008. Child health and the environment: Supplemental bibliographies and epidemiologic evidence summary tables. Located at: http://www.mclaughlincentre.ca/research/child_health/book/index.shtml.

Wigle, D. T., Arbuckle, T. E., Walker, M., Wade, M. G., Liu, S., and Krewski, D. 2006. Environmental hazards: evidence for effects on child health. *J. Toxicol. Environ. Health B* 10:3–39.

Wiklund, K., Dich, J., and Holm, L. E. 1988. Soft tissue sarcoma risk in Swedish licensed pesticide applicators. J *Occup. Med.* 30:801–804.

Wilhelm, M., and Ritz, B. 2003. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994–1996. *Environ. Health Perspect.* 111:207–216.

Wilhelm, M., and Ritz, B. 2005. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. *Environ. Health Perspect.* 113:1212–1221.

Wilkins, J. R. 3rd, and Koutras, R. A. 1988. Paternal occupation and brain cancer in offspring: A mortality-based case-control study. *Am. J. Ind. Med.* 14:299–318.

Wilkins, J. R. 3rd, and Sinks, T. 1990. Parental occupation and intracranial neoplasms of childhood: Results of a case-control interview study. *Am. J. Epidemiol.* 132:275–292.

Willis, W. O., de Peyster, A., Molgaard, C. A., Walker, C., and MacKendrick, T. 1993. Pregnancy outcome among women exposed to pesticides through work or residence in an agricultural area. *J. Occup. Med.* 35:943–949.

Windham, G. C., Hopkins, B., Fenster, L., and Swan, S. H. 2000. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. *Epidemiology* 11:427–433.

Windham, G. C., Shusterman, D., Swan, S. H., Fenster, L., and Eskenazi, B. 1991. Exposure to organic solvents and adverse pregnancy outcome. *Am. J. Ind. Med.* 20:241–259.

Winneke, G., Altmann, L., Kramer, U., Turfeld, M., Behler, R., Gutsmuths, F. J., and Mangold, M. 1994. Neurobehavioral and neurophysiological observations in six year old children with low lead levels in East and West Germany. *Neurotoxicology* 15:705–713.

Winneke, G., Brockhaus, A., Ewers, U., Kramer, U., and Neuf, M. 1990. Results from the European multicenter study on lead neurotoxicity in children: Implications for risk assessment. *Neurotoxicol. Teratol.* 12:553–559.

Winneke, G., Bucholski, A., Heinzow, B., Kramer, U., Schmidt, E., Walkowiak, J., Wiener, J. A., and Steingruber, H. J. 1998. Developmental neurotoxicity of polychlorinated biphenyls (PCBS): Cognitive and psychomotor functions in 7-month old children. *Toxicol. Lett.* 102–103:423–428.

Winneke, G., Kramer, U., Brockhaus, A., Ewers, U., Kujanek, G., Lechner, H., and Janke, W. 1983. Neuropsychological studies in children with elevated tooth-lead concentrations. II. Extended study. *Int. Arch. Occup. Environ. Health* 51:231–252.

Wolfe, W. H., Michalek, J. E., Miner, J. C., Rahe, A. J., Moore, C. A., Needham, L. L., and Patterson, D. G. Jr. 1995. Paternal serum dioxin and reproductive outcomes among veterans of Operation Ranch Hand. *Epidemiology* 6:17–22.

Wollins, D. S., Ferencz, C., Boughman, J. A., and Loffredo, C. A. 2001 . A population-based study of coarctation of the aorta: comparisons of infants with and without associated ventricular septal defect. *Teratology* 64:229–236.

Wood, A. 2007. Compendium of pesticide common names. Located at: http://www.alanwood.net/pesticides/.

Woodruff, T. J., Parker, J. D., and Schoendorf, K. C. 2006. Fine particulate matter (PM2.5) air pollution and selected causes of postneonatal infant mortality in California. *Environ. Health Perspect.* 114:786–790.

World Health Organization. 1990. Environmental health criteria 101. Methylmercury. Located at: http://www.inchem.org/documents/ehc/ehc/ehc101.htm.

World Health Organization. 1999. International consultation on environmental tobacco smoke (ETS) and child health. Located at: http://www.who.int/tobacco/research/en/ets_report.pdf.

World Health Organization. 2000. Assessment of the health risk of dioxins; Re-evaluation of the tolerable daily intake (TDI): Executive summary. *Food Addit. Contam.* 17:223–240.

Wright, J. M., Schwartz, J., and Dockery, D. W. 2004. The effect of disinfection by-products and mutagenic activity on birth weight and gestational duration. *Environ. Health Perspect.* 112:920–925.

Wright, J. M., Schwartz, J., Vartiainen, T., Maki-Paakkanen, J., Altshul, L., Harrington, J. J., and Dockery, D. W. 2002. 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX) and mutagenic activity in Massachusetts drinking water. *Environ. Health Perspect.* 110:157–164.

Wu, T., Buck, G. M., and Mendola, P. 2003. Blood lead levels and sexual maturation in U.S. girls: The Third National Health and Nutrition Examination Survey, 1988–1994. *Environ. Health Perspect.* 111:737–741.

Wu, X., Groves, F. D., McLaughlin, C. C., Jemal, A., Martin, J., and Chen, V. W. 2005. Cancer incidence patterns among adolescents and young adults in the United States. *Cancer Causes Control* 16:309–320.

Wulff, M., Hogberg, U., and Sandstrom, A. I. 1995. Perinatal outcome among the offspring of employees and people living around a Swedish smelter. *Scand. J. Work Environ. Health* 21:277–282.

Wulff, M., Hogberg, U., and Sandstrom-Holmgren, A. 1996. Congenital malformations in the vicinity of a smelter in Northern Sweden, 1973–1990. *Paediatr. Perinat. Epidemiol.* 10:22–31.

Wulff, M., Hogberg, U., and Stenlund, H. 1999. The effect of smelter work on fecundity. *J. Occup. Environ. Med.* 41:678–685.

Wulff, M., Hogberg, U., and Stenlund, H. 2002. Occupational and environmental risks of spontaneous abortions around a smelter. *Am. J. Ind. Med.* 41:131–138 .

Yanez, L., Garcia-Nieto, E., Rojas, E., Carrizales, L., Mejia, J., Calderon, J., Razo, I., and Diaz-Barriga, F. 2003. DNA damage in blood cells from children exposed to arsenic and lead in a mining area. *Environ. Res.* 93:231–240.

Yang, C. Y. 2004. Drinking water chlorination and adverse birth outcomes in Taiwan. *Toxicology* 198:249–254.

Yang, C. Y., Chang, C. C., Chuang, H. Y., Ho, C. K., Wu, T. N., and Tsai, S. S. 2003a. Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan. *Arch. Environ. Health* 58: 649–654.

Yang, C. Y., Chang, C. C., Tsai, S. S., Chuang, H. Y., Ho, C. K., and Wu, T. N. 2003b. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environ. Res.* 91:29–34.

Yang, C. Y., Chang, C. C., Tsai, S. S., Chuang, H. Y., Ho, C. K., Wu, T. N., and Sung, F. C. 2003c. Preterm delivery among people living around Portland cement plants. *Environ. Res.* 92:64–68.

Yang, C. Y., Cheng, B. H., Hsu, T. Y., Chuang, H. Y., Wu, T. N., and Chen, P. C. 2002. Association between petrochemical air pollution and adverse pregnancy outcomes in Taiwan. *Arch. Environ. Health* 57:461–465.

Yang, C. Y., Cheng, B. H., Tsai, S. S., Wu, T. N., Lin, M. C., and Lin, K. C. 2000. Association between chlorination of drinking water and adverse pregnancy outcome in Taiwan. *Environ. Health Perspect.* 108:765–768.

Yang, C. Y., Tseng, Y. T., and Chang, C. C. 2003. Effects of air pollution on birth weight among children born between 1995 and 1997 in Kaohsiung, Taiwan. *J. Toxicol. Environ. Health A* 66:807–816.

Yolton, K., Dietrich, K., Auinger, P., Lanphear, B. P., and Hornung, R. 2005. Exposure to environmental tobacco smoke and cognitive abilities among U.S. children and adolescents. *Environ. Health Perspect.* 113:98–103.

Young, J. G., Eskenazi, B., Gladstone, E. A., Bradman, A., Pedersen, L., Johnson, C., Barr, D. B., Furlong, C. E., and Holland, N. T. 2005. Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology* 26:199–209.

Yu, C. L., Wang, S. F., Pan, P. C., Wu, M. T., Ho, C. K., Smith, T. J., Li, Y., Pothier, L., and Christiani, D. C. 2006. Residential exposure to petrochemicals and the risk of leukemia: Using geographic information system tools to estimate individual-level residential exposure. *Am. J. Epidemiol.* 164:200–207.

Yu, M. L., Guo, Y. L., Hsu, C. C., and Rogan, W. J. 2000. Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: Long-term follow-up interviews of the women from the Taiwan Yucheng cohort. *Int. J. Epidemiol.* 29:672–677.

Yu, M. L., Hsin, J. W., Hsu, C. C., Chan, W. C., and Guo, Y. L. 1998. The immunologic evaluation of the Yucheng children. *Chemosphere* 37:1855–1865.

Zahm, S. H., and Ward, M. H. 1998. Pesticides and childhood cancer. *Environ. Health Perspect.* 106(Suppl. 3):893–908.

Zhang, J., Cai, W. W., and Lee, D. J. 1992. Occupational hazards and pregnancy outcomes. *Am. J. Ind. Med.* 21:397–408.

Zhang, Y. L., Zhao, Y. C., Wang, J. X., Zhu, H. D., Liu, Q. F., Fan, Y. G., Wang, N. F., Zhao, J. H., Liu, H. S., Ou-Yang, L., Liu, A. P., and Fan, T. Q. 2004. Effect of environmental exposure to cadmium on pregnancy outcome and fetal growth: A study on healthy pregnant women in China. *J. Environ. Sci. Health A Tox. Hazard. Subst. Environ. Eng.* 39:2507–2515.

Zhu, J. L., Hjollund, N. H., Andersen, A. M., and Olsen, J. 2006. Occupational exposure to pesticides and pregnancy outcomes in gardeners and farmers: A study within the Danish National Birth Cohort. *J. Occup. Environ. Med.* 48:347–352.

Zierler, S., Theodore, M., Cohen, A., and Rothman, K. J. 1988. Chemical quality of maternal drinking water and congenital heart disease. *Int. J. Epidemiol.* 17:589–594.

Zmirou, D., Gauvin, S., Pin, I., Momas, I., Sahraoui, F., Just, J., Le Moullec, Y., Bremont, F., Cassadou, S., Reungoat, P., Albertini, M., Lauvergne, N., Chiron, M., and Labbe, A. 2004. Traffic related air pollution and incidence of childhood asthma: Results of the Vesta case-control study. *J. Epidemiol. Commun. Health* 58:18–23.

Zou, C., Zhao, Z., Tang, L., Chen, Z., and Du, L. 2003. The effect of lead on brainstem auditory evoked potentials in children. *Chin. Med. J.* (*Engl.*) 116:565–568.