

# Environmental contaminants and pregnancy outcomes

Gayle Windham, Ph.D., and Laura Fenster, Ph.D.

Division of Environmental and Occupational Disease Control, California Department of Public Health, Richmond, California

**Objective:** To review selected environmental, occupational, and other important risk factors for the following adverse pregnancy outcomes: low birth weight (LBW), intrauterine growth retardation (IUGR), and preterm delivery (PTD).

**Design:** The evidence is explored in greater detail for environmental tobacco smoke, drinking water disinfection byproducts, and organochlorine (DDT) and organophosphate pesticides, partly using a weight of evidence approach.

**Main Outcome Measure(s):** Low birth weight and IUGR are surrogate measures of fetal growth that are determined at delivery. Low birth weight is defined as <2,500 grams, and occurs in about 7% of US births. Intrauterine growth retardation is commonly defined as birth weight less than the tenth percentile for gestational week, using a standard population. Preterm delivery is birth at <37 weeks gestational age, and occurs in approximately 12% of US births.

**Result(s):** Numerous factors are associated with these endpoints that may be important to consider in studies of environmental exposures, such as young or old maternal age, race/ethnicity, multiple births, low socioeconomic status, inadequate prenatal care, low maternal weight gain, and infections and premature rupture of the membranes. Environmental contaminants found associated with increased risk of one or more of the endpoints include: tobacco smoke, carbon monoxide, air pollutants, heavy metals, pesticides, chlorination byproducts, and solvents.

**Conclusion(s):** Future research directions include measurement of exposure biomarkers during critical windows and consideration of genetic polymorphisms. (Fertil Steril® 2008;89:e111–6. ©2008 by American Society for Reproductive Medicine.)

**Key Words:** Pregnancy outcomes, low birth weight, preterm delivery, environmental exposures, chemicals, pesticides, environmental tobacco smoke

A healthy outcome of pregnancy is of primary concern to couples and families. The purpose of this presentation is to provide some background on studies of fetal growth and length of gestation, starting with usual classifications and their prevalence, as well as known risk factors. Exogenous exposures that have been associated with these are noted, with a more focused examination of several chemical classes based on a weight of evidence approach.

## ENDPOINTS/OUTCOMES

Fetal growth is generally assessed by surrogate measures at delivery, including length of gestation and fetal size, most commonly birth weight, as these are available on birth certificates. Mean birth weight may be compared between exposure groups or low birth weight (LBW) examined, defined as <2,500 grams. Low birth weight may be because of early delivery or reduced fetal growth in utero, so other measures are used to try to separate these etiologically. Intrauterine growth retardation (IUGR) or small for gestational age (SGA) are defined as less than the tenth percentile of weight for the gestational week of birth, based on a standard population that may be broken down by race, gender, or other characteristics. Low birth weight at term is sometimes examined as well. Low birth weight occurs in 5%–8% of live births in

the United States and in about 2% of term births (1). By definition, SGA occurs in about 10% of births. Length of gestation can be analyzed as a continuous variable, with pregnancies generally considered to be term at 40 weeks after the last menstrual period (LMP). More commonly, preterm delivery (PTD) is examined as the adverse outcome, defined as birth at <37 weeks gestational age, and occurring in approximately 12% of pregnancies in the United States (2). This represents an increase of 30% since 1981, the causes of which are not known (2).

These endpoints are important determinants of later health and morbidity (2, 3). Preterm delivery is the primary cause of death in the first month of life, and is a major cause of long-term health problems, estimated to cost \$26 billion in 2005 (2). Common risk factors for these endpoints include black race, multiple pregnancy, previous LBW or preterm delivery, short interpregnancy interval, older maternal age, and low socioeconomic status. Small for gestational age is also related to low maternal weight gain and inadequate prenatal care, and PTD is related to maternal medical conditions such as infections, urogenital anomalies, and placental abnormalities (4, 5). Common environmental exposures that have been associated with these endpoints (see Table 1) include tobacco smoke, lead, and other heavy metals, particulate air pollution, and pesticides (2, 5, 6). Carbon monoxide is strongly related to reduced fetal growth, and other compounds possibly associated include alcohol and other solvents, polychlorinated biphenyls (PCBs), and water disinfection byproducts.

Reprint requests: Gayle Windham, Ph.D., 850 Marina Bay Pkwy, Bldg. P, Richmond, California 94804 (FAX: 510-620-3638; E-mail: [gayle.windham@cdph.ca.gov](mailto:gayle.windham@cdph.ca.gov)).

**TABLE 1****Selected agents with potential adverse effects on fetal growth or gestational age, by strength of evidence<sup>a</sup>.**

Limited	Moderate	Strong
Carbon tetrachloride	Air pollution	Carbon monoxide
Dioxins/TCDD	Herbicides	Cocaine
PCE/TCE (in water) <sup>b</sup>	Metals (Pb, Hg, As) <sup>b</sup>	Ethanol
Perfluorinated acids	Nicotine	Tobacco smoke <sup>c</sup>
Phenoxyacetic	OC pesticides <sup>b,c</sup>	
Herbicides	OP pesticides <sup>b,c</sup>	
Phthalates	Pentachlorophenol	
	Polychlorinated	
	Biphenyls (PCBs)	
	Solvents	
	Water disinfection	
	Byproducts <sup>c</sup>	

<sup>a</sup> Compiled primarily from CHE Summary of Evidence Website (6) and LaDou, 2007 (5)—see those for details of specific endpoint associations. Bolded compounds are discussed in the text.

<sup>b</sup> PCE = perchlorethylene; TCE = trichloroethylene; metals include lead (Pb), mercury (Hg), and arsenic (As); OC = organochlorinated; OP = organophosphate.

<sup>c</sup> The evidence for these is discussed in detail in Results.

Windham. *Environmental contaminants and pregnancy. Fertil Steril* 2008.

## METHODS

### Weighing the Evidence

When determining whether certain chemicals may be related to a particular health endpoint, the body of evidence is considered, often using a weight of evidence approach as shown by several agencies (7, 8). The criteria for doing this are based on assessing the quality of individual studies as well as evaluating the body of literature, and are loosely based on the Bradford Hill criteria (after Sir Austin Bradford Hill). Individual study quality issues include appropriate study design and population, power, exposure assessment method, and analytic methods including control for confounders and consideration of biases. When evaluating the literature, higher quality studies may (or should be) given more weight; other considerations include the replicability of results in different populations and study designs, the magnitude of effects seen, whether there are dose–response effects (with some caveats), and biologic plausibility. Results across studies may be numerically combined using pooled or meta analyses. In practice, the literature often develops starting with smaller studies and/or crude exposure assessment, progressing to more specific exposure assessment methods and perhaps more specific health endpoints or susceptible subgroups, perhaps finally to incorporating biomarkers of exposure or endpoints.

An alternative approach for evaluating evidence is based on the precautionary principle; for example, rather than having to prove an adverse effect based on numerous studies, early indications of harm or related toxicologic data are more strongly considered. Taking it further, proponents might urge that a chemical should be demonstrated to be safe before being used widely.

The more detailed assessments below are not all based on a formal weight of evidence or meta-analytic approach, but rather present examples of the state of current literature for several chemical groups of concern.

## RESULTS

### Tobacco Smoke Exposure

Active smoking during pregnancy has been causally associated with IUGR, LBW, and PTD (9); infants of smokers are estimated to have twice the risk of LBW or a decrement in mean birth weight of 150–200 g compared with infants of nonsmokers. Because nonsmokers may be exposed to passive smoke, also called environmental tobacco smoke (ETS), studies have examined these pregnancy outcomes in relation to ETS exposure as well. Tobacco smoke contains thousands of compounds; those with potential reproductive toxicity include nicotine, carbon monoxide, polycyclic aromatic hydrocarbons, heavy metals, aromatic solvents, and others. Based on studies measuring biomarkers in the early to mid-1990s, from 40% to nearly 100% of nonsmokers may be exposed to some ETS, although levels have declined as more regulations regarding smoking in public have been instituted (10, 11).

Reviewing the evidence for adverse effects of ETS exposure on reproduction, early studies started with the cruder exposure assessment of a smoking spouse, progressing to ascertaining multiple sources of exposure, and finally biomarkers. Over 30 studies have examined mean birth weight, with the better ones indicating a weight decrement in the range of 25–100 g (12). In an earlier meta-analysis, the adequate studies conducted among nonsmoking mothers yielded

a pooled weight decrement of 31 g (confidence interval (CI): –42, –20) (13). The few studies based on biomarker measurement, for example, of cotinine, a metabolite of nicotine, yield even greater weight decrements among non-smokers (80–100 g for cotinine levels >1 ng/mL), particularly as more sensitive assays have been developed so that a truly not (or very low) exposed comparison group can be identified (12, 14). Of the studies that examined dose–response effects, several found evidence for such trends, further strengthening the argument for causality. At least 20 studies of LBW or SGA have been conducted; the higher quality studies of LBW yielded a pooled odds ratio (OR) of 1.4, or a 40% increase, whereas that for SGA was somewhat lower (13). Some evidence suggests that specific subsets of women may be more susceptible to effects, including older women or non-Whites.

About 10 studies were found on PTD and ETS exposure, with ORs in the same range as for LBW, for example, from 1.2–1.8. Some of these studies also reported greater risk with older maternal age. The two biomarker studies determined higher risks with increasing cotinine or nicotine concentration on the order of 20%–30% per quartile level (14, 15).

### Water Disinfection Byproducts (DBPs)

Public water supplies have been disinfected to eliminate or control water-borne infectious diseases for 100 years, but DBPs may form from the reaction of chemical disinfectants (most often chlorine) with natural organic matter, primarily in surface waters. The adverse reproductive effects of these compounds have been of increasing interest, with the first studies in humans appearing in the late 1980s. Trihalomethanes (THMs) are the most prevalent group of DBPs, comprised of four volatile compounds, and are routinely monitored by water companies, with standards in the United States determined by the Environmental Protection Agency (US EPA). The US EPA has identified nearly 600 DBPs (16), with haloacetic acids (HAAs) and haloacetonitriles (HANs) also considered in more recent studies of reproductive outcomes.

Studies of DBPs and fetal growth or preterm delivery have been hampered by several limitations related to exposure assessment. Many studies have linked water company data to birth records so that large numbers may be included, but some of these studies only examined water source or disinfection process, a rather crude distinction. Trihalomethanes monitoring data from the water system provides more information for comparing exposure levels, but is not necessarily reflective of actual household exposures at the tap, nor of personal habits of water consumption or use, which have only been ascertained in a few studies. Furthermore, the time period examined for monitoring is unlikely to correspond to the entire critical period for exposure, and does not usually take into account moving during pregnancy. A specific biomarker for a DBP has not been available for use in epidemiologic studies thus far, and household environmental measurements are too labor intensive.

The 12–15 studies conducted on fetal growth or PTD and DBPs have been summarized in several review articles (17–19). Examining SGA or IUGR (as well as head circumference), five studies based on the crudest exposure assessment found ORs ranging from 1.0 to 2.0. Eight studies examined THM monitoring data, reporting ORs in the range of 1.0 to 1.5, with the majority on the higher end. One study (20) that used hydraulic modeling data reported an even higher OR of 5.9 (95% confidence interval [CI] 2.0–17.0). Two studies had interview data, one of which found an OR of 2.1 (95% CI 1.1–3.8) for third trimester high THM exposure and SGA (21), and the other found an elevation in risk of IUGR only with a genetic variant of the CYP2E1 gene (OR 13.2, 95% CI 1.2–147) (22). A few studies that examined HAAs found inconsistent results (23–25). Most studies of preterm delivery have not shown increased risks with any measure of DBP exposure. Results from studies of LBW were somewhat intermediate between those of SGA and PTD.

### Organochlorine Pesticides

Organochlorine pesticides were widely used in the United States and worldwide from 1940 through the 1970s, but most have been eliminated or restricted in use following recognition of their persistence in the environment, bioaccumulation in animals and humans, and toxicity in laboratory animals and wildlife (26). Dichlorodiphenyl trichloroethane (DDT) is an organochlorine pesticide and prototype persistent environmental chemical with endocrine disrupting effects (27). Agricultural and commercial use of DDT became widespread after 1945; approximately 1.4 billion pounds of DDT was used in the United States before it was banned for most uses in 1973 (28). The World Health Organization announced in September 2006 plans to resume the use of indoor residual spraying of DDT for the control of malaria throughout Africa (29).

Epidemiologic studies investigating the relationship between DDT and/or its primary metabolite dichlorodiphenyl dichloroethylene (DDE) and adverse fetal growth outcomes and preterm delivery have produced conflicting results. Maternal serum and umbilical cord blood levels of DDT and/or DDE have been related, in some studies, to preterm birth (30–33), decreased birth weight (34–36), or intrauterine growth retardation (30, 37). In other studies, levels of DDT and/or DDE in maternal serum, cord blood, or breast milk were not associated with either decreased infant birth weight (38–44) or preterm birth (36, 40, 41, 45, 46). The study of Longnecker et al. (30) had the largest population size, among the highest DDE levels, and found a dose–response relationship for preterm delivery and SGA.

### Organophosphate Pesticides

Organophosphate pesticides are heavily used, estimated to account for about half of the insecticide use in the United States, but are not persistent (47). Several studies using biomarkers to assess exposure to organophosphates have been

published in the last few years (36, 48–53). Perera et al. (51) found that increasing levels of the organophosphate pesticide chlorpyrifos in umbilical cord blood were associated with decreased birth weight in an ethnically diverse cohort in New York City. In an expanded analysis of this cohort, Whyatt and colleagues (52) determined that birth weight decreased with increasing levels of chlorpyrifos and diazinon during the time period before regulatory actions restricted residential use of these pesticides. Neither Perera nor Whyatt examined gestational age as an outcome.

The acute toxicity of all organophosphates is caused by their inhibition of the enzyme acetylcholinesterase, resulting in an excess of acetylcholine in nerve endings. Measurement of cholinesterase inhibition can provide an integrated assessment of exposure to organophosphate pesticides. However, because of the high degree of individual variability of cholinesterase activity, the only validated measure of exposure is comparison to an individual's baseline levels measured before exposure (54). It is also possible that organophosphates may cause chronic health effects in the absence of detectable cholinesterase inhibition. A case-control study conducted in Mexico found a significant association between acetylcholinesterase activity lower than 20% (with respect to the average in the community during a time when pesticides were not applied) and intrauterine growth retardation (50). Eskenazi et al. (49) reported a reduction in gestational age associated with increased levels of maternal urinary dimethyl phosphate metabolites as well as with decreased umbilical cord cholinesterase in a cohort of low-income Latina women living in an agricultural area; no relationship with birth weight was detected. Willis et al. (53) failed to find an association between plasma cholinesterase levels in a cohort of women potentially exposed to pesticides and birth weight or PTD. The few studies using cholinesterase levels as biomarkers of organophosphate exposure have been impaired by the lack of pre-exposure baseline cholinesterase levels and the uncertain value of group levels in the absence of such comparisons, particularly with respect to null results.

Two studies examined whether genetic differences might modify the association between organophosphate exposure and reproductive outcomes. Berkowitz et al. (48) reported that levels of the urinary metabolite of chlorpyrifos were not associated with decreased birth weight or shortened gestation. However, head circumference was smaller in the children of women with chlorpyrifos exposure and low expression of paraoxonase 1 (PON1), an esterase involved in the detoxification of organophosphates. Wolff et al. (36) found that slow PON1 or PON192 in combination with urinary diethyl phosphate levels were associated with lower birth weight.

## CONCLUSION

In conclusion, based on the preponderance of evidence in different populations with improved exposure assessment, reviews by several agencies generally conclude there is

a consistent, slight effect of ETS exposure on reducing mean birth weight (or slightly increasing the risk of growth retardation), with suggestive evidence of an effect on preterm delivery as well (7, 8). Therefore, women who are pregnant or are attempting to become pregnant should be counseled to avoid areas where exposure to ETS is likely, and regulations concerning smoking in public are important to pursue and enforce.

Studies of water DBPs were limited by exposure assessment issues described; other difficulties in comparing results across studies arise from differences in the populations studied, confounders considered, and variation in exposure levels presented. Nevertheless, the weight of evidence most supports an association between DBP exposure and IUGR or SGA, with little consistent evidence for an effect on preterm delivery. Fewer studies have been done on HAAs and DBPs other than THMs, so that may be an area for additional research, as well as examining genetic variants involved in metabolism of these compounds. Pregnant women concerned about exposure to DBPs can refer to their water company reports on measured levels and if on the high side, choose to drink bottled water. However, most bottled waters are not monitored for these compounds, so the source of water may be important to consider.

Studies of DDT/DDE exposure and reproductive outcomes produced inconsistent results, in part, because of differences in the following: sample size, levels of exposure, potential confounders included, study power, and genetic variability of the study population. However, the weight of evidence suggests that at high levels of exposure, DDT/DDE is associated with adverse fetal growth outcomes and preterm delivery. Future research is recommended to investigate potential interactions between DDT/DDE and other endocrine disrupting chemicals.

Studies of organophosphate exposure and reproductive outcomes have suffered from lack of a standard validated measure of exposure. However, despite inconsistencies in study results, the weight of evidence and precautionary principle suggest that exposure to organophosphates should be avoided during pregnancy. Recommendations for research on organophosphate exposure and pregnancy outcomes include use of a prospective study design, assessment of exposure using validated biomarkers, and consideration of genetic susceptibility.

*Acknowledgments:* We thank Dr. Sarah Janssen for her willingness to share her summary tables of research in the area of environmental and occupational exposures and reproductive outcomes.

## REFERENCES

1. National Center for Health Statistics (NCHS) Website: <http://www.cdc.gov/nchs>. [Accessed January 2007].
2. Institute of Medicine (IOM). Preterm birth: causes, consequences, and prevention. Washington, DC: National Academy Press, 2006.
3. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med* 1985;82:378–82.
4. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiol Rev* 1993;15:414–43.

5. Windham GC, Osorio AM. Female reproductive toxicology. In: LaDou J, ed. Occupational and environmental medicine. 4th ed. Norwalk, CT: Appleton and Lange, 2007.
6. Collaborative on Health and the Environment (CHE). Chemical Contaminants and human disease: a summary of evidence. Online at: <http://database.healthandenvironment.org> [accessed 2 March 2007].
7. National Cancer Institute. Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency, Smoking and Tobacco Control Monograph No. 10. NIH Pub. No. 99-4645. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, 1999.
8. US Dept. of Health and Human Services (USDHHS). The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Washington, DC: USDHHS, Public Health Service, Office of the Surgeon General, 2006.
9. US Dept. of Health and Human Services (USDHHS). Women and smoking: a report of the Surgeon General. Washington, DC: USDHHS, Public Health Service, Office of the Surgeon General, 2001.
10. Centers for Disease Control and Prevention (CDC). Third national report on human exposure to environmental chemicals. Atlanta, GA: National Center for Environmental Health, 2005 (NCEH Pub. No. 05-0570).
11. Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure of the U.S. population to environmental tobacco smoke. The third National Health and Nutrition Examinations Survey, 1988 to 1991. *JAMA* 1996;275:1233-40.
12. Windham GC. Birth weight and gestational age in relation to prenatal environmental tobacco smoke exposure. In: Watson R, Witten M, eds. Environmental tobacco smoke. Boca Raton, FL: CRC Press, 2001.
13. Windham GC, Eaton A, Hopkins B. Evidence for an association between environmental tobacco smoke exposure and birth weight: a meta-analysis and new data. *Paediatr Perinat Epidemiol* 1999;13:35-57.
14. Kharrazi M, Delorenze GN, Kaufman FL, Eskenazi B, Bernert JT, Graham S, et al. Environmental tobacco smoke and pregnancy outcome. *Epidemiology* 2004;15:660-70.
15. Jaakkola JJK, Jaakkola N, Zahlsen K. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. *Environ Health Perspect* 2001;109:557-61.
16. US Environmental Protection Agency (US EPA). The occurrence of disinfection by-products (DBPs) of health concern in drinking water: results of a nationwide DBP occurrence study. Athens, GA: National Exposure Research Laboratory, Office of Research and Development. EPA 2002 600/R-01/068.
17. Bove F, Shim Y, Zeitz P. Drinking water contaminants and adverse pregnancy outcomes: a review. *Environ Health Perspect* 2002;110S: 61-74.
18. Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, Elliott P. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. *Occup Environ Med* 2000;57:73-85.
19. Tardiff RG, Carson ML, Ginevan ME. Updated weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products. *Regul Toxicol Pharmacol* 2006;45: 185-205.
20. Gallagher MD, Nuckols JR, Stallones L, Savitz DA. Exposure to trihalomethanes and adverse pregnancy outcomes. *Epidemiology* 1998;9: 484-9.
21. Savitz DA, Singer PC, Hartmann KE, Herring AH, Weinberg HS, Makarushka C, et al. Drinking water disinfection by-products and pregnancy outcome. *AWWA Res Found* 2005;1-247.
22. Infante-Rivard C. Drinking water contaminants, gene polymorphisms, and fetal growth. *Environ Health Perspect* 2004;112:1213-6.
23. Hinckley AF, Bachand AM, Reif JS. Late pregnancy exposures to disinfection by-products and growth-related birth outcomes. *Environ Health Perspect* 2005;113:1808-13.
24. Porter CK, Putnam SD, Hunting KL, Riddle MR. The effect of trihalomethane and haloacetic acid exposure on fetal growth in a Maryland County. *Am J Epidemiol* 2005;162:334-44.
25. Wright JM, Schwartz J, Dockery DW. The effect of disinfection by-products and mutagenic activity on birth weight and gestational duration. *Environ Health Perspect* 2004;112:920-5.
26. United Nations Environment Programme (UNEP). Regionally based assessment of persistent toxic substances: North America Regional Report. Geneva: United Nations Environment Programme: Chemicals, 2002.
27. National Research Council. Hormonally active agents in the environment. Washington, DC: National Academy Press, 1999.
28. US Environmental Protection Agency (US EPA). DDT regulatory history: a brief survey (to 1975). Washington, DC: US Environmental Protection Agency, 1975.
29. World Health Organization Press release. WHO gives indoor use of DDT a clean bill of health for controlling malaria. 15 September 2006 <http://www.who.int/mediacentre/news/releases/2006/pr50/en/print.html> [accessed 1 March, 2007].
30. Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet* 2001;358:110-4.
31. Ribas-Fito N, Sala M, Cardo E, Mazon C, De Muga ME, Verdu A, et al. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. *Pediatr Res* 2002;52:163-7.
32. Saxena MC, Siddiqui MKJ, Bhargava AK, Seth TD, Krishnamurti CR, Kutty D. Role of chlorinated hydrocarbon pesticides in abortions and premature labor. *Toxicology* 1980;17:323-31.
33. Wasserman M, Ron M, Bercovici B, Wasserman D, Cucos S, Pines A. Premature delivery and organochlorine compounds: polychlorinated biphenyls and some organochlorine insecticides. *Environ Res* 1982;28: 106-12.
34. O'Leary JA, Davies JE, Edmundson WF, Feldman M. Correlation of prematurity and DDE levels in fetal whole blood. *Am J Obstet Gynecol* 1970;106:939.
35. Weisskopf MG, Anderson HA, Hanrahan LP, Kanarek MS, Falk CM, Steenport DM, et al. Maternal exposure to Great Lakes sport-caught fish and dichlorodiphenyl dichloroethylene, but not polychlorinated biphenyls, is associated with reduced birth weight. *Environ Res* 2005;97: 149-62.
36. Wolff M, Engel S, Berkowitz G, Teitelbaum S, Siskind J, Barr DB, et al. Prenatal pesticide and PCB exposures and birth outcomes. *Pediatr Res* 2007;61:243-50.
37. Siddiqui MK, Srivastava S, Srivastava SP, Mehrota PK, Mathur N, Tandon I. Persistent chlorinated pesticides and intra-uterine foetal growth retardation: a possible association. *Int Arch Occup Environ Health* 2003;76:75-80.
38. Bjerregaard P, Hansen JC. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. *Sci Total Environ* 2000;245:195-202.
39. Dewailly E, Bruneau S, Ayotte P, Laliberte C, Gingras S, Belanger D, et al. Health status at birth of Inuit newborn prenatally exposed to organochlorines. *Chemosphere* 1993;27:359-66.
40. Farhang L, Weintraub JM, Petreas M, Eskenazi B, Bhatia R. Association of DDT and DDE with birth weight and length of gestation in the Child Health and Development Studies, 1959-1967. *Am J Epidemiol* 2005;162:717-25.
41. Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H, et al. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect* 2006;114:597-602.
42. Gladen BC, Shkiriyak-Nyzhnyk ZA, Chysovska N, Zadorozhnaja TD, Little RE. Persistent organochlorine compounds and birth weight. *Ann Epidemiol* 2003;13:151-7.
43. Karmaus W, Zhu X. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichloroethylene and birth weight in Michigan fish eaters: a cohort study. *Environ Health* 2004;3:1.
44. Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, et al. Neonatal effects of transplacental exposure to PCBs and DDE. *J Pediatr* 1986;109:335-41.

45. Berkowitz GS, Lapinski RH, Wolff MS. The role of DDE and Polychlorinated Biphenyl levels in preterm birth. *Arch Environ Contam Toxicol* 1996;30:139–41.
46. Torres-Arreola L, Berkowitz G, Torres-Sanchez L, Lopez-Cervantes M, Cebrian M, Uribe M, et al. Preterm birth in relation to maternal organochlorine serum levels. *Ann Epidemiol* 2003;13:158–62.
47. Centers for Disease Control and Prevention (CDC). Third national report on human exposure to environmental chemicals. Spotlight on organophosphate pesticides. Atlanta, GA: National Center for Environmental Health, 2005. Available Online: [http://www.cdc.gov/exposurereport/pdf/factsheet\\_organophosphate.pdf](http://www.cdc.gov/exposurereport/pdf/factsheet_organophosphate.pdf) [accessed 22 Feb 2007].
48. Berkowitz GS, Wetmur J, Birman-Deych E, Obel J, Lapinski R, Godbold J, et al. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect* 2004;112:388–91.
49. Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP, Barr DB, et al. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect* 2004;112:1116–24.
50. Levario-Carrillo M, Amato D, Ostrosky-Wegman P, Gonzalez-Horta C, Corona Y, Sanin LH. Relation between pesticide exposure and intrauterine growth retardation. *Chemosphere* 2004;55:1421–7.
51. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect* 2003;111:201–6.
52. Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Perspect* 2004;112:1125–32.
53. Willis WO, de Peyster A, Molgaard CA, Walker C, MacKendrick T. Pregnancy outcome among women exposed to pesticides through work or residence in an agricultural area. *J Occup Med* 1993;35:943–9.
54. Wessels D, Barr DB, Mendola P. Use of biomarkers to indicate exposure of children to organophosphate pesticides: implications for a longitudinal study of children's environmental health. *Environ Health Perspect* 2003;111:1939–46.