PART III

Environmental Pollution and Congenital Anomalies

CHAPTER III.1 CHEMICAL ENVIRONMENTAL & OCCUPATIONAL EXPOSURES

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Introduction

This Part of the review covers the epidemiological evidence concerning chemical contaminants or pollutants that may be present in air, food or water, including the epidemiological literature on (community) environmental and occupational exposures. Specific chemical exposures discussed are heavy metals, organic solvents, vinyl chloride, polychlorinated biphenyls (PCBs), dioxins and pesticides. Also discussed are exposures, often mixed, through drinking water, air pollution, and residence near industrial sources. Results of occupational studies in relation to job title only are not reviewed but may be mentioned if the same study considered specific chemical exposures. Similarly, studies of domestic activities such as gardening, keeping pets, painting or cleaning are not reviewed but may again be mentioned if the same studies present information on specific chemical exposures. The review focuses on congenital anomalies, but other adverse pregnancy outcomes (spontaneous abortion, low birth weight, preterm births) are also discussed to give more context to the congenital anomaly literature.

The assessment of whether and to what extent environmental pollution causes birth defects in the population also draws on other evidence, principally toxicological data, data from animal studies, and detailed exposure data. This review does not constitute a risk assessment including these sources of evidence. It should be kept in mind when reading this review that "absence of evidence is not evidence of absence". We present in this review the existing epidemiological evidence. We did not set out to draw conclusions as to the weight of evidence for a teratogenic effect of the chemicals considered at the levels of exposure experienced by the community or by the occupationally exposed. The interpretation of the epidemiological evidence presented should keep in mind the methodological issues discussed in Chapter I.2.

Systematic searches of Medline and BIDS were carried out using combinations of the following key words in all their expanded forms: 'abnormalities', 'pregnancy-outcome', 'pregnancy-complications', 'birth-weight', 'environmental-pollution', 'organic-chemicals', 'inorganic-chemicals'. The latest searches were done in June 2003, all papers up to that date were included. Subsequently, abstracts of all papers found in the searches were scanned and relevant papers were selected for review: these included all papers describing original epidemiological studies, published in the English language, available through the British Library.

A separate review has been conducted specifically related to chemicals reported to emanate from landfill sites (Sullivan F, Barlow S, McElhatton P. A review of the potential teratogenicity of substances emanating from landfill sites. www.advisorybodies.doh.gov.uk/landup.htm). Where appropriate, we refer to this review for further detail in order to avoid duplication.

1. Heavy metals

1.1 Lead

Lead has been used in petrol, paints, pipes and plumbing materials, glazing and pottery, batteries, ammunition, flashings, etc. (Wade et al. 1993). The use of lead based residential paints is now banned in many countries and leaded petrol is being phased out. Particulate lead in the atmosphere originates from a variety of sources including vehicle exhausts, combustion of waste, coal and oil, smelters, and battery and cement manufacturing (Wade et al. 1993). Lead leaching into the water supply from old lead piping may be an important source of lead in drinking water (Bound et al. 1997). This section discusses first environmental lead exposures, followed by occupational exposures. Table x summarises studies on congenital anomalies, environmental and occupational. Other pregnancy outcomes are discussed briefly at the end of each section.

Environmental exposures

Several reviews of lead teratogenicity have concluded that evidence for environmental lead exposure to cause structural congenital anomalies in humans is very limited (Bellinger 1994; Davis and Svendsgaard 1987; Ernhart 1992; Mushak et al. 1989; Winder 1993). This is mainly because very few human studies have been carried out. Studies of lead exposure and congenital anomalies are summarised in Table 1.

Needleman et al (Needleman et al. 1984) measured cord blood lead levels in a cohort of 4,354 consecutive births. They found an increase in the incidence of all congenital anomalies and minor anomalies with increasing lead levels. Multiple anomalies or major anomalies showed no association. The most common minor anomalies were haemangiomas and lymphangiomas, minor skin anomalies such as skin tags, and undescended testicles. Lead levels of 15ug/dl (compared to 0.7 ug/dl) were related to a relative risk for all malformations of 2.4 (95%CI 1.7-3.4). In the Port Pirie study (McMichael et al. 1986) blood levels were measured in a cohort of 831 pregnant women resident in and around the Port-Pirie smelter community. 40 infants had congenital anomalies, of which one had multiple, 29 minor and the rest major anomalies. There was no association with blood lead level measured at 14-20 weeks gestation or later. The study gives too little detail of the analysis and results concerning congenital anomalies to judge the strength of these negative results. The study did find a dose-response relationship for pre-term delivery but not for spontaneous abortion, low birth weight, and intrauterine growth retardation. Ernhart et al (Ernhart et al. 1986) studied a cohort of 185 pregnancies and found no association between maternal blood lead level at delivery or cord lead level and pre-term birth, low birth weight or congenital malformation. There were few study subjects

however giving the study limited statistical power to detect a possible effect, and the range of blood lead levels measured was limited (Mushak et al. 1989).

An advantage of all three above studies is that levels of lead were measured in the blood of the mothers or babies, giving relatively accurate exposure estimates. A few studies have used exposure measurements of ecological nature. A recent case-control study in the UK (Bound et al. 1997) found that mothers in areas with a larger proportion of houses with high lead concentration in drinking water had a higher risk having a baby with anencephaly (p=0.010), spina bifida (p=0.015), and all neural tube defects (NTDs) (p=0.004). More deprived areas had higher proportions of houses with high lead concentrations (over the WHO drinking water recommendation of 10μg/l) which explained some of the above relationship. The relationship between lead and anencephaly was still statistically significant after controlling for the effect of deprivation (p=0.05), relationships for spina bifida (p=0.11) and all NTDs combined (p=0.079) were not. Another ecological study relates lead concentrations in domestic water samples to the prevalence of neural tube defects by postcode districts in Glasgow (Macdonell et al. 2000). Lead concentrations correlated well with a sample of maternal blood lead levels. The study found no correlation between the proportion of lead levels over 10ug/l and the prevalence of NTDs in each district. Although a higher prevalence of NTDs was found in more deprived districts, the correlation between lead levels and NTD prevalence was not adjusted for deprivation, making interpretation of these results difficult. A case-control study of water quality in Massachusetts (Aschengrau et al. 1993) reported increases (non statistically significant) in risk of all congenital malformations and cardiovascular defects for women exposed to detectable lead levels in the public drinking water. Water quality in this study was measured at community level. This study is discussed in more detail in section 7.2.3.

Using a population-based registry of congenital anomalies in Italy, Vinceti et al (Vinceti et al. 2001) investigated the risk of birth defects in mothers exposed to environmental lead pollution from a ceramic factory and found higher risks of cardiovascular defects, oral clefts and musculoskeletal anomalies in the exposed group. The excess risks for these specific anomalies decreased over time which corresponded with decreasing environmental lead exposure. The authors considered the co-existing fluoride contamination a less likely explanation of the excesses. For communities living near heavy metal smelters, lead is one of the main exposures of concern although exposure in these communities will often be to a mixture of heavy metals. Studies of smelter communities are discussed in section 7.4.1.

Other pregnancy outcomes such as spontaneous abortion, length of gestation and birth weight have been studied more frequently in relation to lead exposure than congenital anomalies. Early observations have reported spontaneous abortions in humans as a result of lead exposure (Chang et al.

1980) and lead oxide has even been used to induce abortions (Schardein 2000). Few studies have investigated low dose, environmental, lead exposures and risk of spontaneous abortions, and results of these few studies are inconsistent (Ernhart 1992). The Port-Pirie study did not find an association between blood lead levels and risk of spontaneous abortion or stillbirth (McMichael et al. 1986). A cohort study in a Kosovo smelter town finds little evidence of an increase in risk of spontaneous abortion between women from the exposed town and women from an unexposed town (OR 1.1, CI 0.9-1.4) (Murphy et al. 1990). Blood lead levels were three times higher in women from the exposed town compared to unexposed women (see further section 7.4.1). A recent nested case-control study in Mexico found an increasing risk of spontaneous abortion with increasing blood lead levels measured in pregnant women (Borja Aburto et al. 1999).

The number of studies concerning fetal growth and pre-term birth is larger (Andrews et al. 1994; Bellinger 1994; Ernhart 1992; Mushak et al. 1989). These studies are not discussed in detail here. Both positive and negative findings have been reported and several reviews conclude that prenatal lead exposure does appear to be related with an increased risk of pre-term birth and low birth weight (Andrews et al. 1994; Davis and Svendsgaard 1987; Mushak et al. 1989). In positive reports the risk of growth related outcomes (low birth weight, small for gestational age, intra uterine growth retardation) begins to rise at maternal and cord blood lead levels of approximately 12-15μg/dl, levels not much higher than average levels found in the general population (McMichael et al. 1986). The review by Davis and Svendsgaard (Davis and Svendsgaard 1987) also concludes that weight of evidence suggests an effect of prenatal lead exposure on the duration of gestation and birth weight and that such effects can occur at blood levels below 15 ug/dl.

Neurotoxic effects later in childhood (including effects on IQ, language, and behaviour) due to pre and postnatal lead exposure are relatively well-established (Goyer 1996; Mushak et al. 1989) but their discussion falls beyond the scope of this review.

Occupational exposures

Occupational exposure to inorganic lead occurs in lead smelters, construction works, plastics production, jobs with paints and dyes, and in the printing, ceramics, galvanic, and electro-technical industry (Roeleveld et al. 1990). There are few studies of occupational lead exposure and risk of congenital anomaly (Table 1). Kristensen et al (Kristensen et al. 1993) study a cohort of offspring of male workers in the printing industry in Oslo, Norway. Pre-term birth and perinatal deaths were found to be related to job codes with lead or lead and solvent exposure. Cleft lip/palate showed an increased risk in the total printers cohort compared to all births in Oslo (SMR 1.6 CI 0.97-2.5). This was mainly due to an increased risk among male births of fathers exposed to lead (SMR 4.1 CI 1.8-8.1). Other

specific congenital anomaly groups or the group of total congenital anomalies were not related to lead or solvent exposure. Sallmen et al (Sallmen et al. 1992) studied a sample of cases and controls for whom blood lead monitoring of the father had been carried out as part of a larger cohort. They find an increased risk for congenital malformation of 2.4 (95%CI 0.9-6.5) before adjustment for confounding factors. Confounding factors were adjusted for one at the time and adjusted odds ratios ranged from 1.9 to 3.2 with several reaching statistical significance (adjustment for parental smoking OR 3.2, 95%CI 1.0-10.2, and year of discharge OR 3.1 95%CI 1.0-10.0). Because of small numbers of cases and controls analyses controlling for more than one variable at a time was not carried out. Irgens et al (Irgens et al. 1998) compared all births in Norway with possible lead exposure (defined using a job exposure matrix) to births without possible lead exposure. Outcomes studied were low birth weight, preterm birth, neural tube defects, Down syndrome, all major birth defects, perinatal mortality and male births. Statistically significantly raised odds ratios were found for maternal exposure to lead and low birth weight (OR 1.34, 95%CI 1.12-1.60) and neural tube defects (OR 2.87, 95%CI 1.05-6.38). The odds ratio for all major birth defects was raised but did not reach statistical significance (OR 1.25, 95%CI 0.80-1.90). Paternal exposure to lead did not show increased risks in any of the outcomes.

A case-control study of parental occupational exposures and risk of NTD-affected pregnancies among Mexican Americans reported no increase in risk for the exposed mothers (OR=1.1, 95%CI 0.2-5.8) or fathers (OR=1.3, 95%CI 0.8-2.3) (Brender et al. 2002).

Studies of other pregnancy outcomes have focused on spontaneous abortion and low birth weight in relation to occupational lead exposure. A review by Antilla (Anttila and Sallmen 1995) summarises studies on spontaneous abortion and maternal and paternal occupational lead exposure and concludes that for paternal exposure there is some evidence for a causal relationship (based on 4 separate studies), whereas for maternal exposures there was no evidence (based on only 1 study). Two recent studies find a positive relationship between paternal occupational lead exposure and low birth weight in their offspring (Lin et al. 1998; Min et al. 1996).

1.2 Mercury

Mercury is present in the environment as metallic mercury, as inorganic mercury compound, and in organic form. Mercury is used in electrical equipment, dental preparations, paints, fungicides and pesticides, fluorescent lamps, and some batteries (Roeleveld et al. 1990; Wade et al. 1993). Levels of mercury found in fish have been of concern and led to advice to limit intake during pregnancy of tuna, shark, swordfish and marlin (Food Standards Agency 2002)

Organic mercury

Methyl mercury is one of the only environmental chemicals that has been recognised as a human teratogen. Mercury poisoning during pregnancy in residents around the Mina Mata bay in Japan (1953-1971) caused central nervous system anomalies in new-borns (Harada 1978; Koos and Longo 1976). Infants born to exposed mothers showed a complex of neurological symptoms, including cerebral palsy, ataxia, disturbed psychomotor development and mental retardation sometimes accompanied by microcephaly. The mothers did not show symptoms. In Iraq (1971-72) grain treated with methyl mercury was consumed by local populations and hundreds of people died from mercury poisoning. A number of pregnant mothers were hospitalised with mercury poisoning and high blood mercury levels were found in their infants (Koos and Longo 1976; Marsh et al. 1987; Marsh et al. 1980). Similar effects have been reported in case reports after other instances of methyl mercury poisoning (Koos and Longo 1976; Snyder 1971). There is little evidence on dose levels required to cause fetal effects. Marsh et al [Marsh, 1995 #2205) report that a dose of 20 ppm in maternal hair prenatally was enough to cause motor retardation and abnormal neurological signs in infants in Iraq. A study of 131 pregnant women in Peru (Marsh et al. 1995) found hair mercury levels ranging from 1.2 ppm to 30 ppm. The main source of mercury was marine fish consumption. The study found no correlation with child development outcomes including birth weight and neurological development. Reports of a possible relationship between methyl mercury levels and low birth weight in the offspring are conflicting: a study in Greenland (Foldspang and Hansen 1990) finds high maternal and offspring blood methyl mercury levels in 376 Eskimo mothers to be associated with a low mean birth weight, whereas a study of 1000 infants from the Faroe Islands finds high cord blood mercury levels associated with an increased birth weight (Grandjean and Weihe 1993). In both populations marine fish diets are the main source of methyl mercury exposure, and other elements of the fish diet confound the association with birthweight.

Major structural congenital malformations, other than those related to brain damage described above, have not been reported as a result of methyl mercury exposure. However, none of the studies described above were set up to specifically look at such malformations.

Inorganic mercury

Few studies have examined effects of inorganic/metallic mercury on reproduction. A small number of studies have examined adverse pregnancy outcomes in men and women exposed to mercury through work in dentistries, and mercury plants (Table 2). De Rosis (De Rosis et al. 1985) studied a cohort of women working in a lamp factory where exposure to mercury vapour occurred. Exposed women had a higher rate of congenital malformations than women from a comparison plant (7% vs. 3%) but 6 out

of the 7 congenital malformation cases were hip dislocations and a geographical difference in the prevalence of hip dislocation rather than exposure to mercury was thought to explain the high rate. The study finds no difference in other outcomes. A more recent study of women occupationally exposed to mercury vapours finds 3 cases of congenital anomaly (4.2%) in exposed women compared to none (0%) in unexposed women. Numbers of cases are too small to draw any conclusions from this study. Sikorski et al (Sikorski et al. 1987) study a cohort of Polish women exposed to mercury in dental work and find a higher rate of adverse pregnancy outcomes (spontaneous abortions, stillbirths, congenital malformations combined) in exposed (24%) compared to unexposed (11%) women. The number of congenital anomalies amongst exposed women was 6 (5.1%) of which 5 were spina bifida. A larger study of 29,514 male dentists and 30,272 female dental assistants reported no difference in the rate of spontaneous abortion or the incidence of congenital malformations between low and high exposure groups (Brodsky et al. 1985). Exposure was defined by the number of dental amalgam fillings placed per week. Ericson and Kallen (Ericson and Kallen 1989) studied 8,157 infants born to dentists, dental assistants or dental technicians in Sweden and found no increased risks of spontaneous abortion, perinatal death, low birth weight, or congenital malformation.

Paternal exposure to inorganic mercury has been the subject of 2 studies. Alcser et al (Alcser et al. 1989) studied a cohort of 241 workers exposed to mercury and 254 unexposed workers. There was no difference in rates of congenital anomaly. An increase in risk of spontaneous abortion with increasing dose level was seen only before adjustment for confounding factors. A study of 152 exposed workers and 374 controls (Cordier et al. 1991) found an increase in the risk of spontaneous abortion with increasing urine mercury concentration of the father before pregnancy. Congenital anomalies were not studied.

A study by Aschengrau (1989) reported an increase in the frequency of spontaneous abortion related to detectable levels of mercury in drinking water. This study is further discussed in section 7.2.3.

1.3 Cadmium

Cadmium is used in the manufacturing of batteries, electroplating, pigments, paints, silver solders, plastic stabilisers, alloys, and pesticides (Roeleveld et al. 1990; Wade et al. 1993). Metal-refining plants, municipal incinerators and fossil fuel combustion are important air emission sources of cadmium (Wade et al. 1993). Cadmium is present in cigarette smoke and smokers may have two times the cadmium exposure of non-smokers (Wade et al. 1993).

In humans, information about effects of cadmium on pregnancy is very scarce. A few studies have found decreases in birth weight with increase in cadmium levels in hair and placental cadmium (Frery et al. 1993; Huel et al. 1981). Results from these studies are difficult to interpret however, because of the possible interrelationship between cigarette smoke, cadmium, and low birth weight. Two other studies (Berlin et al. 1992; Loiacono et al. 1992) found cadmium levels in women exposed to occupational or environmental cadmium not to be associated with low birth weight in the offspring. Loiacono et al (Loiacono et al. 1992) studied placental cadmium levels in non-smoking women exposed to cadmium from a nearby smelter. Cadmium levels in non-smoking women living near the smelter were similar to levels reported in smokers (see further section on smelters, 7.4.1). Berlin et al (Berlin et al. 1992) reported no relation between placental cadmium levels of female nickel-cadmium battery workers and birthweight of their offspring.

Four case-control studies which study cadmium levels in drinking water (amongst a range of other inorganic chemicals) have reported no association with anencephaly mortality (Elwood and Coldman 1981), cardiac defects (Zierler et al. 1988), congenital malformations, stillbirths and neonatal deaths (Aschengrau et al. 1993) and spontaneous abortion(Aschengrau et al. 1989). These studies are further discussed in section 7.2.3 and summarised in Table 7.x.

1.4 Arsenic

Arsenic occurs naturally in the earth's surface (Wade et al. 1993). In the past arsenic has been widely used in herbicides, fungicides, and wood preservatives, and it is still being used in glass and ceramic production and as a metal alloy. The main industrial sources of arsenic emissions into the atmosphere are metal smelters, coal combustion, and burning of agricultural wastes (Wade et al. 1993).

Case reports have observed fetal death after maternal arsenic poisoning (Schardein 2000), but there is very little other information about effects of prenatal arsenic exposure in humans (Shalat et al. 1996). Nordenson et al. (Nordenson et al. 1978a) found an increased number of chromosomal aberrations among workers exposed to arsenic in a smelter in Sweden emitting arsenic, lead and other potentially toxic chemicals. Separate studies reported an increase in spontaneous abortions but no increase in congenital malformations and a significant decrease in birth weight around the smelter (Nordstrom et al. 1978b; Nordstrom et al. 1979b) (see further section 7.4.1, Table X). A preliminary study in Hungary (Borzsonyi et al. 1992) reports significantly higher rates of spontaneous abortion and stillbirth among populations in high arsenic exposed areas compared to low arsenic exposed areas in Hungary. Exposed areas were those with high concentrations of arsenic in the drinking water, higher

than internationally allowed levels. Zierler et al (Zierler et al. 1988) studied congenital heart defects in relation to concentrations of a range of chemicals (arsenic, barium, cadmium, chromium, lead, mercury, selenium, silver, fluoride, nitrate and sodium) in the drinking water supplied to the town in which the mother lived (see also section 7.2.3, Table X). Arsenic was the only chemical related to an increase in heart defects: concentrations of arsenic above the detection limit were related with a 3-fold increase in the risk of coarctation of the aorta. Aschengrau (Aschengrau et al. 1989) report an increase in risk of spontaneous abortions related to detectable levels of arsenic in drinking water (crude OR 1.3, 95%CI 1.0-1.6). However this increase is not statistically significant when 3 exposure categories are compared and results are adjusted for maternal age, education level, and history of prior spontaneous abortion. In a second case-control study by Aschengrau (Aschengrau et al. 1993) arsenic levels were not associated with risk of congenital anomalies, stillbirths or neonatal deaths (see further sections 7.2.3, Table X).

A recent case-control study (Ihrig et al. 1998) examined the risk of stillbirth in a Texas community where a arsenic pesticide producing facility had been located for 60 years, causing contamination of the surrounding areas. Arsenic exposure was estimated for residences using atmospheric dispersion modelling. Exposure to arsenic was not related to risk of stillbirth amongst Whites and Blacks, but an increased OR of 8.4 (95%CI 1.4-50.1) was found in Hispanic population groups for high compared to no arsenic exposure.

1.5 Chromium

Chromium is used in alloys, electroplating, and pigment manufacturing (Wade et al. 1993). Metal welding is one occupational activity with high chromium exposure (Bonde 1993). Chromium is present in the environment mainly in two oxidation states, hexavalent (Cr VI) and trivalent (Cr III), which differ in physical and chemical properties and toxicity. Cr VI is the most toxic form.

There are very few epidemiological studies of chromium exposure and adverse pregnancy outcomes. Table 3 summarises those studying congenital malformations. Chromium exposure is one of the main concerns related to metal welding, particularly the welding of stainless steel . Other exposures related to welding include Nickel and Manganese. Two studies have studied pregnancy outcomes among fathers working as welders. Bonde et al (Bonde 1993; Bonde et al. 1992) studied a cohort of 10,059 metal workers. Rates of low birthweight, preterm delivery, infant mortality, and congenital anomalies were not increased in this cohort. There was a higher risk of a previous pregnancy resulting in a

spontaneous abortion or termination in this cohort. Hjollund et al (Hjollund et al. 1995) found no increased risk of spontaneous abortion in a cohort of 1,715 metal workers.

A study of environmental chromium exposure studied rates of congenital malformation near an area heavily polluted by chromium waste in Glasgow (Eizaguirre Garcia et al. 2000). There was no evidence that populations living nearest the polluted area had higher risks of congenital malformation. Areas 2-4 km from the area showed the highest malformation risks. Socio-economic deprivation did not explain this pattern.

1.6 Nickel

Only one study examines risk of congenital malformation in relation to Nickel exposure. Chashschin et al (Chashschin et al. 1994) carried out a study of 821 male and 758 female workers in a nickel hydrometallurgy refining plant in Russia. Structural malformations were present in 17% of liveborn infants in the exposed group compared to 6% in a reference group. Relative risks reported were 2.9 for all malformations, 6.1 for cardiovascular malformations and 1.9 for musculoskeletal defects. Confounding factors were not taken into account and the comparison group is poorly described making this study hard to interpret.

2. Organic solvents

Solvents are organic chemical compounds used to dissolve, suspend, or change the physical properties of other materials (Valciukas 1994). Solvents include aliphatic hydrocarbons (heptane, hexane, cyclohexane), halogenated hydrocarbon (trichloroethylene, tetrachloroethylene, chloroform), aromatic hydrocarbons (xylene, toluene, benzene), and aliphatic alcohols, glycols and glycol ethers. Solvents are used in many different industries (in formulation of adhesives, cleaning materials, pesticides, photographic industry, pharmaceutical industry, metal cleaning, dry cleaning, paint industry and many others) and can be found in dry-cleaning products, anaesthetics, and many common household products such as spray adhesives, spray paints, inks, dyes, glues, and petrol.

Information about the effects of solvent exposure on pregnancy in humans comes mainly from case reports after solvent abuse, occupational studies, and studies on the effects of exposure to organic solvents (including chlorination by-products) in drinking water. Drinking water studies discussed in section 7.2.1 and 7.2.2. The Sullivan and Barlow review provides an in depth discussion of the animal and human literature on specific solvents that are of interest in relation to landfill gas. These include: benzene, carbon tetrachloride, chloroform, ethanol, formaldehyde, dichlorobenzenes, 1,1-dichloroethane, 1,2-dichloro-ethylene, ethylbenzene, tetrachloroethylene, toluene, trichloroethylene, and xylenes. Out of these organic solvents, Sullivan and Barlow classify benzene, chloroform, 1,2-dichloroethylene, ethyl benzene, formaldehyde, tetrachloroethylene and trichloroethylene as 'chemicals of possible interest in the landfill gas exposures' (i.e. " chemicals for which animal and/or human data indicate there may be teratogenic potential (or potential for other important reproductive effects) at relatively low dose/exposures").

Occupational exposure to solvents

Exposure to solvents may occur in a variety of occupational settings including dry cleaning, painting, printing, laboratory work, medical work, rubber manufacturing, shoe-making and the electronics industry. There have been a number of reviews of effects of parental occupational exposures, including organic solvents, and adverse pregnancy outcomes (Lindbohm 1995; Roeleveld et al. 1990; Rosenberg et al. 1987; Sever 1994; Taskinen 1990b). Table 4 summarises all studies that have studied the risk of congenital malformation in relation to occupational solvent exposure or occupations where solvents are the main or one of the main exposures of concern. A total of 35 studies have been published in this area. Again, we refer to the Sullivan and Barlow review for in depth discussion of animal and human studies relating to specific solvents.

An important issue in the study of occupational exposures and congenital malformation risk is the assessment of exposure. The studies included in table 4 have used a range of surrogate measures to assess exposure to solvents. The most common sources used in the congenital anomaly studies reviewed are routinely recorded job titles, job-exposure matrices and questionnaires/interviews of the parent. None however, uses more specific exposure measurements such as environmental or personal monitoring. In assessing exposure to solvents, often a number of job-titles are combined to define "solvent exposure". The use of surrogates of exposure will generally limit a study's potential to find a true relationship, as non-differential misclassification of exposure biases a relationship toward no association. Most of the studies in table 4 will be subject to such bias. In studies where parents gave information about occupational exposures in interviews or questionnaires, differential information bias is also of concern (Sever 1994) i.e. where parents of children with malformations remember or report exposure differently from parents of children without malformations.

Findings relating to the total group of malformations and specific malformation subgroups

Almost all studies of occupational solvent exposure and risk of congenital malformations have used a case-control design apart from cohort studies of rubberworkers (Axelson et al. 1983), laboratory workers (Axelsson et al. 1984), and electronics workers (Lipscomb et al. 1991). These cohort studies have generally not been able to study congenital anomalies in detail because numbers of cases were very small. The main outcome of interest in these studies is spontaneous abortion. One recent cohort study of mixed solvent exposures specifically studied congenital malformations. This study reported a large (13-fold) and statistically significant increase in the risk of all major congenital malformations combined (Khattak et al. 1999). The number of cases of congenital malformation in the exposed group of women (n=125) was 13, in the non-exposed group (n=125) one malformation occurred. Congenital malformations in the exposed group included neural tube defects (2), cardiac defects (2), renal abnormalities (2), diaphragmatic hernia (1), micropenis (1), other central nervous system defect (1). The group also contained four cases which would generally not be considered major malformations (laryngomalacie (2), inguinal hernia, and unspecified clubfoot). Information on congenital malformations was obtained from maternal interviews so reporting bias may have occurred, explaining some of the increased risk found.

Maternal solvent exposures estimated from a variety of sources have been found to be related to the risk of total malformations (all defects combined) (Clarke and Mason 1985; Cordier et al. 1997; Khattak et al. 1999; Kyyronen et al. 1989; McDonald et al. 1987; Silberg et al. 1979) although the absence of such a relationship has also been reported (Axelson et al. 1983; Axelsson et al. 1984; Lindbohm et al. 1983; Lipscomb et al. 1991; Taskinen et al. 1994). Paternal exposures are discussed in a separate section below. The positive associations were found for a wide range of exposures:

exposure to spray paint adhesives (Silberg et al. 1979), work in the leather industry (Clarke and Mason 1985), aromatic solvents (McDonald et al. 1987), 'other solvents' (Kyyronen et al. 1989), glycol ethers (Cordier et al. 1997), and mixed occupational solvent exposure (Khattak et al. 1999). A recent meta-analysis of 5 studies of first-trimester solvent exposure and risk of congenital anomalies calculated a statistically significant odds ratio for major malformations (1.64; 95% CI 1.16-2.30) (McMartin et al. 1998). Groups of malformations studied were different in the 5 studies, and varied from cardiac defects only to all major malformations combined. Also, little definition was given of how different studies measured 'solvent exposure'. One of the five studies measured styrene exposure only. Confounding factors were not considered, nor were the criteria for selection of the five studies clear.

The groups of congenital malformations most frequently studied in relation to occupational solvent exposure are oral clefts (cleft lip/cleft palate), central nervous system defects (including neural tube defects), and cardiovascular defects. Oral clefts are studied in ten studies, 6 report some significant association with solvent exposure (Bianchi et al. 1997; Cordier et al. 1997; Cordier et al. 1992; Garcia and Fletcher 1998; Holmberg et al. 1982; Laumon et al. 1996). Holmberg et al (Holmberg et al. 1982) find 14 oral cleft case mothers compared to 4 control mothers reporting solvent exposure at work or home. Cordier (Cordier et al. 1992) reports an increased risk of oral clefts in relation to solvent exposure assessed from a job exposure matrix. Laumon et al (Laumon et al. 1996) find an increased risk of oral clefts for exposure to solvents and specifically halogenated aliphatic solvents. A multi-centre European case-control study found maternal occupational exposure to glycol ethers (estimated from a job exposure matrix) related to an increased risk of cleft lip (Cordier et al. 1997). In two studies (Bianchi et al. 1997; Garcia and Fletcher 1998) leatherworkers are found to have an increased risk of oral clefts.

Central nervous system defects were studied in 9 separate studies (Bianchi et al. 1997; Cordier et al. 1997; Cordier et al. 1992; Garcia and Fletcher 1998, Brender, 2002 #2815; Holmberg 1979; Kurppa et al. 1983; McDonald et al. 1987; Olsen 1983). Positive relationships with maternal occupational solvent exposure were found for the total group of central nervous system defects and 'home or work exposure to solvents' (Holmberg 1979) and work as painter (Olsen 1983). An increased risk of neural tube defects was found for maternal occupational exposure to glycol ethers by Cordier et al (Cordier et al. 1997). A case-control study of parental occupational exposure among Mexican Americans and risk of NTD-affected pregnancies reported an increased risk for mothers exposed to glycol ethers (OR ∞; 95% confidence intervals 1.8 to ∞) and any solvents (OR ∞; 95% confidence intervals 2.4 to ∞) (Brender et al. 2002). Case mothers were more likely to work as cleaners compared to control mothers (Odds ratio 9.5; 95% CI 1.1 to 82.2) and were also more likely to work in health care (OR 3.0; 95% CI 1.0 to 9.0). Mothers with NTD-affected pregnancies were also more likely to have solvent

exposure outside the work place (OR 1.9; 95% confidence intervals 1.0 to 3.6). Among the activities examined, stripping and refinishing of furniture were most strongly associated with NTD-affected pregnancies (OR 4.4; 95% confidence intervals 0.8 to 31.1).

Cardiac anomalies have been studied in detail in the Baltimore-Washington Infant study (Ferencz et al. 1997) and in a series of Finnish studies (Tikkanen and Heinonen 1988; Tikkanen and Heinonen 1991a; Tikkanen and Heinonen 1991b; Tikkanen and Heinonen 1992a; Tikkanen and Heinonen 1992b; Tikkanen et al. 1988). The Baltimore-Washington Infant study, a large case-control study of over 3,000 cardiac anomaly cases, found little evidence of a relationship between solvent exposure and the total group of cardiac defects (Ferencz et al. 1997). However, odds ratios of more than 3 were found for some specific defects including transposition of the great arteries and hypoplastic left heart. This shows the potential importance of studying specific defects rather than heterogeneous groups of defects. Tikanen et al have published a series of articles relating to a Finnish case-control study (Tikkanen and Heinonen 1988; Tikkanen and Heinonen 1991a; Tikkanen and Heinonen 1991b; Tikkanen and Heinonen 1992a; Tikkanen and Heinonen 1992b; Tikkanen et al. 1988). The numbers of cases and controls differ from paper to paper because different study years were included. Mothers of cases and controls were interviewed about a wide range of exposures in the home and at work. The first article in the series reports on a limited number of cases and controls and finds no risks related to any maternal or paternal exposure (Tikkanen et al. 1988). Subsequent articles report an increased risk of all cardio-vascular malformations and especially ventricular septal defects in relation to maternal solvent exposure at work (Tikkanen and Heinonen 1988; Tikkanen and Heinonen 1991a; Tikkanen and Heinonen 1991b; Tikkanen and Heinonen 1992b). It is not clear why different subsets of years were examined in different years and the inconsistency of analysis makes interpretation difficult. Other studies which have included the total group of cardiac defects as a subgroup have not reported increased risks of cardiac defects (total group) in relation to solvent exposure (Bianchi et al. 1997; Cordier et al. 1997; Cordier et al. 1992; Fixler and Threlkeld 1998; Garcia and Fletcher 1998; Kurppa et al. 1983; McDonald et al. 1987).

Studies generally have more statistical power to detect increases in the risk of the relatively common malformation groups, such as central nervous system defects, oral clefts and cardiac defects, than in the risk of rarer anomalies. Also these more common defects are more likely to be the focus of specific studies. Other, less common, groups of defects, including digestive system anomalies (Cordier et al. 1992), gastroschisis (Torfs et al. 1996), intestinal agenesis and urinary anomalies (McDonald et al. 1987), have been related to occupational solvent exposure, but in single studies only. Interestingly, an increased risk of multiple congenital anomaly (i.e. a baby with 2 or more major congenital malformations) has been reported in 4 separate studies in relation to solvent exposure

(Cordier et al. 1992), glycol ether exposure (Cordier et al. 1997) and leather work (Bianchi et al. 1997; Garcia and Fletcher 1998).

Findings relating to specific exposure or specific occupations

The majority of studies investigate exposure to organic solvents as one group of chemicals, not distinguishing between different types of solvents. A range of subgroups of solvents have been studied by McDonald (McDonald et al. 1987), Torfs (Torfs et al. 1996) and Laumon (Laumon et al. 1996). Cordier et al (Cordier et al. 1997) report on one specific group of solvents, glycol ethers. Positive relationships were reported in these studies between aromatic solvents and all congenital defects and urinary defects (McDonald et al. 1987), aliphatic hydrocarbons and aromatic hydrocarbons and gastroschisis (Torfs et al. 1996), halogenated aliphatic solvents and oral clefts (Laumon et al. 1996), and glycol ethers and oral clefts, neural tube defects and multiple anomalies (Cordier et al. 1997).

El-Zein et al (2002) identified a cohort of 28 female factory workers in Mexico who had significant solvent exposure, specifically to ethylene glycol monomethyl ether (EGME). They had 41 offspring before, during or after their employment. Six of the offspring (born to five mothers) were exposed in utero, and all had significant dysmorphic features at examination and a higher level of chromosome aberrations on cytogenetic assays than the offspring not exposed in utero.

A Californian study (Shaw et al. 2003a) investigated maternal occupational exposure to 74 chemical groups in a case control study of oral clefts (divided into four subgroups), conotruncal heart defects and limb deficiencies. Due to the many associations being analysed (6 times 74), the authors reported odds ratios of greater than 1.5 based on at least 10 subjects (cases and controls combined). Conotruncal heart cases were associated with maternal occupational exposure to aliphatic hydrocarbons (OR 1.6, 0.8-3.3), organic dyes (OR 5.0, 1.3-16.7) and phenol compounds (OR 3.1, 0.9-9.9). Exposure to aliphatic hydrocarbons was associated with increased risk of limb anomalies (OR 1.6, 0.7-3.8). Isolated cleft lip with or without cleft palate was associated with exposure to organic dyes (OR 2.7, 0.9-7.7). Isolated cleft palate anomalies was associated with exposure to aromatic amines (OR 1.5, 0.5-5.6), aliphatic hydrocarbons (OR 2.2, 0.9-5.7), ketones (OR 2.3, 0.7-9.1), and sulfides and disulfides (OR 1.8, 0.6-6.8). Multiply malformed cleft palate cases were associated with glycol ethers (OR=2.3, 95%CI 0.8-7.0) and aliphatic hydrocarbons (OR=1.5, 95%CI 0.5-7.0). However some of these associations could have arisen by chance due to the small numbers exposed to the different chemicals and the large number of comparisons conducted. An earlier study by the same authors (Shaw et al. 2001) found an increased risk of NTD-affected pregnancies associated with a range of chemicals in a one case-control dataset, but none of these findings were confirmed in a

second dataset, suggesting at least some of the initial findings may have been due to chance, especially given the small numbers of exposed women.

Specific occupations that have been implicated are laboratory work, work in pharmaceutical industry, dry cleaning, work in the leather industry, cleaning and health care occupations, and agricultural and fishing [Roeleveld, 1990 #1457; Taskinen, 1990 #78; Lindbohm, 1995 #1005; Brender 2002, Shi 2001]. Other chemical exposures (mainly heavy metals and pesticides) are likely also to occur in these occupations.

Paternal occupational solvent exposure

Several studies report on the risk of congenital malformation in relation to paternal occupational solvent exposure (Brender and Suarez 1990; Kristensen et al. 1993; McMartin et al. 1998; Olshan et al. 1991; Sever 1995; Taskinen 1990a) (Table 4). In three of these, solvent exposure or occupations with expected solvent exposure were not related to the risk of congenital malformation (McMartin et al. 1998; Sever 1995; Taskinen 1990a). Kristenen et al (Kristensen et al. 1993) study a cohort of printing workers and find an increased risk of cleft lip and/or palate in this cohort. Olshan et al (Olshan et al. 1991) study malformation risks in 58 occupational groups and report increased risks of spina bifida, cleft palate and hypospadias for 'some occupations with potential solvent exposure' as well as occupations with potential exposure to wood or wood products, metals, and pesticides Brender and Suarez (Brender and Suarez 1990) find an increased risk of anencephaly in relation to paternal occupational solvent exposure with painters having the highest risk. A further study among Mexican Americans (Brender et al. 2002) found no association between paternal solvent exposure and neural tube defects.

A case-control study of neural tube defects in California did not find any excess risk associated with paternal occupational solvent exposure (OR=0.8, 95%CI 0.5-1.3) (Shaw et al. 2002). In contrast, this study found elevated risks in comparison with professional/managerial occupations, after adjusting for various risk factors including maternal education and ethnicity, for spina bifida in association with farming/forestry/fishing (OR 1.5, 95% CI 0.7 to 3.1), precision production/craft/repair (OR 1.5, 95%CI 0.9 to 2.7), operators/fabricators/labourers (OR 1.7, 95%CI 1.0 to 2.9), technical/sales/administrative (OR 1.8, 95%CI 1.0 to 3.3), and military (OR 3.0, confidence interval 1.0 to 9.1). Limitations of the study include reliance on occupational groupings as exposure surrogates and reliance on maternal report of paternal occupation (Shaw et al. 2002).

3. Vinyl chloride and styrene

Vinyl chloride (also known as vinyl chloride monomer, VCM) is extensively used as a base for polyvinyl chloride (PVC) products. Stryrene is a solvent extensively used in the manufacturing of plastics and is structurally similar to vinyl chloride. Both vinyl chloride and styrene are discussed in the Sullivan and Barlow (Sullivan et al.). In their review, vinyl chloride is classified under group 1: 'chemicals of possible interest' (i.e. " chemicals for which animal and/or human data indicate there may be teratogenic potential (or potential for other important reproductive effects) at relatively low dose/exposures"). Sullivan and Barlow classify styrene under group 3: 'chemicals of no/unlikely interest' (i.e. "chemicals for which animal and/or human data demonstrate there is unlikely to be teratogenic potential (or potential for other important reproductive effects), or for which effects have only been demonstrated at very high dose levels"). This section and table (Table 5) give a brief overview of all studies investigating human exposure to vinyl chloride and styrene and associated risks of adverse pregnancy outcomes. Some overlap with the Sullivan and Barlow review is likely.

Studies on reproductive effects of vinyl chloride and styrene in humans concentrate on genetic anomalies via mutagenic effects of these chemicals. Vinyl chloride is mutagenic and carcinogenic in humans (Sullivan et al.). Styrene has shown mutagenic activity in humans in some but not all studies (Sullivan et al.). Literature on adverse pregnancy outcomes and especially congenital malformations is scarce.

Occupational exposures

A study by Infante et al (Infante et al. 1976a) compared pregnancy outcomes in wives of VCM polymerisation workers with controls and reported increased fetal death rates for pregnancies occurring after exposure. In a Finnish study work in the plastics and styrene industry was related to incidence of spontaneous abortions (Hemminki et al. 1980), but in other studies neither spontaneous abortions (Harkonen and Holmberg 1982) nor congenital malformations (Harkonen et al. 1984) were related to occupational styrene exposure.

Subsequent studies of workers employed in the plastics industry have reported increased risks of adverse pregnancy outcomes including spontaneous abortions and low birth weight (Ahlborg et al. 1987; Lemasters et al. 1989; Lindbohm 1993; McDonald et al. 1988) but findings of these studies are not consistent with regard to the type of plastic chemical related to adverse effects. Lindbohm et al report an increased risk of spontaneous abortion for workers working with polyurethane but not with styrene or PVC (Lindbohm 1993), Ahlborg et al (Ahlborg et al. 1987) report an increased of adverse pregnancy outcomes combined for workers working with PVC plastics but not with styrene and

polyurethane, and McDonald et al (McDonald et al. 1988) report increased risks of spontaneous abortion for working with styrene, polyolefin and polyvinyl. Lemasters et al (Lemasters et al. 1989) study risk of low birth weight in relation to styrene exposure in the plastics industry and find lower birth weights in the offspring of styrene exposed workers but no dose-response relationship was found.

Environmental exposures

Five studies have investigated risk of congenital malformation, in particular central nervous system defects, in areas where PVC polymerisation plants were located in the US and Canada (Edmonds et al. 1978; Edmonds et al. 1975; Infante et al. 1976b; Rosenmann et al. 1989; Theriault et al. 1983). Most of these studies reported no association between distance of residence to the vinyl chloride plants or parental occupation in the plants and risk of congenital malformation. Infante (Infante et al. 1976b) reported an increased risk of congenital malformation in 3 communities where PVC plants were located compared to the entire State of Ohio and found increased risks of CNS defects, cleft lip and palate, club foot and defects of the genital organs in these communities. A case-control study in the same area did not find an association between parental occupation in the plants or residence near the plants and risk of anencephaly and spina bifida (Edmonds et al. 1975). Theriault (Theriault et al. 1983) carried out a case-control study to follow up reported high rates of birth defects in a community with a PVC plant. Although the high birth defect rates were confirmed in the community, no evidence was found for a relationship with occupation of the parents in the PVC plant or distance of residence from the plant. Rosenmann et al (Rosenmann et al. 1989) found a trend of decreasing risk of central nervous system defects with increasing distance from one of two PVC plants studied in New Jersey. No statistical significance test is reported for this trend. There was no evidence for a trend in risk of all congenital malformations. Odds ratios comparing CNS defects in distance bands close to the plant (0-1, 0-2, 0-3, 0-4 , 0-5, 0-10, 0-15 km) to those further away (>15 km) are increased but do not reach statistical significance. Overall, exposure assessment is weak in these studies and as Sullivan and Barlow conclude, an association between VCM exposure and adverse pregnancy outcome has not been substantiated.

4. Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are important environmental pollutants because of their high potential for bioaccumulation. PCBs have been used in wide range of products, including hydraulic fluids, plasticizers, transformers and capacitors, and carbon-less copy paper (Harrad et al. 1994). The production of PCBs has been banned by Western countries since the 1970s. Some PCBs have dioxin-like biological activity (see also next Section on dioxins).

Japan and Taiwan

PCBs have been reported to be human teratogens (Brent and Beckman 1990). The first indication that PCBs are teratogenic in man came in the consumption of rice oil contaminated with PCBs, causing the "Yusho" (oil disease) epidemic in Japan in 1968. Apart form PCBs other contaminants like furans were found in the rice oil. Among 13 exposed mothers, who all had the Yusho disease, 2 stillbirths were reported and babies were born with skin stains (cola-coloured babies), conjunctivitis and neonatal jaundice (Kuratsune et al. 1972). All live born babies were also below the mean weight for gestational age and 5 were small for gestational age. After poisoning of cooking oil with PCBs in Taiwan in 1979 similar effects were noted: exposed children were shorter and lighter, and had skin, nail, and teeth anomalies (Rogan et al. 1988). One study reported a very high rate of infant death in babies who had been born with hyperpigmentations (8/38, 20.5%) (Hsu et al. 1985). A study of 163 live births born to 78 PCB poisoned women in Taiwan found proportions of low birth weight and premature babies to be significantly higher than in a control population who had not been exposed to PCBs (LBW 28% vs 6.3%, prematurity 25% vs 8%) (Yen et al. 1994). A study of 128 babies exposed transplacentally or through breast milk to PCBs found developmental delays in early life, especially in those that had exhibited neonatal symptoms of PCB poisoning (Lai et al. 2001; Yu et al. 1991). Prenatally exposed boys were found to have smaller penises at puberty, and perinatal exposure has also been shown to be associated with dental defects at age 7-11 years (Wang et al. 2003). Men exposed to PCBs before age 20 years were more likely to have a female baby than unexposed men (del Rio Gomez et al. 2002). Interpretation of the Taiwan findings was complicated by the fact that the PCBs were contaminated by unusually high levels of dibenzofurans which may be responsible for some or all of the observed effects.

Congenital malformations

Very few studies have examined the risk of congenital malformations related to PCB exposure outside the Japan and Taiwan food poisoning incidents. An alleged cluster of facial malformations in a Mexican town where mothers were possibly exposed to PCBs, was not found to be linked to PCB

exposure in a subsequent investigation of serum PCB levels and the pattern of anomalies (Garza et al. 1991). An ecological study in New York State found similar rates of fetal death, low birth weight and congenital malformation in a population potentially exposed to PCBs, dioxins and furans from an electrical transformer firer compared to a comparison population (Fitzgerald et al. 1989). A Swedish study compared malformation and fetal death rates (Rylander and Hagmar 1999), miscarriages and stillbirths (Axmon et al. 2000), and low birth weight (Rylander et al. 2000) in fishing communities on the East coast of Sweden where pollution with persistent organochlorine compounds including PCBs is high, with fishing communities on the West coast where such pollution is low. The study reports no difference in malformations, fetal deaths, miscarriages or stillbirths between the East coast and West coast cohorts. Low birth weight was found to be increased in the East coast cohort.

Low birth weight and other pregnancy outcomes

Subsequent to the Japan and Taiwan poisoning incidents a number of studies have examined the effects of in-utero exposure to PCBs and other organochlorine compounds and growth retardation. Decreases in birth weight (Fein et al. 1984; Rylander et al. 1998; Rylander et al. 1996; Rylander et al. 2000), increases in birth weight (Dar et al. 1992), and no relationship (Rogan et al. 1988) have been reported in relation to PCB exposure from the consumption of contaminated fish. One occupational study reports a decrease in birth weight relating to PCB exposure amongst women working in a capacitor plant (Taylor et al. 1989). A Dutch study found levels of PCB in cord plasma to be related to a decrease in birth weight (Patandin et al. 1998). Risk of spontaneous abortion was not found to be related to consumption of fish or estimated PCB exposure in a cohort of women who consumed sport fish from Lake Ontario (Mendola et al. 1995). A small case-control study in New York found maternal serum levels of PCBs and DDE not to differ between preterm and term deliveries (Berkowitz et al. 1996).

Dutch studies of developmental delay associated with prenatal exposure are reviewed later under “dioxins”. An American study of 858 infants measured Bayley Scales of Infant Development at 6 and 12 months, finding prenatal PCB exposure to be associated with lower psychomotor scores (Gladen et al. 1988). A study of psychometric function of Swedish conscripts found no effect of prenatal or postnatal exposure due to their mother’s consumption of fish (Rylander and Hagmar L 2000). A prospective American study of 50,000 pregnancies found no relation between PCB measured in maternal serum during pregnancy and mental or psychomotor scores at 8 months of age (Daniels et al. 2003).

5. Dioxins and phenoxy herbicides

Dioxins are persistent organochlorine compounds which are formed during high-temperature combustion processes and as by-products during the production of chlorinated phenols such as chlorphenoxy herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Agent Orange is a mixture- of 2,4-D and 2,4,5-T used by the US military in Vietnam. The most potent dioxin is considered to be 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Dioxins accumulate in fatty foods, and exposure of the general population is primarily from food (Food Standards Agency 2001). Highest concentrations are found in meat, fish, egg and dairy products, but cereals, fats and oils contribute significant proportions of total intake because of high levels of consumption.

Adverse pregnancy outcomes as a result of dioxin exposures have been studied in dioxin contamination accidents in Seveso and Missouri, in occupationally and environmentally exposed cohorts, in Vietnam veterans, and in populations exposed to phenoxy herbicide spraying. Studies have been summarised in Table 6. Evidence for adverse reproductive effects of dioxins, Agent Orange and phenoxy herbicide spraying have been reviewed in a number of review articles (Lilienfeld and Gallo 1989; Silbergeld and Mattison 1987; Skene et al. 1989; Sterling and Arundel 1986b).

Seveso and other environmental and occupational dioxin exposures

In 1976 an accident at a factory producing trichlorophenol released a cloud of toxic materials including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the area of Seveso, Italy. The quantity of TCDD released into the environment was large but was never precisely determined. The prevalence of chloracne (acute effect of exposure) was high in residents in the area immediately surrounding the factory, zone A, and lower but still raised in two areas with low and very low exposure, areas B and R. Mastroiacovo et al (Mastroiacovo et al. 1988) studied birth defects in the Seveso population up to 5 years after the accident. A total of 26 babies were born in zone A, none of which had major malformations, 2 of which had minor defects. Rates of major malformations in zone B and R were similar to those in a control area. Although the study does not find an increase in risk of congenital malformations following dioxin exposure, the number of births in the highly exposed area was too small to draw firm conclusions.

A subsequent study of the Seveso population has found that the sex ratio of children born between 1977 and 1996 was biased towards females the more the fathers (but not mothers) had been exposed to TCDD (Mocarelli et al. 2000). A retrospective cohort study of women who resided in areas A and

B could find no clear effect of exposure on the birthweight or gestational age of their future offspring {Eskenazi, 2003 #2911] but study is ongoing.

In Missouri, dioxin contamination of soil in a residential area prompted a study of reproductive outcomes (Stockbauer et al. 1988). Infant, fetal, and perinatal deaths, low birth weight, and birth defects were compared in an exposed area, based on the proximity of the maternal address to the location of the dioxin contamination, and an unexposed area. Increased risks were reported for infant, fetal, and perinatal deaths but none reached statistical significance. Numbers of birth defects were very small and no statistically significant increases in risk were found.

A Finnish study (Vartiainen et al. 1998) found a relationship of decreasing birth weight of the child with increasing concentrations of dioxins and furans in breast milk samples, but only when pregnancies of any parity were analysed. Analyses restricted to primiparea did not show a relationship. The authors found their model for evaluation of dioxins and PCBs in breast milk to be valid for primiparea only, since for subsequent children they did not have information on duration of breastfeeding of previous children and time period between children.

One occupational study was conducted amongst wives of employees of a chemical industry who had been exposed to dioxins during the processing of chlorphenols (Townsend et al. 1982). The study found no increase in risk of any of the reproductive outcomes studied (spontaneous abortions, stillbirths, infant deaths and congenital malformations) in the exposed group.

Another occupational study of paternal exposure was conducted among fathers working at a sawmill where chlorophenate wood preservatives had been used (Dimich-Ward et al. 1996). Again, contamination with dioxins of the wood preservatives was the main cause of concern. Chlorophenate exposure was based on expert raters' estimations of hours of exposure applied to specific time windows before conception and during pregnancy. The study reports increased risks of eye malformations (particularly cataract), anencephaly and spina bifida, and genital anomalies. No associations were found for low birthweight, prematurity, stillbirths or neonatal deaths.

A study of pregnant teachers exposed to chlorophenol wood preservatives in day care centres (Karmaus and Wolf 1995) measured concentrations of chlorophenol and dioxin in the indoor air and constructed an exposure matrix of vulnerable time windows for each pregnancy based on job history and indoor air measurements. Reduced birth weight and length were found in pregnancies exposed to the wood preservatives. The study controlled for smoking, socio-economic status and other potential confounding factors.

Vietnam veterans and residents

Studies of the effects of Agent Orange spraying in Vietnamese residents have not been published in Western scientific journals but have been summarised by Constable and Hatch (Constable and Hatch 1985) and Sterling and Arundel (Sterling and Arundel 1986a). Two types of studies were carried out: studies of reproductive outcomes in couples who lived in areas that were sprayed with Agent Orange and studies of Vietnamese soldiers who served in South Vietnam. Ascertainment of birth defects and other reproductive outcomes is a concern in all these studies. Rates of birth defects reported in the Vietnamese studies were low compared to those found in Western countries. Although the quality of the studies is difficult to judge, they do report increased risks of miscarriages, stillbirths, molar pregnancy and birth defects in residents of the sprayed areas and increased risks of birth defects in offspring of fathers who served as soldiers.

Studies of Vietnam veterans principally concern male-mediated effects only. Erickson et al (Erickson et al. 1984) studied the risk of major structural congenital malformations in the offspring of US veterans who served in Vietnam. The study found no increase in risk of all malformations or most subgroups of malformations in children of all military veterans, Vietnam veterans or Vietnam veterans with self-reported exposure to Agent Orange compared to fathers who had not served in the military. Cleft lip showed a statistically significantly increased risk in all veterans and a relationship with an Agent Orange exposure index. Spina bifida and coloboma also showed relationships with the Agent Orange exposure index. Nail anomalies were increased in children of Vietnam veterans. Many comparisons were made and some of these associations would have been found by chance alone. Estimates of Agent Orange exposure used in the study are likely to have been fairly inaccurate, as the authors discuss. A similar study in Australia (Donovan and R 1984) found no increase in the risk of birth defects amongst fathers who had served in Vietnam compared to fathers who had been in the army but had not served in Vietnam. Seven subgroups of malformations were analysed and no increase in risk in any of these groups was found. In this study no estimates of Agent Orange exposure were available. A survey of Tasmanian Vietnam veterans (Field and Kerr 1988) reports distinct patterns of central nervous, skeletal and cardiac malformations in the children of veterans but no formal statistical comparisons were made with a non-veteran control group. The veteran group also showed a statistically significant higher number of fetal and infant deaths. No confounders were taken into account.

Wolfe et al (Wolfe et al. 1995) study a cohort of Operation Ranch Hand veterans who were responsible for aerial spraying of herbicides in Vietnam. Serum dioxins concentrations were measured as part of the study. Ranch Hand veterans were grouped into background, low and high serum dioxin categories and compared with a group of veterans who were not involved in herbicide spraying. Results of the study are ambiguous. Increases in risk were found for some congenital malformation

subgroups (circulatory system and heart, genital system, urinary system) in the low dioxin category compared to the control group but these increases were not seen in the high exposure category. For all major malformations combined the OR was 1.7 (1.1-2.7) in the low dioxin category and 1.2 (0.8-1.2) in the high exposure category. The authors noted 2 cases of spina bifida in the highly exposed group among 268 liveborn infants, more than would be expected. Spontaneous abortions and stillbirths also show no clear relationship with dioxin exposure categories. A subsequent study (Michalek et al. 1998) of preterm birth, intrauterine growth retardation and infant death in the same cohort reports increased risks for preterm birth and infant death in the high and background categories. No increases are found for intrauterine growth retardation. Again, these patterns do not indicate a clear relationship with dioxin exposure.

Stellman et al (Stellman et al. 1988) report on reproductive and other health outcomes in 2,858 veterans who had served in Vietnam and 3,933 servicemen who had not. The study reports an increased risk of spontaneous abortion in wives of Vietnam veterans, with a dose-response relationship of increasing risk with increasing Agent Orange exposure estimates. There was no difference in the birthweight of offspring of Vietnam veterans and other servicemen. A case-control study (Aschengrau and Monson 1989) finds no increase in risk of spontaneous abortion in wives of Vietnam veterans compared to wives of men with no known military service.

"Background" dioxin levels and developmental effects

A series of Dutch studies have been investigating the effects of prenatal and postnatal exposure to "background" levels of dioxin and dioxin-like PCBs, in an industrial and rural area of the Netherlands. There has been particular interest in neurological development, mental and psychomotor scores. Interpretation is complicated by confounding by breastfeeding, since breastfeeding is associated with higher socio-economic status and also with higher dioxin exposure of the infant. One of these studies suggested no effect on mental or psychomotor score by 18 months, although effects at 3 and 7 months were detected (Koopman-Esseboom et al. 1996) and an earlier report had suggested a small negative effect of transplacental but not postnatal exposure (Huisman et al. 1995). A related study found that in utero exposure to environmental levels of dioxins and dioxin-like PCBs was negatively associated with birth weight and postnatal growth until 3 mo of age, but there was no detectable effect thereafter up to the last measurements at 42 months (Patandin et al. 1998). At 42 months of age, higher prenatal exposure to dioxin was associated with poorer cognitive functioning (Patandin et al. 1999).

Phenoxy herbicide spraying

One ecological study (Field and Kerr 1979) has reported a statistically significant correlation between annual neural tube defect rates and 2,4,5-T usage in Australia. Other ecological studies have not reported an association between 2,4,5-T usage and cleft lip and/or palate in Arkansas (Nelson et al. 1979), and stillbirths, neural tube defects, clefts, and cystic kidney in Hungary (Thomas 1980). An ecological study of spraying of 2,4,5-T in New Zealand found no association with central nervous system malformations, but a significant association with talipes (Hanify et al. 1981) A cohort study of pesticide applicator reported no increase in risk of congenital malformations, stillbirths, and spontaneous abortions for pesticide applicators compared to other agricultural workers (Smith et al. 1981). When grouping the pesticide applicators over 3 groups with no exposure, exposure to other chemicals and exposure to 2,4,5-T, again no increase in risk of the above outcomes is found in relation to exposure (Smith et al. 1982). A cohort study of nearly 6,000 pregnancies among farm residents in Ontario (Arbuckle et al. 1999) reported an association between risk of early spontaneous abortions (<12 weeks gestation) and pre-conceptional use of phenoxy herbicides at the farm. This could be due to either maternal or paternal exposures. A stronger association was found if the husband did not wear protective equipment during application. First trimester exposure to phenoxy herbicides was not associated with an increased risk of spontaneous abortion.

6. Pesticides

Pesticides are highly toxic substances that are being added to the environment for the purpose of killing or injuring some form of life. It has been estimated that 45-50,000 different pesticides are produced world-wide based on 600 different active ingredients (Tuormaa and FORESIGHT 1995). Pesticides can be divided in three main categories: insecticides, fungicides, and herbicides (Box 1).

Box 1: categories of pesticides (National Research Council, 1993)

Insecticides	chlorinated hydrocarbons	DDT, aldrin, dieldrin, lindane
	organophosphates	malathion and parathion, dichlorvos
	Carbamates	aldicarb, profam
Herbicides	chlorophenoxy compounds	2,4-Di- and 2,4,5-Tri chlorophenoxyacetic acid
	Triazinen	atrazine, simazine, alachlor
	dipyridyl compounds	paraquat, diquat
Fungicides	Carbamates	benomyl, carbendazin
	Dithiocarbamates	maneb, thiram, zineb
	Others	captan, folpet

Human exposure to pesticides can occur in the environment as a consequence of water, air, or food contamination, or in occupational situations. The main occupational activities with exposure to pesticides are pesticides production plants, pesticides distribution companies, agriculture, gardening, livestock, public health programs (e.g. malaria, rodent control), and other occupational activities (e.g. wood preservatives, weed control) (Garcia 1998). The possible teratogenic effects of pesticides in humans have long been the subject of controversy. This section summarises studies that examine congenital malformations as an outcome in relation to pesticide exposure (Table 7). Studies of other pregnancy outcomes are many and these are not included in this section. Studies on the risk of congenital malformations associated with phenoxy herbicides have been discussed in section 5. In depth reviews of pesticides and congenital malformations and other pregnancy outcomes have been published elsewhere (Arbuckle and Sever 1998; Garcia 1998; Nurminen 1995; Nurminen 2001; Sever et al. 1997). The main problems in studies of pesticide exposure and adverse pregnancy outcome are inaccurate exposure assessments, with no measurement of dose of exposure and little ability to distinguish between different types of pesticides.

Studies on pesticides and congenital malformations can broadly be divided into those that study occupational exposures and those that study residence near or in areas where pesticides are used or sprayed. We also discuss some case reports and cluster reports in relation to pesticide exposure.

Occupational exposure

Studies of occupational exposure to pesticides have used fairly crude exposure classifications such as 'occupational exposure to pesticides' (Blatter et al. 1997; Kurppa et al. 1983; Pastore et al. 1997; Rupa et al. 1991; Shaw et al. 1999; Zhang et al. 1992), 'work in agriculture' (Garcia et al. 1998; Garcia et al. 1999; Kristensen et al. 1997; Lin et al. 1994; Nurminen et al. 1995; Schwartz and LoFerfo 1988; Schwartz et al. 1986), 'work in floriculture' (Restrepo et al. 1990a; Restrepo et al. 1990b), 'work as agricultural pilot' (Roan et al. 1984) and 'work as pesticide applicator' [Garry, 1996 #1730). Only few of the occupational studies are able to distinguish between different classes of pesticides (Garcia et al. 1998; Lin et al. 1994). Table 8 shows that both positive and negative relationships with risk of congenital malformation have been reported. Several studies report no association between risk of total malformations and maternal pesticide exposure (Kurppa et al. 1983; Shaw et al. 1999), paternal pesticide exposure (Roan et al. 1984), or exposure of either parent (Brender et al. 2002; Kristensen et al. 1997; Schwartz et al. 1986). Positive associations for total malformations are reported by Restrepo (Restrepo et al. 1990a; Restrepo et al. 1990b) for maternal and paternal work in floriculture, by Rupa (Rupa et al. 1991) for paternal pesticide spraying, by Garry (Garry et al. 1996) for paternal work as pesticide applicator, by Garcia (Garcia et al. 1998) for paternal occupational exposure to various categories of pesticide ingredients, and by Garcia (Garcia et al. 1999) for maternal agricultural activity. The study by Garcia et al (Garcia et al. 1998) is one of the only studies distinguishing different pesticide classes. This study reported raised ORs for paternal exposure to aliphatic hydrocarbons, inorganic compounds, glufosinate and pyridil derivates. There was no evidence of a relationship with organophosphates, carbamates, organochlorines, chloroalkylthio fungicides and organosulfurs.

Dibromochloropropane (DBCP) is a nematocide with recognized adverse effects on human fertility by suppressing spermatogenesis (Potashnik and Porath 1995). A series of publications following a cohort of men who were occupationally exposed to DBCP examines whether DBCP exposure has led to congenital malformations and spontaneous abortions after exposure (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988; Potashnik and Porath 1995). The cohort is very small, 30 workers. Pregnancies before and after exposure were compared. The studies do not show any evidence of an increase in the rate of malformations or spontaneous abortions in pregnancies after exposure.

Limb defects are the malformation subgroup most frequently reported to be associated with occupational pesticide exposure (Kricker et al. 1986; Kristensen et al. 1997; Lin et al. 1994; Schwartz and LoFerfo 1988; Schwartz et al. 1986). Kricker et al (Kricker et al. 1986) report an OR of 3.4 for maternal pesticide exposure in work, home and garden during the first trimester. Schwartz (Schwartz et al. 1986) find an OR 2.3 for maternal or paternal work in agriculture. A follow-up study did not confirm this relationship for occupational exposures although an increased risk of limb defects was found in relation to residence in pesticide use areas (Schwartz and LoFerfo 1988). Lin et al (Lin et al. 1994) specifically study limb reduction defects and find an association with parental occupational pesticide exposure only for limb defects associated with other defects, not for isolated defects. Odds ratio estimates in this study are similar for all categories of pesticides studied (fungicides, herbicides, insecticides). Kristensen et al (Kristensen et al. 1997) find an increased risk of limb reduction defects related to two out of over ten pesticide exposure indices used (pesticide purchase figures and grain farming).

Newspaper reports of a cluster of anophthalmia and microphthalmia in relation to benomyl (a fungicide) in England prompted several investigations of this suggested link. In Italy an ecological study reported no relation between benomyl use and anophthalmia/ microphthalmia rates (Spagnolo et al. 1994). This study also reports on a case-control investigation which found no increase in risk of anophthalmia/microphthalmia among parents employed as farmers. In Norway, a cohort pregnancies to farming families was used examine a possible relationship between benomyl exposure and anophthalmia/ microphthalmia (Kristensen and Irgens 1994). Parents were classified as exposed if they worked in greenhouses or orchards, or with field vegetables or grains at specific times of the year. Only one exposed case of anophthalmia/microphthalmia was found and the rate of anophthalmia/ microphthalmia in the entire cohort was not raised. In England, a raised risk of anophthalmia and microphthalmia was observed in rural areas (Dolk et al. 1998a) but no further analysis of pesticide exposure could be performed. Overall, these studies gave little support to an association between benomyl and anophthalmia/microphthalmia.

Other subgroups of anomalies for which increased risks in relation to occupational exposure have been reported are central nervous system defects (Kristensen et al. 1997; Nurminen 1995; Zhang et al. 1992), haemangiomas (Restrepo et al. 1990a), orofacial clefts (Nurminen 1995), urogenital defects including hypospadias and cryptorchidism (Garry et al. 1996; Kristensen et al. 1997), circulatory/respiratory defects (Garry et al. 1996), gastrointestinal defects (Garry et al. 1996) and musculoskeletal defects (Garry et al. 1996). A study of hypospadias found no association with occupation as gardener or farmer (Weidner et al. 1998)

A retrospective cohort study in the Philippines (Crisostomo and Molina 2002) which surveyed birth outcomes in a number of villages found that birth defects (as determined by physical examination) were more common (3.5% of births, 12 cases) in the group that used pesticides conventionally compared to the group that practiced integrated pest management (0.9% of births). However, the very low prevalence of birth defects detected limits the interpretation of this study, although deficiencies in birth defect detection may have applied equally to both types of exposed household. A higher rate of spontaneous abortions was also found in this study associated with conventional pesticide use.

Residential exposure

Studies of residential exposure to pesticides have used proxy measures of exposure such as pesticide usage of the area of residence, residence in or near pesticide application areas, or residence near agricultural crops. One ecological study reports increased risks of cleft lip and/or palate in relation to pesticide use in county of residence in two US states (ORs 2.85 and 1.68). A case-control study in New Brunswick (White et al. 1988) finds an association between risk of spina bifida, but not of cleft lip, cleft palate or renal agenesis, and a pesticide usage exposure index. Schwartz et al (Schwartz and LoFerfo 1988) report increased risks of limb reduction defects in areas with high agricultural activity and high pesticide use. A cohort study in the San Fransisco Bay area (Thomas et al. 1992) finds a relationship between residence in malathion spraying areas and risks of total malformations, limb defects, and orofacial clefts. Garry et al (Garry et al. 1996) report high risks of central nervous system defects, circulatory/respiratory defects, gastrointestinal defects, urogenital defects, musculoskeletal defects and total malformations (the same anomalies found to be related to occupational exposure – see above) in relation to residence in crop-growing regions. A case-control study of cryptorchidism in Spain finds increasing rates of the anomaly in relation to increasing pesticide use of municipality of residence. In a Californian study (Shaw et al. 1999), increased risks of neural tube defects were found for residence living within ¼ mile of a agricultural crop. Risks of orofacial clefts, conotruncal heart defects, and limb anomalies were not raised in this study. Another Californian study [Bell, 2001 #2641] finds fetal deaths due to congenital malformations to be associated with residential proximity (within 1 mile) to pesticide application areas for 4 out of 5 pesticide classes studied: phosphates, carbamates, endocrine disruptors and halogenated hydrocarbons.

Other studies have not found a relation between MATDA application areas (Li et al. 1986), heptachlor contamination (Le Marchand et al. 1986), malathion application (Grether et al. 1987), DBCP contaminated drinking water (Whorton et al. 1989) and total congenital malformation rates.

A subset of data from the Baltimore-Washington Infant Study was used to investigate possible associations between cardiac anomalies and maternal exposure to pesticides during the first trimester

of pregnancy and in the three months preceding pregnancy. Transposition of the great arteries (TGA) was the only cardiac anomaly significantly associated with maternal pesticide exposure (Odds ratio=2.0; 95% confidence interval 1.2 to 3.3). Analysis by type of pesticide showed significant associations between TGA and exposures to rodenticidal chemicals and herbicides, but not to insecticides. Adjusting for race, socio-economic status, maternal age, maternal smoking and alcohol use, family history of heart defects and paternal pesticide exposures, an odds ratio of 4.7 (95% confidence interval 1.5 to 14.2) was reported for exposure to rodenticides and an odds ratio of 2.8 (95% confidence interval 1.2 to 6.9) was reported for exposure to herbicides (Loffredo et al. 2001).

Case reports and cluster reports

In California, 35 agricultural workers became ill after entering a field contaminated with a mixture of 2 organophosphate insecticides and a carbamate insecticide (Romero et al. 1989). One of the workers was 1 month pregnant when exposure occurred and subsequently gave birth to a baby with multiple cardiac defects, coloboma, microphthalmia, cerebral and cerebellar atrophy and facial anomalies. There was no family history of malformations. An unusual pattern of malformations was found in 4 children whose mothers had been exposed to Chlorpyrifos (an organophosphate pesticide) during the first trimester of pregnancy (Sherman 1996). The 4 cases had similar patterns of defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples and genitalia, as well as growth retardation and mental retardation. None had family history of birth defects. In a Hungarian village, out of 15 live births in a two year period in a Hungarian village, 11 were affected by congenital abnormalities and 6 were twins (Czeizel et al. 1993). Four out of the 11 affected children had Down syndrome. Teratological factors, familial inheritance and consanguinity were ruled out. Trichlorofon (an organophosphate pesticide) was used extensively at local fish farms. No congenital abnormalities occurred in the two years after the chemical treatment of fish was banned. In Spain, a range of rare dysmorphologic syndromes were reported in an area with intensive farming (Reche 1999). Acute pesticide intoxication was reported to be a common problem in this area. The report does not describe family histories.

7. Mixed and Unspecified Environmental Exposures

7.1 Air pollution

This section discusses the evidence for adverse pregnancy outcomes in relation to ambient air pollutants (with no particular source described) including particulates, sulphur dioxide (SO2), nitrogen oxides (NOx) and carbon monoxide (CO). Air pollution related to specific industrial sources is described elsewhere for specific pollutants. Studies are summarised in Table 8.

There are hardly any studies of the association between ambient air pollution and risk of congenital malformation. One study in South Moravia reports a high prevalence of congenital malformations in a district with high levels of SO2 and other pollutants (Smrcka and Leznarova 1998). The study gives little detail about methods used and does not formally compare prevalence with other districts. A report of high levels of congenital malformations in Cracow as a result of high levels of air pollutants could not be followed up because the original study was published in Polish only (Guminska 1993). One recent study has examined the risk of birth defects in relation to outdoor air pollution in California (Ritz et al. 2002). This study reports an increase in risk of cardiac defects, including ventricular septal defects, in relation to carbon monoxide exposure. Odds ratios of around 3 were found comparing the lowest with the highest quartile of CO exposure during the 2nd month of pregnancy. There were no relationships with NO_2, ozone, or PM_{10}. Orofacial clefts showed no relationship with any of the pollutants. Other birth defects were not studied.

Other adverse pregnancy outcomes, especially low birth weight and preterm birth, have more commonly been studied in relation to ambient air pollution. In an early report Williams et al linked decreased birth weight to air pollution in Los Angeles (Williams et al. 1977). Hemminki and Niemi (Hemminki and Niemi 1982) find increased risks of spontaneous abortion related to levels of hydrogen sulphide but not SO2 and carbon disulfide in a region in Finland. In the last decade a number studies have investigated the association between air pollution and low birth weight and prematurity in more detail. The results of these studies are quite consistent in showing positive relationships (Table 9). Inconsistencies still exist in the type of outcome affected - fetal growth or preterm birth, the period of exposure during pregnancy of importance, the extent to which some of the associations reported may be due to socio-economic confounding, and the exact pollutants responsible for the reported increases. Biological mechanisms that have been suggested to explain the reported associations include: a mutagenic effect of PAHs adhered to PM10 particles (Sram 1999) or of other air pollutants, rheological factors including blood viscosity and clotting affecting placental functioning, and intrauterine infections, but evidence for all these is limited (Bobak 2000; Bobak

2001). Mechanisms (rheological factors, DNA damage) may be similar to those involved in the adverse effects of cigarette smoking on low birth weight and other pregnancy outcomes, although fetal exposures to air pollution are likely to be lower (Bobak 2000). Recent individual studies of the association between outdoor air pollution and adverse pregnancy outcome are described below in detail and summarised in Table 8.

An ecological study in the Czech Republic of live births 1986-88 also found an association between SO_2 and low birth weight (Bodin et al. 1999). The odds ratio of low birth weight for 50 $\mu g/m^3$ increase in SO_2 was 1.10 (1.02-1.17). The study used annual district averages to assess exposure; because individual data were not available, the possible confounding by socio-economic status could not be excluded. Total suspended particles (TSP) and NOx did not show an association with low birth weight independent of SO2. There was no association between stillbirths and air pollutants. Further analyses of the Czech national birth register linked with air pollution data found both low birth weight and prematurity to be associated with SO_2 and somewhat less strongly with TSP (Bobak 2000). There was no association between any pollutant and IUGR. Associations with low birth weight and prematurity were marginally stronger for exposures in the first trimester than other trimesters, and were not attenuated at all by adjustment for socio-economic factors or month of birth. Adjusted ORs of low birth weight for 50 $\mu g/m^3$ increases in air pollutants were 1.20 (95%CI 1.11-1.30) for SO_2 and 1.15 (1.07-1.24) for TSP in the first trimester, and adjusted ORs of prematurity were 1.27 (1.16-1.39) for SO_2 and 1.18 (1.05-1.31) for TSP in the first trimester. The association between low birth weight and air pollutants was largely explained by low gestational age.

In another Czech study, the Czech - US EPA study (Dejmek et al. 1999), the risk of intrauterine growth retardation (IUGR) was increased in term births when mothers were exposed to high levels of outdoor PM10 in the first month of pregnancy, after controlling for maternal characteristics. The OR was 2.64 (1.48-4.71) for comparing high (>50 $\mu g/m^3$) vs low (=<40 $\mu g/m^3$) level of PM10. Exposure in later months of pregnancy were not related to IUGR.

A study in 4 residential areas of Beijing, China, reported a significant dose-response relationship between maternal exposures to sulphur dioxide (SO_2) and total suspended particles (TSP) during the last trimester and the risk of low birth weight (Wang et al. 1997) and premature birth (Xu and Ding 1995). Low birth weight (above 37 weeks gestation) was associated with SO_2 and TSP in the last trimester of pregnancy, with OR 1.11 (1.06-1.16) and 1.10 (1.05-1.14) for 100 $\mu g/m^3$ increase in SO_2 and TSP, respectively, after controlling for maternal age, residential area, infant gender, and gestational age. Exposure in earlier trimesters were not positively related to birth outcomes. There was an association between prematurity and short term variation in SO_2 and TSP, with OR of 1.21 and 1.10 (per 100 $\mu g/m^3$) respectively (Xu and Ding 1995).

A study in Southern Californian found the risk of low birth weight among singletons born between 37 and 44 weeks of gestation to be increased among babies of mothers exposed to high levels (above 95 percentile) of carbon monoxide in the last trimester (OR 1.22, 95%CI 1.03-1.44) (Ritz and Yu 1999). Only few data on other pollutants were available, and their effects were not analysed. As carbon monoxide was correlated with NO_x (r=0.62) and PM10 (r=0.39), it is possible that birth weight could also be related to other pollutants. There were no effects of carbon monoxide in earlier trimesters.

A second Californian study investigated associations between measurements of CO, NO2, ozone and PM10, and preterm birth (Ritz and Yu 2000). A 20% (9-33%) increase in preterm birth per 50ug/m3 PM10 was found for average PM10 exposure over 6 weeks before the birth. Averaging exposure over the first month of pregnancy this increase was 16% (6-26%). For CO an increase of 13% (8-18%) per 3 ppm was found for exposure 6 weeks before birth and 4% (1-9%) for exposure during the first month of pregnancy.

Rogers et al (Rogers et al. 2000) estimated the combined annual TSP/ SO2 exposure at homes of very low birth weight babies and control births. The risk of very low birth weight was found to be increased in high (above 95th percentile) exposure homes compared to low (below median) exposure homes, OR 2.88 (95% CI 1.16-7.13) after adjustment for race, smoking, maternal age, family income, parental education, and other factors. There was some evidence of a trend of increasing risk with increasing exposure. There was no control for gestational age so it is not possible to separate effects on fetal growth and preterm birth in this study.

Bobak et al (Bobak 2001) found a strong relationship between mean birth weight of members of the 1946 British birth cohort and an air pollution index based on coal consumption. Birth weight was 87 grams lower in the most polluted versus the least polluted areas. Adjustment for confounding factors gender, father's social class, mother's education, and region did not change the association. Levels of air pollution, both outdoor and indoor, in 1946 were much higher in Britain than they are today.

A number of studies have also reported positive associations between ambient air pollution and infant mortality (Bobak and Leon 1992; Bobak and Leon 1999a; Woodruff et al. 1997). Effects seem particularly related to respiratory mortality and sudden infant deaths. An in depth discussion of these outcomes falls beyond the scope of this review.

7.2 Drinking water contamination

Studies of the effects of drinking water contamination on human reproductive outcomes can be divided into three broad groups according to the exposure of interest: 1) chlorinated and aromatic solvents (trichloroethylene, benzene) entering drinking water from leaking underground storage tanks, landfill, and other waste disposal facilities; 2) trihalomethanes, which are formed when chlorine disinfectant reacts with organic matter in the drinking water; and 3) inorganic contamination (examples: nitrates, fluoride, etc). Some overlap between these three sections may exist. Studies are summarised in Table 9.

7.2.1 Chlorinated and aromatic solvents

In Woburn, Massachusetts, toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells. Residents of Woburn reported a cluster of 12 leukaemia cases in children and a first study confirmed that this number was significantly higher than expected on the basis of national rates (Cutler et al. 1986). The problems with cluster analyses are discussed in Part I, Chapter I.2 of this Report. Because of lack of information on exposure to the contaminated wells it was not possible in this first report to link the leukaemia cases with exposure to the well-water. Lagakos et al (Lagakos et al. 1986) followed up these findings by compiling an exposure score for residential zones in Woburn, using information on what fraction of the water supply in each zone had come from the contaminated wells annually since the start of the wells. Childhood leukaemia incidence, perinatal deaths, congenital anomalies and childhood disorders were studied in relation to the exposure scores. A significant excess was found again comparing leukaemia rates for Woburn with national rates and an association was found between leukaemia incidence and exposure scores. The pregnancy outcome survey found associations with eye/ear congenital anomalies and central nervous system/oral cleft/chromosomal anomalies (mostly Downs syndrome), but not with low birth weight or most childhood disorders. Pregnancy outcomes were self-reported in this study but because residents were not aware of their exact exposure score the authors conclude that it is unlikely that this led to substantial differential reporting.

A number of studies followed the contamination of two drinking water wells in Santa Clara County, California, with chlorinated solvents that had leaked from an underground waste storage tank. Residents living near one of the contaminated wells reported a cluster of adverse pregnancy outcomes, mainly spontaneous abortions and congenital heart defects. A first investigation (Swan et al. 1989) confirmed a significant excess of cardiac anomalies in the service area of the water company that operated the contaminated well compared to an unexposed area. The excess was found within the potentially exposed time period and not in an unexposed time period after the well was closed. The authors conclude that the solvent leak was an unlikely explanation for the excess of cardiac anomalies

found because the excess occurred mainly in the first 12 months of the exposed time period, and there was a significant (p=0.03) deficit of cases during the second 8 months corresponding to the time when exposure was thought to be more certain. However, it is unclear when the leak started and the potentially exposed period was defined beforehand as the full 20 months' period. A second study in the same area reported an increased risk of all congenital malformations combined and spontaneous abortions (Deane et al. 1989). A follow-up study including a second exposed area did not observe an increase in either outcome in this second area, even though it was thought to have the same water exposure as the original area (Wrensch et al. 1990a). An exposure study estimating monthly concentrations of solvents in each census tract, found no difference in probability of exposure between women with adverse pregnancy outcomes and women with normal births (Wrensch et al. 1990b). Subsequent studies investigating water consumption in Santa-Clara County report significant associations between reported tap water consumption and risk of cardiac defects (Shaw et al. 1990) and spontaneous abortions (Deane et al. 1992; Wrensch et al. 1992), regardless of whether women lived in areas that received contaminated water. As the authors of these studies point out, recall biases cannot be excluded. A more recent prospective study followed up these investigations in the original Santa Clara region and two other regions (Swan 1998). The prospective design eliminated recall bias. The study found an increased risk of spontaneous abortion in the original region but not in the two other regions, suggesting contamination in this region to be responsible for the increase. Little was known in this study about the constituents of the water in the 3 regions.

In Tuscon Valley, California, groundwater and drinking water wells were found to be contaminated with trichloroethylene and, to a lesser extent, dichloroethylene and chromium. Goldberg et al (Goldberg et al. 1990) compared families of cases with cardiac malformations with households from the general population and found parents of cases to be significantly more likely to have been working or living in the contaminated area. The control selection in this study is seriously doubtful: the exposure of parents of cases was compared with the exposure of household members of the general population (not births) which does not take account of the distribution of births in the population. Also, it is unclear whether the hospital-based registry that provided the cases covered the total study population. Exposure classification was very poorly described and the study included a time period after which contaminated wells were closed (Rodenbeck et al. 2000). For these reasons, the results of this study are unlikely to be reliable.

A recent study in the Tuscon Valley (Rodenbeck et al. 2000) used an environmental dose-reconstruction study to estimate exposure to the contaminated drinking water wells. Low birth weight and very low birth weight were compared in exposed and unexposed census tracts. Unexposed census tracts were carefully selected to include similar populations (for ethnic and socio-demographic factors) to the unexposed tracts. An association (non-statistically significant) was found between

maternal exposure to trichloroethylene via drinking water and risk of very low birth weight (<1500g). There was no association with low birth weight (<2500g).

A cross sectional study in New Jersey studied levels of organic solvents and total trihalomethanes in the drinking water in 75 towns (Bove et al. 1995). Outcomes studied were low birth weight, very low birth weight, small for gestational age, pre-term birth, and major groups of birth defects (central nervous system, cardiac, oral clefts). The study included over 81,000 live births and fetal deaths. All residents of the same town were assigned the same exposure level. Odds ratios of more than 1.5 were found for total birth defects and carbon tetrachloride; central nervous system defects and trichloroethylene, dichloroethylene, and carbon tetrachloride; neural tube defects with trichloroethylene, dichlroethylene, carbon tetrachloride, and benzene; oral clefts with trichloroethylene, tetrachloroethylene, dichloroethyelene, and carbon tetrachloride; and major cardiac defects with 1,2 dichloroethane and benzene. Results for trihalomethanes are discussed in section 7.2.2 below. The study also reports associations between low birth weight, small for gestational age, and very low birth weight and levels of carbon tetrachloride in the drinking water.

An ecological study in Michigan (Witkowski and Johnson 1992) investigated low birth weight rates in counties with documented ground or surface water contamination by benzene and chlorinated solvents from polluted sites. A positive relationship was found between the percentage low birth weight babies in a county and an index of water pollution, adjusting for teenage pregnancies, prenatal care level, and income. The authors give no explanation of how the pollution indices were calculated making this study difficult to interpret.

A recent study in North Carolina (Sonnenfeld et al. 2001) studied birth weight, small for gestational age, and preterm birth in relation to tetrachloroethylene contamination of drinking water at a Marine Corps Base. There was little evidence for an overall association between tetrachloroethylene exposure and the main outcomes studied. However, associations were found in older mothers and mothers with histories of fetal loss showing a decrease in birth weight and increase in risk of having a small-for-gestational-age infant in exposed mothers in these groups.

7.2.2 Chlorination by-products

Chlorination by-products are halogenated solvents, predominantly trihalomethanes (THM): chloroform, bromodichloromethane, dibromochloromehtane, and bromoform. Studies of pregnancy outcomes in relation to water chlorination by-products have been reviewed by Reif et al (Reif et al. 1996), Nieuwenhuijsen (Nieuwenhuijsen et al. 2000) Bove et al (Bove et al. 2002) and Graves et al (Graves et al. 2001). These reviews discuss exposure assessments as the major weakness in these

studies, since in all studies water supply of whole communities was used as a proxy of the intake of chlorination by-products by individual mothers, assuming for example that mothers did not use private wells or water filtration systems, or drink bottled water. Table 9 summarises studies of chlorination by-products.

Congenital Malformations

A case-control study by Aschengrau (Aschengrau et al. 1993) investigated the relationship between source of drinking water, treatment of drinking water, and levels of trace elements and congenital malformations, stillbirths, and neonatal deaths. The study reports increased ORs for the consumption of chlorinated compared to non-chlorinated drinking water for stillbirths and congenital malformations (OR 1.5; 95%CI 0.7-2.1). This study was the first to report an association with water chlorination but had no information on levels of chlorination by-products in the water. Exposure classification was crude: communities with chlorinated drinking water compared to communities without. The study was mainly set up to investigate levels of heavy metals (see also section 'lead') and inorganic trace elements in the drinking water. The results of this part of the study are discussed in section 7.2.3.

Shaw et al report in a short paper (Shaw et al. 1991) the findings of further analyses of the case-control study of congenital cardiac defects reported in section 7.2.1 above (Shaw et al. 1990). Information on whether a mother's residence received chlorinated water during the first trimester of pregnancy was analysed in combination with the mother's reported consumption of tap water in that period. There was no increase in the risk of cardiac defects for women who reported drinking tap water and lived in a residence receiving chlorinated tap water. A further study by Shaw et al (Shaw et al. 2003b) investigating possible associations between THMs and NTDs, orofacial clefts and conotruncal heart defects found no clear pattern of association between exposure and risks of the specific congenital anomalies.

The New Jersey study by Bove et al (Bove et al. 1995) discussed in section 7.2.1 also investigated the association between total trihalomethanes levels in the drinking water in 75 New Jersey towns and adverse pregnancy outcomes. Odds ratios of more than 1.5 were found for TTHM levels of >100 ppb compared to <=20 ppb and risk of all birth defects (OR 1.57), central nervous system defects (OR 2.59), neural tube defects (OR 2.96), oral clefts (OR 3.17), major cardiac defects (OR 1.83), and small for gestational age (OR 1.50). Evidence for a trend in risk with TTHM level was found for all birth defects, central nervous system defects, neural tube defects, and small for gestational age. Mean birth weight was found to be associated with TTHM levels in a dose-response manner.

The New-Jersey study was follow-up by a case-control study of neural tube defects (Klotz and Pyrch 1999). This study improved exposure assessment by estimating exposure at the critical time for neural tube closure and at the residence of the mother at that time. Cases and controls were interviewed to obtain information about tap water ingestion, bathing and showering, time at swimming pools, use of vitamin supplements and other possible confounding factors. The study reported an odds ratio of 1.6 (95%CI 0.9-2.70) for exposure to >40 ppb of TTHM compared to <5 ppb. Surface water as a source of drinking water was associated with an odds ratio of 1.5 (95%CI 0.9-2.5). Surface water is more likely than groundwater to undergo chlorination. Other disinfection by-products, haloacetic acids and haloacetonitriles, were not associated with NTD risk.

In cross-sectional survey of 141,077 births in Norway (Magnus et al. 1999), exposure to chlorination by-products was measured for each municipality by combining the proportion of the population served by chlorinated water and the reported colour of the drinking water. A high colour indicated high concentrations of dissolved carbon in the water and thereby high levels of disinfection. Municipalities with high colour and high proportion chlorination were classified as exposed, areas with low colour and low proportion chlorination were classified as unexposed. Adjustments were made for maternal age, parity, place of birth, population density, and industry profile of the municipality. The study found an increased of risk of all congenital malformations (OR 1.14; 95%CI 0.99-1.31) and urinary tract defects (OR 1.99; 95%CI 1.10-3.57) in exposed compared to unexposed municipalities. An update of this study with a larger study population (184,676 infants) found the risks of any defect, cardiac, respiratory system and urinary tract defects were higher in the exposed group compared to the reference group (Hwang et al. 2002).

A retrospective cohort study in Nova Scotia, Canada, linked 50,755 births to TTHM levels of the water supply serving the mother's address at relevant exposure times (Dodds et al. 1999). Outcomes studied were low birth weight, very low birth weight, small for gestational age, preterm birth, stillbirths, neural tube defects, cleft defects, cardiac defects, and chromosomal abnormalities. Only stillbirths showed a statistically significant association with high TTHM levels (>100ug/l vs <50ug/l)). The RR for chromosomal abnormalities was 1.38 but did not reach statistical significance (95%CI 0.73-2.59). Adjustments were made for income level, smoking, maternal age, and parity. A second part of the study analyses congenital malformations in relation to chloroform and bromodichloromethane (BDMC) exposure (Dodds and King 2001). Exposure to BDMC (>20ug/l) was related to an increased risk of neural tube defects (RR 2.5, 95%CI 1.2-5.1) and a decreased risk of cardiac malformations (RR 0.3, 95%CI 0.2-0.7). There were no associations with chloroform exposure and no statistically significant increased or decreased risks of oral clefts and chromosomal anomalies.

Other Pregnancy outcomes

A case-control study in Iowa (Kramer et al. 1992) investigates the association between levels of chloroform in drinking water and low birth weight, prematurity and intrauterine growth retardation. Exposure to chloroform and other THMs was measured by municipalities of residence. The study reports a statistically significant increase in IUGR related to chloroform levels of >=10ug/l (OR 1.8; 95%CI 1.1-2.9), and non-significant increases in IUGR related to dichlorobromomehtane >=10ug/l (OR 1.7; 95%CI 0.9-2.9) and in LBW related to chloroform >=10ug/l (OR 1.3; 95%CI 0.8-2.2).

A case-control study in North-Carolina (Savitz et al. 1995) investigated the association between TTHM levels and spontaneous abortion, low birth weight and preterm delivery and found no evidence of an association between TTHM concentrations in the drinking water of the area of residence of the mother and risk of any of these outcomes. The study did find increasing consumption of tap water to be associated with a decreasing risk of spontaneous abortion.

Gallagher et al (Gallagher et al. 1998) report on a retrospective cohort study in Denver and find increased risks of low birth weight (OR 2.1; 95%CI 1.0-4.8) and term low birth weight (OR 5.9; 95%CI 2.0-17.0) for TTHM concentrations of >=61 ppb compared to <20 ppb. Preterm delivery was not related to TTHM exposure in this study.

Waller et al (Waller et al. 1998) used measurements of total and individual trihalomethanes combined with reported tap water consumption to estimate exposure to THMs of 5,144 pregnant women. Women who drank >=5 glasses of tap water containing >=75ug TTHM per day had an increased OR of 1.8 (95%CI 1.1-3.0) for spontaneous abortion compared to women who drank < 5 glasses containing <75ug TTHM. Of the individual trihalomethanes, only bromodichloromethane exposure showed an association with risk of spontaneous abortion.

A recent study in Norway (Jaakkola and P 2001) reported no increases in risk of low birth weight, small for gestational age, and pre-term delivery for children born in municipalities with exposure to water chlorination (high colour and chlorination) compared to municipalities with low exposure to chlorination (low colour, no chlorination). The study finds a small decrease in the risk of pre-term delivery in exposed areas (OR 0.91, 0.84-0.99).

Other methods of drinking water disinfection

Three studies (Kallen and Robert 2000; Kanitz et al. 1996; Tuthill et al. 1982) investigate the effects on pregnancy outcomes of alternative methods of water disinfection where instead of chlorine, chlorine dioxide or sodium hypochlorite are used for disinfection. By-products of these treatments are

chlorites and chlorates (Kanitz et al. 1996; Tuthill et al. 1982). Tuthill et al (Tuthill et al. 1982) compare two communities, one which used chlorination and the other which used high levels of chlorine dioxide for disinfection of drinking water. The study reports higher rates of prematurity in the chlorine dioxide community. Rates of birth defects and fetal and neonatal mortality did not differ between communities. Kanitz et al (Kanitz et al. 1996) find no increases in risk of low birth weight and prematurity in relation to water disinfection by chlorine dioxide or sodium hypochlorite compared to no water disinfection in an ecological Italian study. Kallen et al (Kallen and Robert 2000) compare areas with chlorine dioxide disinfection and areas with sodium hypochlorite disinfection with areas where no drinking water disinfection is used and examine a large range of pregnancy outcomes. Significant increases are found in prematurity and low birth weight in sodium hypochlorite areas compared to no disinfection areas. The study finds no effects for other outcomes, including a range of congenital anomaly subgroups, and either of the two water disinfection methods.

A brief summary of all studies discussed in this section, by outcome of interest, is shown in Table 10, adapted and updated from Mills et al (Mills et al. 1998).

7.2.3 Inorganic drinking water contamination

Inorganic contaminants in drinking water studied in relation to congenital malformation risk include heavy metals, other elements, nitrates, nitrites, fluoride, and water hardness. This section is divided into studies on fluoride levels, water hardness, mixtures of inorganic substances and nitrate levels in drinking water.

Water Hardness

Large differences in the prevalence of neural tube defects in the British Isles gave rise in the 1970s to theories that the hardness of local water supply could be responsible for this difference. Water hardness is a measurement of total calcium and magnesium levels of the water. This theory was tested in several studies (Table 9). Generally, associations between rates of neural tube defects and water hardness reported in ecological studies have not been substantiated by case-control studies.

Early ecological studies correlated malformation rates in areas with average water hardness levels and reported negative relationships of higher rates of anencephaly (Fedrick 1970), perinatal mortality from anencephaly and central nervous system defects (Lowe et al. 1971) in areas with softer water supplies. Morton et al (Morton et al. 1976) used the same South Wales areas studied by Lowe and analysed tap water in 20 randomly selected houses in each of these areas. This study finds aluminium positively

related to rates of central nervous system defects and calcium, barium and copper negatively. There was little adjustment for possible confounding factors such as socio-economic status in these studies.

Case-control studies in Glasgow and Cardiff followed up these results by analysing tap water in houses of mothers of cases with anencephaly (Wilson et al. 1973) and neural tube defects (St Leger et al. 1980) and controls. Levels of a range of trace elements including water hardness, lead, copper and iron were found not to differ between cases and controls in these studies. The Cardiff study (St Leger et al. 1980) found a lower level of zinc in tap water of cases compared to controls.

In Canada an ecological study in 36 cities found a negative relationship between mortality rates from anencephalus and levels of magnesium in the water supply. This relationship persisted after adjustment for the mean income level of each city. Total water hardness and calcium levels showed no relationship. A further case-control study (Elwood and Coldman 1981) found no association between levels of 14 elements, including calcium and magnesium, in the water supply of the mother's area of residence and risk of death from anencephaly. Water hardness was not related to risk of congenital malformations, stillbirths or neonatal deaths in Aschengrau's case-control study (Aschengrau et al. 1993).

Range of inorganic chemicals

Zierler et al (Zierler et al. 1988) studied congenital heart defects in relation to concentrations of a range of chemicals (arsenic, barium, cadmium, chromium, lead, mercury, selenium, silver, fluoride, nitrate and sodium) in drinking water. Arsenic was the only chemical related to an increase in heart defects: concentrations of arsenic above the detection limit were related with a 3-fold increase in the risk of coarctation of the aorta. Detectable selenium levels were related to a decrease in risk of coarctation of the aorta. There was no association between the risk of the total group of congenital heart defects or 4 subgroups of heart defects and the other chemicals studied a range of inorganic elements in drinking water and congenital malformations, stillbirths, and neonatal deaths.

Exposure to selenium was studied in northern Italy after tap water became accidentally contaminated with high levels of selenium over a number of years (Vinceti et al. 2000). The study examined body weight and length of newborns and stillborns to women exposed to high levels of selenium but found no evidence for an increase in these outcomes. Rates of spontaneous abortions were increased but not statistically significant (RR 1.73, 95%CI 0.62-4.80). Rates of congenital malformations in the exposed region were similar to those expected, but numbers were very small.

Aschengrau 1993 et al (Aschengrau et al. 1993) studied a range of trace elements (arsenic, barium, cadmium, chromium, lead, mercury, selenium, silver, fluoride, sodium, potassium, iron, manganese, copper, sulphate, chloride, silica, ammonia, nitrate, nitrite, hardness, alkalinity and pH) in relation to risk of congenital malformations, stillbirths, and neonatal deaths. Statistically significant positive relationships (increasing risks with increasing levels) were found between the risk of major malformations and silver, stillbirths and lead, cardiac defects and lead, central nervous system defects and potassium, and ear face and neck anomalies and silver. A decreased risk of major malformations was found with increased fluoride levels.

In a similar study design Aschengrau (Aschengrau et al. 1989) examines the risk of spontaneous abortion in relation to trace elements (same range as above). This study reports an increase in the frequency of spontaneous abortion related to detectable levels of mercury, high levels of arsenic, potassium, and silica, moderately hard water, and surface water. Decreases in spontaneous abortion risk are reported for high levels of alkalinity and sulphate and any detectable level of nitrate.

A study in north Cornwall examined outcomes of pregnancy after an incident where aluminium sulphate was added to the local water supply accidentally (Golding et al. 1991). 92 pregnancies in the affected area during the contamination incident were compared to pregnancies in the area before the incidents and pregnancies in an unexposed area. The study reports no excess of perinatal deaths, low birth weight, preterm birth, or congenital malformation in the affected area. There was however an increased rate of talipes among the exposed pregnancies. The numbers of cases with adverse pregnancy outcomes were very small which makes it difficult to draw strong conclusions from this study. Reproductive effects of aluminium are studied in only 2 other studies (Morton et al. 1976; St Leger et al. 1980) and of these only Morton reports a positive association between Aluminium levels in drinking water and risk of central nervous system defects.

Nitrates

In Australia, reports of a high incidence of perinatal mortality due to congenital malformations in one district led investigators to study the local water supply of that area. Nitrates were found to be high in the drinking water in this area, especially in groundwater sources. A case-control study (Dorsch et al. 1984) compared drinking water source and nitrate levels of the source for 258 cases of congenital malformation and their matched controls. The study reported an increased risk of congenital malformations for those consuming groundwater and for those consuming water with high levels of nitrates. The nitrate association showed a dose-response effect with an OR of 2.6 for medium levels (5-15 mg/l) and an OR of 4.0 for high levels (>15 mg/l) compared to nitrate levels of <5 mg/l. Risks

for central nervous system and musculo-skeletal defects especially were raised for mothers consuming water from groundwater sources.

A Canadian case-control study (Arbuckle et al. 1988) reported a non-statistically significant increase in risk of central nervous system defects (OR 2.30, 95%CI 0.73-7.29) related to high nitrate levels (26 ppm vs 0.1 ppm) in drinking water, but only for private well water sources. Municipal well water sources showed a non statistically significant decrease in risk of central nervous system defects with increased nitrate levels. Possible reasons for the different results for different water sources are not discussed by the authors of this study. The following potential confounding factors were taken into account: total daily water consumption, family income, parents' education level, father's place of birth, mother's place of birth, parents' ethnicity, and chloride levels in drinking water.

The study described above by Aschengrau (Aschengrau et al. 1989) finds a decrease in the risk of spontaneous abortion associated with detectable levels of nitrate (OR 0.5, 95%CI 0.2-0.9).

A Californian population-based case-control study of neural tube defects (Croen et al. 2001) found that exposure to nitrate in groundwater at concentrations above the 45 mg/litre maximum contaminant level was associated with increased risk for anencephaly (Odds ratio 4.0; confidence interval 1.0-15.4). Risk for anencephaly increased for mothers with the highest nitrate exposure 36-67 mg/litre in groundwater compared with nitrate exposure less than 5 mg/litre (Odds ratio 6.9; confidence interval 1.9- 24.9). This increased risk remained after adjusting for identified anencephaly risk factors. No increased risk for anencephaly was reported in mothers with exposure to mixed water sources containing the same levels of nitrate which the authors suggest implies that something other than nitrate exposure is contributing to the increased risk for anencephaly. No increased risk associated with nitrate in groundwater was reported for spina bifida. Nitrate exposure through diet was also not associated with increased risk for neural tube defects.

Fluoride

Early reports in the 50s suggested a link between that fluoridation of water supplies might result in an increase in the frequency of Down Syndrome (Erickson 1980). A subsequent comparison of overall Down Syndrome rates in fluoridated and non-fluoridated areas in Massachusetts found no evidence for a difference (Needleman et al. 1974). Analysis of data from 51 American cities also found no difference in maternal age specific Down Syndrome rates between fluoridated and non-fluoridated areas (Erickson 1980). There are no reports of a link between fluoridation and any other type of birth defect, apart from Aschengrau (Aschengrau et al. 1993) who report a decrease in the risk of major

malformations with detectable water fluoride levels (OR 0.4, 95%CI 0.2-1.0). Evidence for any relationship between water fluoridation and the prevalence of birth defects is limited.

7.3 Hazardous and municipal waste sites

This section includes studies adverse pregnancy outcome in relation to residence near of hazardous waste sites. Routes of exposure generally include a range of possible routes, often no specific exposure routes are indicated. A few studies have investigated pregnancy outcomes related to incidents of drinking water pollution from waste disposal sites. These have been discussed in the 'drinking water' section – 7.2.1.

The majority of studies evaluating possible health effects in human populations living near landfill sites investigate communities near one specific waste disposal site ('single-site' studies), frequently in response to concerns from the public about reported contamination from the site, or reported clusters of disease. A small number of studies have addressed the risks of living near waste sites independent of whether the sites caused concern, by a-priori specifying a number of sites for study. These will be referred to as 'multi-site' studies. Single and multi-site studies are discussed separately. Studies included in this section are summarised in Table 11. A general problem in many landfill studies is the lack of exposure data.

7.3.1 Single site studies

The investigation of single landfill sites has been important as a response to community concerns; many of the single-site studies discussed below are prompted by public concerns. They may be prone to recall and reporting biases. Single-site studies have sometimes examined a vast range of possible health outcomes, often without a specific disease hypothesis being proposed a-priori. Such 'fishing expeditions' are thought to be of less scientific value than studies that start with a clear hypothesis (Upton 1989). Including these 'fishing expeditions' in evaluating the consistency of findings across multiple studies is important nevertheless when assessing evidence for health risks. A less avoidable problem in single-site studies is that the size of populations living near waste sites is generally small and, especially when the outcome is a rare condition such as congenital anomaly, this can seriously limit the statistical power of an investigation to detect anything but high relative risks.

Large quantities of toxic materials (residues from pesticide production) were dumped at the landfill of Love Canal, New York State, during the 1930s and 40s, followed by the building of houses and a school on and around the landfill in the 1950s. By 1977 the site was leaking and chemicals were

detected in neighbourhood creeks, sewers, soil, and indoor air of houses. This led to one of the most widely known and publicised incidents of environmental pollution from landfill. Exposure of Love Canal residents, although not well-understood, may have occurred via inhalation of volatile chemicals in home air or via direct contact with soil or surface water (Paigen et al. 1987). The drinking water supply was not contaminated. Chemicals detected at Love Canal were primarily organic solvents, chlorinated hydrocarbons and acids, including benzene, vinyl chloride, PCBs, dioxin, toluene, trichloroethylene, and tetrachloroethylene. Two studies report on the risk of adverse pregnancy outcomes in Love Canal residents.

Vianna and Polan (Vianna and Polan 1984) found an excess of low birth weight (less than 2500g) during the period of active dumping (1940-53) in areas of Love Canal where exposure had been highest. Rates of low birth weight between 1960-78 after the site had been closed were comparable to upstate New York as a whole. It is not clear whether exposure from Love Canal was highest during the active dumping period, or during the period after the site was closed, when the building of houses near the site increased and the landfill was leaking.

A study by Goldman et al (Goldman et al. 1985) reported a three-fold risk of low birth weight for children exposed during gestational life to the Love Canal area compared to that for control children born elsewhere, in a period covering 1965-1978. Data were analysed separately for homeowners and renters so that groups of similar socio-economic status were compared, and after allowing for confounding factors the risk of low birth weight was significantly increased for homeowners only. This finding is difficult to interpret. In the same study an increased risk of birth defects was observed for both homeowners and renters. Information on birth defects relied mainly on reports from parents. Some recall bias can therefore be suspected, in particular for defects of lesser severity, but this is unlikely to account for the entire association found for major birth defects.

Berry and Bove (Berry and Bove 1997) studied birth weight at the Lipari Landfill in New Jersey, a site for municipal and industrial waste. Leachate from the site migrated into nearby streams and a lake adjacent to a residential area. Inhalation of volatile chemicals emitted from the landfill and contaminated waters was thought to be the most important exposure pathway. The site closed in 1971 after complaints of residents, but the heaviest pollution was estimated to have occurred during the late 1960s to the mid-1970s. The study found a convincing increase in proportion of low birthweight babies (<2500 g) and a lower average birth weight in the population living closest (within a radius of 1 km) to the landfill in the time period when potential for exposure was thought to be greatest (1971-1975), compared to a control population. Although information on some confounding variables such as smoking, alcohol consumption, and socio-economic status was not available, mothers in the exposed area were more highly educated and therefore appeared to be of higher socio-economic

status. One would expect a higher birth weight in areas of higher socio-economic status, so as the authors point out, confounding by socio-economic status does not explain the lower birth weight found. In time periods before and after heavy dumping and off-site pollution birth weights were higher in the area closer to the site than in the control area which supports the hypothesis that pollution from the waste site may have been related to low birth weight in the community close to the site.

A range of reproductive effects including low birth weight was studied around the large BKK hazardous waste disposal site in Los Angeles County, California (Kharrazi et al. 1997), after previous investigations of vital records found that trends in low birth weight and neonatal deaths corresponded closely with times and quantities of dumping at the landfill. Results for the whole study period showed no increase in adverse reproductive effects, but during the period of heaviest dumping birth weights were significantly lower in exposed areas than control areas, using odour complaint frequency zones to classify exposure. All results were adjusted for education, income, and race. The decrease in mean birth weight found in the high odour complaint zone was small (59 grams) compared to that found in the Lipari Landfill study (192 grams) and was less than a third of birth weight reductions caused by smoking during pregnancy (Berry and Bove 1997). Odour complaint frequency zones corresponded better with vinyl chloride monitoring data and meteorology around the site than did census tract areas or distance based (<0.7 miles) exposure zones, and this was therefore thought to be the most accurate method for classifying exposure. Using census tract or distance based exposure zones smaller decreases in mean birth weight were found (35.2 grams, p=0.02 and 20.4 grams, p=0.25 respectively).

Miron Quarry, a large (the third largest in North-America) municipal solid waste site in Montreal, Quebec has prompted studies on both reproductive outcomes (low birth weight and pre-term births) (Goldberg et al. 1995b) and cancers (Goldberg et al. 1995a). Gas from the site was the main environmental and health concern and a range of volatile organic compounds (VOCs), including a number of recognised or suspected human carcinogens, had been detected in the gas. An excess of 20% in low birth weight was found among babies of mothers who were living in the high exposure area adjacent to the landfill at the time of delivery, taking account of confounding factors such as education and age of the mother. No excess was found in the low exposure zone compared to a control area. Exposure zones were based on proximity to the site and accounted for the direction of dominant winds. Control areas were selected to be similar to exposure areas on a number of sociodemographic variables so as to limit the potential for confounding. The cancer study used the same exposure zones and control areas and found an increase in the incidence of cancers of the stomach, liver, prostate, and lung for men, and stomach and cervix/uterus for women. Incidences of cancers of other organ sites were not increased in the exposed areas.

At the Drake Superfund Site, an industrial chemical dump, in Pennsylvania, widespread on and off-site contamination of groundwater, soil and surface water with organic (benzene, chlorinated benzene, phthalates) and inorganic (arsenic, mercury) compounds, prompted a cancer mortality and birth defects study (Budnick et al. 1984) and a community health survey (Logue and Fox 1986). Air monitoring near the site identified a small number of organic compounds but the main exposure route was thought to be direct contact with surface waters and soil in recreational areas near the site. Budnick et al (Budnick et al. 1984) found an increase in mortality from bladder cancer (probably explained by occupational exposures), but no excess in risk of birth defects was found in 4 counties surrounding the waste site compared to regional and national rates.

Concerns about health effects from a landfill in Wales prompted a geographical study of rates of congenital malformations, low birth weight, spontaneous abortion and other health outcomes near the site (Fielder et al. 2000). Findings show an increase in malformation rates in 5 wards near the site compared to 22 other wards in Wales. However, this increase was found both before and after operations at the site started. Reports of a cluster of gastroschisis in the area near the landfill were confirmed by this study (RR 4.8, 95% CI 1.6-11.1). Rates of other adverse pregnancy outcomes (low birth weight, spontaneous abortion) were not increased.

A further study near another landfill in Wales (Fielder et al. 2001) compared routinely collected population-based health data from 3 potentially exposed electoral wards to 18 unexposed wards matched for socio-economic deprivation. Before the landfill site opened, the rate of births reported to the Office for National Statistics (ONS) with a congenital anomaly in the exposed wards was not significantly different from that in the unexposed wards (Relative risk=1.13; 95% confidence interval 0.78-1.62). When the site opened the rate of births with a congenital anomaly in the exposed wards was 1.9 times that of the unexposed wards. When minor anomalies were excluded from analysis, the relative risk decreased from 1.9 to 1.5. Further analysis comparing the exposed wards to 8 other control wards showed no statistical difference between the exposed and unexposed control wards. The authors advise caution interpreting the data, as ONS notification is voluntary and hence the data are not always accurate or complete.

A study of one of the largest hazardous waste sites in North America located in Sydney Nova Scotia (Dodds and Seviour 2001) compared the rates of adverse birth outcomes among residents in Sydney with the county and province. After adjusting for maternal age and parity a 25% increase in the rate ratio for all major anomalies was found among residents of Sydney compared to Nova Scotia residents (RR=1.25, 95% confidence intervals 1.04-1.51). The rate ratio for neural tube defects among Sydney residents was significantly increased relative to Nova Scotia (RR=1.83, 95% confidence intervals 1.08-3.09). Most other congenital anomaly subgroups (Cardiovascular, Genito-

urinary, ENT, and chromosomal), also had raised rates, but these were not statistically significant. Analysis of adverse birth outcomes in residents from the neighbouring county (Cape Breton County) with similar occupational and lifestyle characteristics, showed consistently higher rates of congenital anomalies in the Sydney population with the exception of musculoskeletal anomalies. There was no evidence of higher rates of low birthweight or intrauterine growth restriction in Sydney. A higher prematurity rate was observed in both Sydney and the rest of its county.

7.3.2 Multi-site studies

The problems with single-site studies prompted by community pressures have increasingly been recognised and recently several large studies have investigated adverse health effects near sets of hundreds of sites selected independently of community concerns or reported disease clusters. These studies have the additional advantage of large numbers of subjects which would give them enough statistical power to detect small increases in risk of rare disease such as birth defects. They also largely avoid the problems of publishing bias associated with single site studies, where only positive findings achieve publication. On the other hand, their large scale makes exposure assessment even more complicated than in single-site studies, as adequate information must be collected for each of many sites. A number of the studies discussed below have used the U.S. National Priority Listing (NPL) of hazardous waste sites developed by the U.S. Environmental Protection Agency for the selection of their sites. The NPL ranks all hazardous waste sites in the U.S. deemed to be of considerable threat to the environment or public health. NPL sites have been relatively well assessed with respect to the potential or actual migration of hazardous chemical substances from the sites through ground water, surface water, and air (National Research Council 1991). Most multi-site studies however, were not able to distinguish between different types and pathways of contamination and, in absence of better exposure data, based their assessment of exposure on distance of residence from the sites or residence in an area with a site. Exposure misclassification, if non-differential, may be expected to dilute true effects in these investigations.

Shaw et al (Shaw and Malcoe 1992) carried out a study on the risk of congenital malformations and low birth weight in areas with landfills, chemical dump sites, industrial sites, and hazardous treatment and storage facilities in the San Francisco Bay area, California. Census tracts were classified as *a)* no hazardous site in area, *b)* hazardous site in area but no evidence of human exposure, and *c)* hazardous site and plume in the area with evidence of potential human exposure. A small increase (1.5-fold) in risk was found for heart and circulatory malformations in the areas with potential human exposure. This increased risk was present across chemical classes and exposure routes. Risk of other malformations or low birth weight was not significantly increased. Results were adjusted for some potential risk factors (maternal age, race, sex of child, birth order) but not for socio-economic status.

Sosniak et al (Sosniak et al. 1994) investigated the risk of adverse pregnancy outcomes for people living within 1 mile of a total of 1281 NPL sites over the entire U.S. The risk for low birth weight and other pregnancy outcomes (infant and fetal death, prematurity, and congenital anomaly) was not associated with living near a site after taking into account a large number of potential confounding factors, including socio-economic variables, collected through questionnaires. However, only around 63% of women originally sampled for the study returned the questionnaire and were included in the study. Also, it is unclear how congenital anomalies were defined and no subgroups of malformations were studied.

Geschwind et al (Geschwind et al. 1992) investigated the risk of congenital malformations in the vicinity of 590 hazardous waste sites in New York State. A 12% increase in congenital malformations was found for people living within 1 mile of a site. For malformations of the nervous system, musculo-skeletal system, and integument (skin, hair, and nails), higher risks were found. Some associations between specific malformation types and types of waste were evaluated, and found to be significant. A dose-response relationship (higher risks with higher exposure) was reported between estimated hazard potential of the site and risk of malformation, adding support to a possible causal relationship. However, a follow-up study of Geschwind's findings found no relation between two selected types of malformations (central nervous system and musculo-skeletal) and living near a hazardous waste disposal site (Marshall et al. 1997). The study did report an increased risk of central nervous system defects for those living near solvent or metal emitting industrial facilities. Subjects for the first two years of this study were also included in Geschwind's study, and two more years were studied. Marshall et al (Marshall et al. 1997) attempted to improve the exposure measurement in the first study by assessing the probability of specific contaminant-pathway combinations in 25 sectors of the 1 mile exposure zones (Marshall et al. 1997). The risk of particular pathways or contaminant groups could not be investigated, however, because of limited numbers of cases in each subgroup.

A study by Croen et al (Croen et al. 1997) based exposure measurement on both residence in a census tract containing a waste site and on distance of residence from a site. Three specific types of birth defects: neural tube defects, heart defects, and oral clefts were studied. Little or no increase in the risk was found using either measure of exposure. Risk of neural tube (2-fold) and heart defects (4-fold) were increased for maternal residence within 1/4 mile of a site although numbers of cases and controls were too small (between 2 and 8) for these risk estimates to reach statistical significance. Births were ascertained from non-military base hospitals only and the authors point out that the increased risk of NTD may have resulted from lower ascertainment of exposed controls than exposed cases where exposure zones included military bases. Military-base residents with NTD-affected pregnancies may have been more likely to deliver in non-military hospitals than military-base residents with unaffected pregnancies.

A European multi-site study reported a 33% increase in risk of all non-chromosomal birth defects combined for residents living within 3 km of 21 hazardous waste landfill sites in 10 European regions (Dolk et al. 1998b). Neural tube defects and specific heart defects showed statistically significant increases in risk. Confounding factors such as maternal age and socio-economic confounding did not readily explain the results. A second part of the study recently reported a similar increase in risk of chromosomal anomalies (OR1.41, 95%CI 1.00-1.99) (Vrijheid et al. 2002). The study included both open and closed sites that ranged from uncontrolled dumps to relatively modern controlled operations. This disparity makes it difficult at this stage to conclude, if indeed the association is causal, whether risks are related to landfill sites in general or whether specific types of sites may be posing the risks.

A study of all landfill sites in England, Scotland and Wales, investigated the risk of congenital malformations, and low and very low birth weight outcomes in populations living within 2 km of a landfill site (Elliott et al. 2001). The study included over 9,000 landfill sites. Eighty percent of the population of Great Britain lived within 2 km of a landfill site identified by the study. Statistically significant increases in risk were reported for the following outcomes around all waste sites combined: all congenital anomalies (OR 1.01, 99%CI 1.003-1.023), neural tube defects (OR 1.05, 99%CI 1.01-1.10), hypospadias (OR 1.07, 1.04-1.10), abdominal wall defects (OR1.08, 1.01-1.15)), low birth weight (OR1.05, 1.05-1.06), and very low birth weight (OR1.04, 10.3-1.05). Findings for sites that were licensed to take special (hazardous) waste were generally similar to non-special sites. When comparing the period pre-site operation (when available) to post-opening (for all sites), some of the excess risks were found in both periods. In this study, only 20% of the country was available as reference population and the comparability of the 'landfill' and 'reference' areas therefore raises questions. Also, if risks were associated with a particular group of 'high-risk' landfill sites such a finding would be lost in the overall comparison of over 9,000 sites in this study.

A case-control study of 36 cases of complex and severe L transposition of the great arteries (l-tga), within the Baltimore Washington Infant Study database reported two spatial clusters of this condition, and identified hazardous waste sites as well as other industrial releases in the areas of these clusters. No statistical methods for identifying clusters were reported, and it was not made clear whether hazardous waste sites were more of a problem in these areas than others. The authors reported that the two identified areas did not have more cardiac anomalies as a whole (Kuehl and Loffredo 2003 2805).

7.4 Other industrial point sources

This section covers literature on sources of environmental pollution not already covered in one of the preceding section on air pollution, drinking water contamination, or hazardous waste landfill sites. These are mainly studies of communities living near point sources of industrial pollution or more generally in polluted areas. Exposures are mostly mixed and in many of the studies specific pollutants have not been identified. The section is divided into smelters, incinerators, other industrial point sources, and areas of industrial contamination. Table 12 summarises the studies.

7.4.1 Smelters

A series of studies investigated pregnancy outcome in communities living near and employees working in a copper smelter in Sweden (Nordenson et al. 1978a; Nordenson et al. 1978b; Nordstrom et al. 1978a; Nordstrom et al. 1978b; Nordstrom et al. 1979a; Nordstrom et al. 1979b). The smelter emitted a number of potentially toxic chemicals, of which arsenic, lead, mercury, cadmium and sulphur dioxide were of most concern. The first in the series (Nordstrom et al. 1978b) examines birth weight and finds birth weight in offspring of employees of the smelter and two communities living close to the smelter to be significantly lower than in two comparison communities. Parity distributions were similar in all communities but it is not clear how well the communities compared on other potential confounding factors such as socio-economic status. Spontaneous abortions were studied using similar methodology (Nordstrom et al. 1978a). The highest frequency of spontaneous abortions was found in the area closest to the smelter and the lowest frequency in the area furthest away. Again, parity was the only potential confounding factor examined. Spontaneous abortions were also found to be increased amongst employees at the smelter if they were employed during pregnancy (Nordstrom et al. 1979a). Birth weight was reported to be lower in employees than in a community control population (Nordstrom et al. 1979a) but this comparison population is poorly described and the use of a community control population seems doubtful. Congenital malformations were compared in 6 areas surrounding the smelter as well as employees of the smelter (Nordstrom et al. 1979b). There was no difference between the 6 areas in the rate of malformations, areas closest to the smelter had similar rates to areas further away. Employees who worked during pregnancy had higher malformation rates than those who did not. Again, no confounding factors were accounted for. Findings of this series of papers are hard to interpret because of poorly described methodology and lack of control for confounding variables.

A more recent study by Wulff et al (Wulff et al. 1996) follows up the findings of the Nordstrom series with a cohort of children born between 1973 and 1990 in the region. Exposure was defined as living

within 20 km of the smelter. All employees of the smelter lived in this exposed area and 20% of children living in the exposed area had a parent working at the smelter. Slightly more congenital malformations occurred among exposed children compared to unexposed children (OR 1.15, 95%CI 0.95-1.39). The study did not take account of potential confounding variables. A second study (Wulff et al. 1995) reported no difference in birthweight or perinatal death (1961-1991) between children born to smelter employees or residence near the smelter and those in a reference group.

Saric (Saric 1984) compares a community living near a lead smelter in Croatia with a control community. The smelter had given rise to large concentrations of lead, zinc and cadmium in the air, soil and household dust in nearby areas. The spontaneous abortion rate in the smelter community was nearly twice that in the control community. Twinning rates were similar in the two communities. The report gives little information about the comparability of the two communities.

The study of the Port-Pieri smelter community (McMichael et al. 1986) found an increased risk of pre-term birth with increased blood lead levels but did not find an association with congenital malformations, spontaneous abortion, or stillbirth. This study is discussed in more detail in the section on Lead (section 1.1).

Three reports have been published studying pregnancy outcome near a lead smelter in Kosovo. Murphy et al (Murphy et al. 1990) compare rates of spontaneous abortion between women living in the town where this smelter is located and women living in a town without significant lead exposure (see also section 1.1). The mean blood lead level was 0.77 um/L in women living in the exposed town and 0.25 umol/L in women living in the unexposed town. Rates of spontaneous abortion were similar in the two towns (adj OR 1.1, 95%CI 0.9-1.4). Adjustments were made for maternal age, smoking, ethnic group and maternal education. In the same cohort, Factor-Litvak et al (Factor-Litvak et al. 1991) found no difference in mean birth weight and mean length of gestation between the exposed and unexposed town. Also, they found no significant relationships between maternal blood lead levels measured at mid-pregnancy, at delivery, or in the umbilical cord, and either birth weight, length of gestation or preterm delivery. Loiacono et al (Loiacono et al. 1992) used data from this cohort to study the association between cadmium levels in the placenta and low birth weight in the offspring of non-smoking women (see also section 1.3). Although cadmium levels in the smelter community were high (comparable to concentrations reported previously in smoking women), the study found no association between cadmium level and mean birth weight.

Philion et al (Philion et al. 1997) studied rates of intrauterine growth retardation in a Canadian city where a large lead smelter is located. The risk of intrauterine growth retardation (term infant with birth weight < 2500g) for women in the smelter city was decreased, although not statistically

significantly (OR 0.83, 95%CI 0.64-1.08), in comparison with a control city. The two cities had similar demographic characteristics and the authors therefore believed there was little difference in alcohol, tobacco and drug use.

7.4.2 Incinerators

Incineration uses controlled combustion to dispose of a wide range of wastes. Incinerators are potential sources of airborne pollutants. Pollutants of concern for health impacts include a wide range of inorganic compounds (CO, NOx, Sox, HCl); heavy metals, specifically cadmium, lead, mercury, chromium and arsenic; and organic compounds specifically dioxins and furans, polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs) (National Research Council 2000). Incinerators with modern combustion design, practices, and air pollution control equipment generally show much reduced emissions compared to old, uncontrolled incineration facilities. Pregnancy outcomes associated with specific pollutants have been discussed in previous sections, this section discusses evidence for adverse pregnancy outcomes in communities living near waste incinerators. There has been very little epidemiological study of the risk of congenital malformation or any other pregnancy outcome in populations living near incinerators.

A study in Forth Valley, Scotland (Scottish Home and Health Department 1988), investigated a cluster of microphthalmia around a chemical incineration plant. The study compared microphthalmia prevalence rates in six health board areas and found large variation in rates but no obvious increase in the area where the incinerator was located. Firm conclusions about the occurrence of microphthalmia near the incinerator could not be drawn from this study because of uncertainty about the completeness of case ascertainment. The report concluded that if a problem did exist it was a very small one.

In Sweden, concern about a cleft lip and palate cluster near a local refuse incinerator led to a study of cleft lip and palate prevalence in all districts in Sweden where incinerators were located (Jansson and Voog 1989). The study found no evidence for an increase in prevalence of cleft lip and palate in the areas studied since the start of the incinerators.

In Amsterdam, the Netherlands, incineration of chemical waste was linked to a local cluster of orofacial clefts in the 1960s (ten Tusscher et al. 2000). An investigation of this possible link compared deliveries at a clinic located near the incinerator with those at a clinic in another part of the city. The rate of orofacial clefts at the clinic near the incinerator was nearly four-fold the rate at the comparison clinic. A peak in the rate was found to coincide with the active years of the incineration process. The extent to which this was a post-hoc cluster investigation (i.e. the incinerator was implicated as a cause of the cluster because of the temporal and spatial association with the cluster) is unclear, but under

those circumstances simple comparison with another clinic would not yield statistically valid p-values. There is little information on how comparable the two clinics were, nor on whether location of clinic was a good proxy for location of maternal residence.

7.4.3 Other industrial point sources

In West-Germany, concerns about thallium exposures from a cement factory prompted a study into the risk of congenital malformations in residential areas near the factory (Dolgner et al. 1983). The rate of major congenital malformations was higher than expected on the basis of the entire state (0.8 expected, 5 observed, O/E=6.25). However, the malformation rate for the entire state is likely to be an underestimation due to incomplete reporting in a voluntary reporting system.

Kallen et al (Kallen and Thorbert 1985) studied pregnancy outcomes in three parishes near a chemical plant which had caused pollution of water and air in surrounding areas. Pregnancy outcomes (miscarriages, malformation, perinatal deaths) in the three parishes were compared with the entire county. There was no increase in rates of miscarriage or malformations. Perinatal deaths were higher than expected, especially amongst twins.

Axelsson et al (Axelsson and Molin 1988) examined the risk of spontaneous abortion in a community living near petrochemical industries in Sweden. The industries produced ethylene, polyethylene, chlorine, vinyl chloride, polyvinyl chloride, ethylene oxide, amines, glycols and phthalates. The main route of exposure was thought to be through air. The community living near the industries was divided into those living nearest (area A) and those living further (area B). Both these areas were compared with a control community. The odds ratio for spontaneous abortion was 1.21 (95%CI 0.76-19.91) in area A compared to the control community and 0.79 (0.37-1.69) in area B. A high risk of spontaneous abortion (OR 6.6, 2.3-19.2) was found in a small sample of women working in the industries. Overall, there was little evidence that living near the industries increased risk of spontaneous abortion.

Bell et al (Bell et al. 1991) examined the association between birth weight and exposure to methylene chloride in residents near a Kodak plant in New York State. Methylene chloride is an organic solvent widely used in industry and in household products (Bell 1991). The study classified census tracts according to a dispersion model of methylene chloride into high, moderate, low and no exposure. After adjustment for confounding variables, birth weight was slightly lower (18.7 g, $p>0.10$) in the high exposure tracts compared to the no exposure tracts. Nevertheless, there was no evidence of a higher risk of low birth weight (<2500g) in high exposure areas.

In Hungary, Czeizel et al (Czeizel et al. 1999) studied congenital malformation rates in a population living within 25 km from a acrylonitrile factory. The total malformation rate was lower in the region where the plant was located than the Hungarian baseline prevalence. The rate of skeletal system anomalies was significantly higher than the Hungarian baseline, whereas 14 other malformation groups had lower rates. Three anomalies: pectus excavatum, undescended testis and clubfoot showed significant time-space clustering in the study region but there is no indications that such clusters were related to exposure from the acrylonitrile factory.

A study in the UK compared risk of low birth weight, stillbirth, and congenital abnormality in areas near steel and petrochemical industry with areas further away (Bhopal et al. 1999). The study found no evidence for increased risks of any of the outcomes in areas nearest the industries. The comparison populations were similar in socio-economic characteristics.

A single maternity hospital case-control study of adverse reproductive outcomes in an area adjacent to a petrochemical plant in southern Brazil (Oliveira et al. 2002) found little difference between the observed and expected rates of specific malformations comparing residents within 10 km of the plant (OR=0.37, 95%CI 0.07-1.72) and within the prevailing wind direction path to those with least residential exposure. Confidence intervals were wide. Visual inspection did not reveal any clustering within the 10 km exposed area, but it was not stated whether varying population density might have obscured clustering on visual inspection.

A retrospective cohort study in Cumbria, England reported no increased risk of stillbirths, lethal congenital anomaly or neonatal deaths associated with proximity to hazardous industrial sites between 1950 and 1993. Landfill sites or incinerators were excluded from the study's definition of hazardous sites. A proxy measure of exposure was computed using distance of maternal residence from sites at time of birth, with the assumption that each site represented an equal hazard. Relative risks were adjusted for social class, year of birth, multiple birth status and birth order. An increased risk of congenital heart defects was found in the time period 1983-1993 only (OR=1.06, 95%CI 1.02-1.10), which may have been a chance finding due to the large number of outcome groups and time periods analysed (Dummer et al. 2003).

7.4.4 Residence in contaminated areas

The Brazilian town of Cubatao is reported to be one of the most polluted in the world. A study (Monteleone Neto and Castilla 1994) compared the rate of congenital malformations in Cubatao with reference rates from a congenital anomaly registry network covering 102 hospitals in South America

(ECLAMC). The Cubatao survey used similar methods of case ascertainment and case definition as ECLAMC. A higher than expected prevalence rate was found for polydactyly only. Lower than expected rates were found for congenital hip dislocation, etiologic syndromes other than Down Syndrome, multiple congenital anomalies, and other syndromes (sequences, associations). Lower rates in both hip dislocation and multiple congenital anomalies were attributed to under ascertainment of minor defects.

A Norwegian study compared mean birth weight of births an industrial area of Norway with that of births in less polluted urban and rural areas (Hansteen et al. 1998). Birth weights were lowest in the industrial areas (3,517g) and highest in rural areas (3,618g, $p<0.05$). The study controlled for a large number of confounding factors including social class.

In Argentina, an ecological study compared rates of congenital malformations in 21 counties according to indicators of industrial activity (Castilla et al. 2000). Counties were grouped into 80 sectors of industrial activity. Significant associations ($p<0.01$) were found between textile industry and anencephaly, and between manufacture of engines and microcephaly. The study controlled for socio-economic level of the county.

8. Endocrine disrupting chemicals and hypospadias

Recent interest in relation to environmental pollution has focused on the possibility that male reproductive abnormalities, hypospadias and cryptorchidism (undescended testes), have been increasing in prevalence in the decades preceding the 1980s, along with a range of adult male reproductive system health outcomes (Sharpe and Skakkebaek 1993; Toppari et al. 1996) Although the evidence for the increasing trends is disputed, the possibility that all of these apparent increases are related to increasing exposures to endocrine disrupting chemicals in the environment is an active and important area of present research. Endocrine disrupting chemicals include many pesticides, dioxins and PCBs, phthalates and heavy metals such as cadmium, mercury and lead (van Tongeren et al. 2002), and are present in mixed exposure sources such as waste releases and industrial releases. We have not in this review sought to classify chemicals by mechanism of action, and relevant literature is reviewed in this Chapter under each chemical category. It is worth commenting however on the specific case of hypospadias, which has been little studied directly in relation to environmental pollution or any of the specific chemical categories.

There is some evidence that the prevalence of hypospadias increased from the 1960s to the 1980s, but not thereafter, in Europe and USA (Paulozzi 1999). However, it has become clear that interpretation of surveillance over time of hypospadias prevalence is problematic, since the more minor distal forms may be variably diagnosed, treated and reported (Dolk et al. 2004). The strength of the evidence therefore lies partly in the concomitant increase of several male reproductive abnormalities, partly in the biological plausibility of an endocrine aetiology for hypospadias (Baskin et al. 2001).

A cohort study found vegetarian diet to be a risk factor for hypospadias, with the implication that high soy (a phyto-estrogen) intake or pesticide intake may be causal factors (North et al. 2000). A study of residents near hazardous waste landfill sites found a raised risk of hypospadias among other congenital anomalies, but no specific chemic exposures were characterised (Dolk et al. 1998b). Studies of parental work in agriculture or gardening have found either no association with hypospadias (Garcia et al. 1999; Schwartz et al. 1986; Weidner et al. 1998) or a positive relationship (Kristensen et al. 1997). More general studies of occupation and birth defects have identified several occupations with increased risk of hypospadias, such as paternal work as vehicle mechanic (Irgens et al. 2000), paternal work in forestry and logging, carpentry and woodwork, as service station attendants (Olshan et al. 1991) but these associations were detected among many combinations of occupations and different birth defects, and may be chance associations which have yet to be replicated. Another occupational study of paternal exposure was conducted among fathers working at a sawmill where chlorophenate wood preservatives, contaminated by dioxin, had been used (Dimich-Ward et al. 1996). The study reported increased risks of genital anomalies, as well as eye

malformations (particularly cataract), anencephaly and spina bifida. A study of occupational exposure to endocrine disrupting chemicals, as judged from job title of hypospadias cases reported to a national database for England and Wales, revealed no overall associations with seven classes of endocrine disrupting chemicals, but an association with occupation as a hairdresser in the later part of the study period only (Vrijheid et al. 2003). This may be a chance finding, but given that hairdressers are exposed to a range of chemicals and constitute relatively large numbers of employed women, needs further study.

Table 1: LEAD and congenital malformations

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Findings
Environmental Exposures						
(Needleman et al. 1984)	births in Boston, US	cohort	4,354 consecutive births	cord blood lead levels	total malformations, major malformations, minor malformations, LBW, preterm birth	increase in risk of total malformations and minor malformations with increasing lead levels
(McMichael et al. 1986)	pregnancies in Port-Pieri smelter community, Australia	cohort	831 pregnant women	maternal blood lead levels measured at 14-20 weeks gestation, 32 weeks, and at delivery. Cord blood lead levels.	spontaneous abortion, pre-term delivery, late fetal death, LBW, congenital malformation	increased risk of pre-term birth with increased lead levels. No association for congenital malformation, spontaneous abortion, or stillbirth
(Ernhart et al. 1986)	Cleveland, Ohio, US	cohort	185 maternal blood lead, 162 cord blood lead	maternal blood lead, cord blood lead	gestational age, LBW, , congenital malformation	no association
(Bound et al. 1997)	Lancashire, UK	case-control	364 cases with neural tube defects; controls: 531 cardio vascular defects, 156 alimentary tract defects, 205 urinary tract defects	percentage of houses in electoral ward with more than 10ug/l lead in drinking water	anencephaly, spina bifida, all neural tube defects	increased risk of anencephaly, spina bifida and all NTDs before adjustment for deprivation. Statistically significant increase in anencephaly risk (p=0.05) after adjustment
(Macdonell et al. 2000)	Glasgow UK	ecological	residents in Glasgow postcode districts supplied by one reservoir	proportion of samples within postcode districts with more than 10ug/l lead in drinking water	prevalence of neural tube defects	no association, but no adjustment for confounding factors
(Aschengrau et al. 1993)	Massachusetts	case-control	1039 congenital anomaly cases, 77 stillbirths, 55 neonatal deaths, 1177 controls	quality of public drinking water in area of residence: levels of heavy metals, inorganic substances, chlorination vs. no chlorination	congenital malformations, stillbirths, neonatal death	Also increased ORs for lead and all congenital malformations (2.1 0.6-7.2) , lead and cardiac defects (2.2, 0.9-5.7); potassium and NTDs; water chlorination and congenital malformations and stillbirths
(Vinceti et al. 2001)	Emilia Romagna region, Italy	population-based	11,568 births in study area and 97,468 births in control area	Blood lead levels identified the study area as heavily polluted with lead	Major congenital anomalies	Increased risk of cardiovascular defects in the exposed area (OR 2.59, 1.68-3.82) which decreased over time mirroring the decrease in exposure. Also increased ORs reported for oral clefts (2.28, 1.16-4.07) and musculoskeletal anomalies (1.60, 1.03-2.38)

Occupational Exposures

(Kristensen et al. 1993)	workers in printing industry in Norway	cohort	6,251 children born to fathers working in printing industry	paternal exposure: 4 exposure groups on the basis of job codes at time of conception: lead only, solvents only, lead and solvents, other (unexposed)	LBW, SGA, preterm birth, early preterm birth, late abortion, stillbirth, early neonatal death, perinatal death, birth defects	increased risk of preterm birth and perinatal deaths related to lead or lead + solvents exposure. Increased risk of cleft lip/palate (SMR 1.6, 0.97-2.5) among all fathers employed in printing industry compared to all births in Oslo; No increase in risk of other congenital anomalies or all congenital anomalies.
(Sallmen et al. 1992)	Finland	nested case-control	children born to fathers biologically monitored for inorganic lead: 27 malformed cases, 57 non-malformed controls.	paternal blood lead levels around conception for sample (27 cases, 57 controls).	all congenital malformations	increased risk for blood levels >=1 umol/l compared to <1 umol/l (OR 2.4 CI: 0.9-6.5). OR varies form 1.9 to 3.2 when adjusted for confounding factors one at the time.
(Irgens et al. 1998)	Norway	cohort	births in Norway between 1970 and 1993	maternal and paternal occupational lead exposure (from job exposure matrix)	Low birth weight, preterm birth, neural tube defects, Down syndrome, all major birth defects, perinatal mortality and male births.	increased risks of low birth weight and neural tube defects for maternal exposure; no increase in risk related to paternal exposure.
(Brender et al. 2002)	Texas-Mexico border	case-control	184 cases, 225 controls	maternal and paternal interview	Neural tube defects	Maternal exposure OR = 1.1 (0.2-5.8) Paternal exposure OR = 1.3 (0.8-2.3)

Table 2: INORGANIC MERCURY and congenital malformation

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Findings
(De Rosis et al. 1985)	workers in lamp factory	cohort	153 women in lamp factory, 293 women in comparison factory	work in lamp factory with exposure to mercury vapour	spontaneous abortion, low birth weight, congenital malformation, perinatal deaths, postneonatal deaths	higher malformation rate in exposed women, however, majority of cases were hip dislocation.
(Elghany et al. 1997)	workers in factory using liquid mercury	cohort	46 exposed women (72 pregnancies), 19 unexposed women (32 pregnancies)	work in production area where liquid mercury was used	spontaneous abortion (early/late), perinatal death, congenital anomaly	no difference in most outcomes. Higher rate of malformation in exposed vs unexposed group (4.2% vs 0%)
(Sikorski et al. 1987)	dentists and dental assistants in Poland	cohort	81 exposed women (117 pregnancies), 34 unexposed women (63 pregnancies)	hair mercury levels	spontaneous abortion, stillbirths, congenital malformation	higher rate of total adverse pregnancy outcomes in exposed women (24% vs. 11%). No comparisons for separate outcomes.
(Brodsky et al. 1985)	dentists and dental assistants	cohort	29,514 male dentists, 30,272 female dental assistants	number of dental amalgam restorations placed per week (0-40 = low exposure, >40= high exposure)	spontaneous abortion, congenital malformation	no difference in rate of spontaneous abortion or congenital malformation for maternal or paternal exposure
(Ericson and Kallen 1989)	dentists, dental assistants, dental technicians in Sweden	cohort	8,157 infants born to mothers working in dental occupations	work in dental occupations	spontaneous abortion, perinatal death, low birthweight, congenital malformation	no difference between observed and expected rates
(Alcser et al. 1989)	workers in mercury plant	cohort	241 exposed male workers, 254 unexposed male workers	work with mercury and high urine mercury levels	spontaneous abortion, congenital malformation	no difference in rate of spontaneous abortion or congenital malformation

Table 3: CHROMIUM and congenital malformation

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Findings
Chromium						
(Bonde 1993; Bonde et al. 1992)	metal workers	cohort	10,059 metalworkers, 3569 infants	work in stainless steel welding and mild steel welding vs. unexposed	birthweight, preterm delivery, infant mortality, congenital malformation, spontaneous abortion	no increase in low birthweight, preterm delivery, infant mortality, and congenital anomalies. Increased risk of spontaneous abortion in previous pregnancy
(Eizaguirre Garcia et al. 2000)	Glasgow residents	ecological	residents near chromium polluted area	distance of residence (0-10 km) from chromium polluted area	congenital malformation	highest risk of congenital malformation 2-4 km from polluted area - no evidence for link with chromium exposure

Table 4. Occupational SOLVENTS exposure and congenital malformations

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main findings
Maternal						
(Silberg et al. 1979)	Oklahoma	case-control	112 cases with congenital malformations, 116 controls	questionnaire on the use of spray adhesives in the home	congenital malformation	spray adhesives significantly more often used in homes of cases
(Holmberg 1979; Holmberg and Nurminen 1980)	Finland	case-control	120 cases with central nervous system (CNS) defects; 120 matched controls	interview information on solvent exposure at work or home	CNS defects	case mothers significantly more often reported exposure to solvents than control mothers (14 vs. 3)
(Holmberg et al. 1982)	Finland	case-control	378 cases with oral clefts; 378 matched controls	interview information on solvent exposure at work or home	oral clefts	case mothers significantly more often reported exposure to solvents than control mothers (14 vs. 4)
(Kurppa et al. 1983) (same study as H+N 80)	Finland	case-control	cases: 289 CNS defects, 421 oral clefts, 200 skeletal defects, 137 cardiovascular defects; matched controls, 1 per case (includes cases from 3 above studies)	interview information on occupational exposure to solvents, pesticides, decay preventing agents, disinfectants, metals, radiation	CNS defects, oral clefts, skeletal defects, cardiovascular defects	no association
(Olsen 1983)	Denmark	case-control	613 cases with intestinal, limb, cleft lip/palate defects and 83 cases with central nervous system defects; controls: 1735 children with other disorders	job title: laboratory worker; painter, printer, typographer, etc.	intestinal, limb, cleft lip/palate defects in relation to laboratory work; CNS defects in relation to painter and other solvent exposure	increased risk of CNS defects among painters
(Lindbohm et al. 1983)	Finland	case-control	cases of congenital anomaly and spontaneous abortions; controls: normal births	rubberworkers: membership of the union of Rubber and Leather workers	spontaneous abortion, congenital malformation	no increase in risk of congenital malformation; increased risk of spontaneous abortion in footwear department
(Axelson et al. 1983)	rubberworkers in Sweden	cohort	84 exposed pregnancies; 63 unexposed pregnancies	workers in tyrebuilding department of rubberplant	spontaneous abortion, threatening abortion, congenital malformation	increased risk of total adverse pregnancy outcomes (due to abortions not congenital malformation)

(Axelsson et al. 1984)	laboratory workers in Sweden	cohort	1160 pregnancies	questionnaire information: laboratory work, exposure to solvents	spontaneous abortion, perinatal death, congenital malformation	slight increase in spontaneous abortions among lab workers; no increased risk of congenital malformation among workers exposed to solvents
(Clarke and Mason 1985)	Leicestershire, UK	case-control	cases: perinatal deaths, controls: livebirths	job title: leatherworker	perinatal deaths, congenital malformations as cause of perinatal death	increased risk of perinatal deaths due to congenital malformations (OR=3.1)
(McDonald et al. 1987)	Montreal, Canada	case-control	301 cases of congenital malformation, 301 matched controls	occupational exposure to aliphatic solvents, aromatic solvents, plastics, metals, oils, detergents, gases, pesticides, miscellaneous	congenital malformation; subgroups of congenital malformation: CNS, cleft lip/palate, cardiac, gastrointestinal, genital-urinary, miscellaneous	exposure to aromatic solvents more often reported in cases than controls (18 vs. 8), mainly due to urinary defects (9 vs 0) and exposure to toluene (11 vs 3)
(Kyyronen et al. 1989)	Finland	case-control	247 cases of spontaneous abortion, 33 cases of congenital malformation; matched controls	dry-cleaning work, exposure to tetrachloroethylene	spontaneous abortion, congenital malformation	increased risk of spontaneous abortion for high tetrachloroethylene exposure; no increase of congenital malformations for tetrachloroethylene exposure; increased risk of congenital malformation for exposure to 'other solvents'.
(Ahlborg 1990)	laundry and dry-cleaning workers in Sweden	case-control	116 cases of adverse pregnancy outcome (spontaneous abortion, perinatal death, congenital malformation, low birth weight), 241 controls	dry-cleaning work; questionnaires to distinguish between high exposure to tetrachloroethylene , low exposure, unexposed	spontaneous abortion, perinatal death, congenital malformation, low birth weight	no increase in risk of adverse pregnancy outcomes. Outcomes not analysed separately
(Olsen et al. 1990)	Denmark, Norway, Sweden, Finland	4 case-control studies	cases of adverse pregnancy outcomes; matched controls	high exposure to tetrachloroethylene, low exposure, unexposed	spontaneous abortion, low birth weight, congenital malformation, stillbirth	increased risk of spontaneous abortion in Finland; no increased risk of other outcomes combined
(Lipscomb et al. 1991)	California	cohort	1105 pregnant women	exposure to solvents and/or work in electronics industry	spontaneous abortion, congenital malformation, low birth weight, preterm birth	increased risk of spontaneous abortion for solvent exposure; increased risk of LBW amongst electronics workers; no increase of congenital malformation

(Tikkanen et al. 1988)	Finland	case-control	160 cases, 160 controls	interview information: exposures at home, work; occupational titles. Maternal and paternal exposure	cardiovascular defects	no increased risks related to any maternal or paternal occupational exposures
(Tikkanen and Heinonen 1988)	Finland	case-control	569 cases, 1052 controls	interview information: exposure to solvents at work	cardiovascular defects	increased risk of cardiovascular malformations (OR 1.3; CI 0.8-2.2) and ventricular septal defect (OR 1.5, CI 1.0-3.7)
(Tikkanen and Heinonen 1991a)	Finland	case-control	573 cases, 1055 controls	interview information: work and home exposures including solvents	cardiovascular defects	increased of ventricular septal defect for solvent exposure (same as above) (OR 1.5, CI 1.0-3.7) ; no increased risks for other exposures
(Tikkanen and Heinonen 1991b)	Finland	case-control	150 cases, 756 controls	interview information: work and home exposures including solvents	ventricular septal defects	increased risk of ventricular septal defects in relation to solvent exposure at work (OR 1.8, CI 1.0-3.4)
(Tikkanen and Heinonen 1992c)	Finland	case-control	50 cases, 756 controls	interview information: work and home exposures including solvents	atrial septum defects	no association with solvent exposure
(Tikkanen and Heinonen 1992b)	Finland	case-control	406 cases, 756 controls	interview information: occupational exposures including solvents	cardiovascular defects	increased risk of : all cardiac defects and overall chemical exposure; all defects and exposure to dyes, lacquers, paints; VSD and solvent exposure.
(Tikkanen and Heinonen 1992a)	Finland	case-control	406 cases, 756 controls	interview information: home exposure including solvents	cardiovascular defects	no increased risks with chemical exposures at the home
(Cordier et al. 1992)	France	case-control	325 cases of congenital malformation, 325 matched controls	JEM: solvents and other exposures	congenital malformations: CNS, urinary, oral clefts, digestive, musculoskeletal, chromosomal, cardiac, multiple	increased risk of oral clefts for exposure to solvents during pregnancy and mothers working as janitors and cleaners; increased risk of digestive system and multiple anomalies for solvent exposure during and before pregnancy
(Taskinen et al. 1994)	Finland	case-control	36 cases of congenital malformation and 105 controls; 206 cases of spontaneous abortion and 329 controls	laboratory work: exposure to solvents and other chemicals	spontaneous abortion, congenital malformation, low birth weight	increased risk of spontaneous abortion for exposure to toluene, xylene, formaline. No associations with congenital malformation

(Laumon et al. 1996)	France	case-control	200 cases, 400 controls	interviews on occupation and exposures: exposure to solvents and 9 subgroups of solvents	cleft lip and/or cleft palate	increased risk of clefts in relation to exposure to all solvents (OR 1.62, CI 1.04-2.52) and halogenated aliphatic solvents (OR 4.4, CI 1.41-16.15)
(Torfs et al. 1996)	California	case-control	110 cases, 220 controls	interviews: medical exposures, home exposures, occupational exposures (solvents, colorants, glycols, dyes)	gastroschisis	increased risk of gastroschisis for solvent exposure (OR 3.8, CI 1.6-9.2) (mainly due to aliphatic and aromatic hydrocarbons) , colorants, X-rays, and certain medications
(Ferencz et al. 1997)	Baltimore-Washington	case-control	3377 cases of cardiac malformations, 3572 controls	interviews with parents : lifestyle and environmental factors including home and occupational exposure to solvents	cardiac defects	ORs of >3 found for solvent exposure and transposition of great arteries, hypoplastic left heart, coarctation of aorta
(Cordier et al. 1997)	6 regions in Europe	case-control	984 cases, 1134 controls	maternal occupational exposure to glycol ethers (JEM)	total congenital malformations, subgroups of malformations	increased risk of total malformations in relation to glycol ether exposure (OR 1.44, CI 1.10-1.90); increased risks of neural tube defects, multiple anomalies, and cleft lip
(Bianchi et al. 1997)	Florence, Italy	case-control	1791 cases of congenital malformation, 3223 control births	4 occupational groups: health services, hairdressers, textile dye workers, leather workers	congenital malformations: CNS, cardiac, oral clefts, digestive, external genital, internal genital, limbs, musculoskeletal, Integument, chromosomal, multiple	increased risk of oral clefts for leatherworkers, increased risk of multiple anomalies for textile dye workers
(Garcia and Fletcher 1998)	Spain	case-control	261 cases of congenital malformation; 261 controls	work in leather industry	congenital malformations: CNS, cardiac, oral clefts, hypospadias, multiple	significantly increased risk of oral clefts; non-significant increases in hypospadias and multiple anomalies
(Fixler and Threlkeld 1998)	Dallas	case-control	89 cases, 82 controls	maternal illness, drug consumption, substance use, chemical exposures in home or workplace	congenital heart defects in Down Syndrome	no increased risk in any of the categories of maternal exposure, including solvents
(Khattak et al. 1999)	Toronto, Canada	cohort	125 exposed pregnant women, 125 unexposed	occupational exposure to solvents (as reported to counselling programme)	congenital malformations	13 cases of congenital malformation in exposed group, 1 in unexposed group (OR 13.0 CI 1.8-99.5)

(Brender et al. 2002)	Texas-Mexico border	case-control	184 cases, 225 controls	maternal and paternal interview	Neural tube defects	Increased risk of neural tube affected pregnancies in case mothers exposed to glycol ethers (9 cases, no controls) and any solvents (7 cases, no controls)
(El-Zein et al. 2002)	factory workers, Mexico	nested case-control	41 offspring to 28 female workers, 6 exposed cases during pregnancy.	all workers exposed to EGME (ethylene glycol monomethyl ether), timing determined at interview	congenital dysmorphism/abnormalities on examination, levels of chromosomal aberrations on cytogenic assay	all six exposed cases affected
(Shaw et al. 2003a)	California	case-control	218 case mothers, 146 control mothers	interview: task-specific exposure to 74 different chemicals	cleft lip and/or cleft palate, conotruncal heart defect, limb deficiency	increased risk of conotruncal heart cases associated with occupational exposure to aliphatic hydrocarbons, organic dyes, phenol compounds. Increased risk in limb anomalies associated with aliphatic hydrocarbons. Increased risk in clefts associated with organic dyes, aromatic amines, aliphatic hydrocarbons and sulfides.
(Shaw et al. 2001)	California	case-control	538 cases, 539 control mothers (study 1); 265 case mothers, 481 control mothers (study 2)	interview: task-specific exposure to 74 different chemicals	Neural tube defects	Potential associations in study 1 were not replicated in study 2, based on screening for OR>5 in study 1, but other meta-analysis methods may have given different results.
paternal						
(Taskinen et al. 1989)	workers in Finland	nested case-control	120 cases of spontaneous abortion and congenital malformation	questionnaire on paternal exposure to solvents (including specific groups of solvents)	spontaneous abortion, congenital malformation	increased risk of spontaneous abortion for overall paternal solvent exposure, exposure to aromatic hydrocarbons, xylene, miscellaneous solvents, dusts. No associations with congenital malformation
(McDonald et al. 1989)	Montreal Canada	cohort	47,822 pregnancies	24 paternal occupational groups	spontaneous abortion, congenital malformation	no increased risk in congenital malformation for any of the occupational groups. 10% increase in spontaneous abortion in mechanics and repairers
(Brender and Suarez 1990)	Texas	case-control	727 cases of anencephaly, 1464 controls	occupation of father from birth certificate classified according to solvent and pesticide exposure	anencephaly	OR 2.53 (1.56-4.10) for exposure to solvents, OR 3.43 (1.83-6.43) for painters, OR 1.28 (0.77-2.13) for pesticides

(Olshan et al. 1991)	British Columbia	case-control	14,415 livebirths with congenital malformation; 2 controls per case	paternal occupation: 58 occupational groups	congenital malformation: 20 groups of malformation	increased risk of spina bifida, cleft palate, hypospadias, for some occupations with potential solvent exposure. Also many other associations
(Kristensen et al. 1993)	workers in printing industry in Norway	cohort	6,251 children born to fathers working in printing industry	paternal exposure: 4 exposure groups on the basis of job codes at time of conception: lead only, solvents only, lead and solvents, other (unexposed)	LBW, SGA, preterm birth, early preterm birth, late abortion, stillbirth, early neonatal death, perinatal death, birth defects	increased risks of preterm birth, late abortions and solvent exposure; Increased risk of cleft lip/palate (SMR 1.6, 0.97-2.5) among all fathers employed in printing industry compared to all births in Oslo; No increase in risk of other congenital anomalies or all congenital anomalies.
(Blatter et al. 1997)	Netherlands	case-control	122 case fathers, 411 control fathers	interviews on occupation, tasks, exposures, including solvent exposure	spina bifida	no association with solvent exposure; significant association with welding fumes, cleaning agents, pesticides, dusts
(Brender et al. 2002)	Texas-Mexico border	case-control	184 cases, 225 controls	maternal and paternal interview	Neural tube defects	No increased risk of neural tube affected pregnancies in case fathers exposed to glycol ethers and any solvents
(Shaw et al. 2002)	California	case-control	538 NTD cases, 539 non-malformed controls	maternal interview for paternal job title	neural tube defects	Increased risk of neural tube defects associated with following paternal occupations: cooks, janitors and cleaners, farm workers, gardeners. Paternal solvent exposures OR=0.8 (0.5-1.3).
(Shi et al. 2002)	Singapore	population-based	237,755 live births (3293 birth defect cases)	occupational data collected at different government sources, regarding occupation and industry	all birth defects and 22 large groupings.	Increased risk of birth defects associated with parental occupations (both maternal and paternal) in agricultural and fishing industries, based on small numbers (numbers not given). Nothing solvent related.

Table 5: VINYL CHLORIDE and STYRENE and adverse pregnancy outcome

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main findings
Occupational Exposure						
(Infante et al. 1976a)	VCM polymerisation workers	cohort	wives of workers exposed to vinyl chloride monomer (VCM)	high VCM exposure: VCM workers; low/no VCM exposure: PVC and rubber workers	fetal death	increased risk of fetal death amongst VCM exposed workers
(Hemminki et al. 1980)	chemical workers in Finland	cohort	9,000 female workers	branch of chemical industry	spontaneous abortion	increased in risks of spontaneous abortion in plastics and styrene industry, viscose rayon industry, laundry work and pharmaceutical industry
(Harkonen and Holmberg 1982)	plastics workers in Finland	cohort	67 exposed women, 67 unexposed	exposure to styrene	spontaneous and induced abortions; number of births; number of pregnancies	no significant differences
(Harkonen et al. 1984)	plastics industry in Finland	cohort	2209 workers (men and women)	exposure to styrene	congenital malformation	no increased risk of congenital malformation
(Lindbohm et al. 1985)	plastics industry in Finland	case-control	44 cases of spontaneous abortion, 123 live born controls	information from occupational physician on occupation, tasks, and type of plastics handled; exposure to styrene plastics, PVC plastics, polyurethane	spontaneous abortion	increased risk of spontaneous abortion for workers processing polyurethane. No increase for exposure to styrene or PVC plastics
(Ahlborg et al. 1987)	plastics industry in Norway and Sweden	case-control	Sweden: 44 cases, 88 controls; Norway: 10 cases, 20 controls	information from company on exposures, duration, process, etc; exposure to styrene plastics, PVC plastics, polyurethane; exposure to heated and nonheated plastics	combined: spontaneous abortion, perinatal death, low birthweight, congenital malformations	increased OR for PVC exposure in Sweden. No increased OR for styrene or polyurethane exposure
(McDonald et al. 1988)	plastics industry in Montreal	cohort	193 pregnancies	Information on process, type of plastics, tasks; exposure to polyvinyl, polystyrene, polyurethane, and polyolefin	spontaneous abortion	significantly increased risk for working with polystyrene, non-sign increase in risk for working with polyolefin and polyvinyl

(Lemasters et al. 1989)	plastics industry in US	cohort	1535 women	styrene exposure levels estimated from work process, intensity, and product	birth weight	offspring of exposed women lower birth weights than unexposed women ; no dose-response
Environmental Exposure						
(Infante et al. 1976b)	Ohio	ecological	residents of 3 communities compared to entire state of Ohio	residence in community with VC polymerisation facility	birth defects	statistically significant excess of birth defects in 3 states with VC facility, particularly CNS defects, cleft lip and palate, club foot and defects of the genital organs
(Edmonds et al. 1975)	Ohio	case-control	15 cases of anencephalus and spina bifida; 30 controls	occupation in PVC facility or residence within 2 miles of facility	anenchepalus and spina bifida	no association with occupation in or residence near PVC plant
(Edmonds et al. 1978)	West Virginia	case-control	46 cases with CNS defects; 46 matched controls	occupation in PVC plant; distance of residence at birth from PVC plant	CNS defects	no association with occupation in or residence near PVC plant
(Theriault et al. 1983)	Canada	case-control	68 cases with congenital malformations; 68 matched controls	parental occupation in PVC plant; distance of residence from PVC plant.	congenital malformations	excess of birth defects in community where PVC plant was located, but no association with occupation in or residence near PVC plant
(Rosenmann et al. 1989)	New Jersey	case-control	51 cases of congenital malformation; matched controls	distance of residence from two PVC plants	congenital malformation, CNS defects	no statistically significant increases found. Some evidence of decreasing risk of CNS defects with increasing distance from one of the plants.

Table 6: DIOXINS and PHENOXY HERBICIDES and adverse pregnancy outcome

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main Findings
Environmental and occupational dioxin exposures						
(Mastroiacovo et al. 1988)	Seveso, Italy	ecological	births in area of Seveso after accident	residence in high, low, and very low dioxin exposure zones compared to control area	congenital malformations	No major malformations in high exposure zone (out of 26 births). No increase in malformation rate in low and very low exposure zones compared to control area
(Stockbauer et al. 1988)	Missouri, US	geographical	410 births in exposed area, 820 unexposed births	residential proximity to a dioxin contaminated area	fetal, infant, and perinatal deaths, low birth weight, congenital malformations	Increases in risk of fetal, infant, and perinatal deaths, low birth weight, but not statistically significant
(Vartiainen et al. 1998)	Finland	cohort	167 births	breast milk samples of dioxins, furans, and PCBs	birth weight	slight decrease in birth weight in all children with increasing dioxins and furans in milk; no relationship for primiparae
(Townsend et al. 1982)	Dow chemical industry, US	cohort	737 conceptions in exposed group, 2031 in unexposed group	paternal work in chlorophenol processing, job exposure matrix for low, medium, high exposure	spontaneous abortions, stillbirths, infant deaths, congenital malformations	no relationship between dioxin exposure and reproductive outcomes
(Dimich-Ward et al. 1996)	sawmill workers, Canada	nested case-referent	19,675 births to 9,512 fathers who had worked in sawmills	paternal exposure to chlorophenate wood preservatives in sawmill estimated from job title and duration.	prematurity, low birthweight, stillbirth, neonatal death, congenital malformation	increased risks in eye malformations, spina bifida and anencephaly, and genital anomalies
(Karmaus and Wolf 1995)	teachers, Germany	cohort	49 exposed and 507 unexposed pregnancies	maternal exposure to chlorophenol wood preservatives in day care centres estimated from indoor air measurements and job history	birth weight and length	significant decrease in mean birth weight and length in exposed group
Agent Orange						
(Erickson et al. 1984)	Vietnam veterans, US	case-control	4,815 cases with congenital malformations, 2,967 controls	father served in military, father served in Vietnam, self-reported exposure to Agent Orange, Agent Orange exposure index	congenital malformations	no increase in risk in all congenital malformations combined and most subgroups.

(Donovan and R 1984)	Vietnam veterans, Australia	case-control	8,517 cases with congenital anomalies; 8,517 matched controls	father served in Vietnam	congenital malformations	no increase in risk in all congenital malformations combined or malformation subgroups.
(Field and Kerr 1988)	Vietnam veterans, Tasmania	cohort	357 veterans, 281 non-veterans	father served in Vietnam	congenital malformations and other pregnancy outcomes	more fetal and infant deaths in veterans. More malformations but no formal testing
(Wolfe et al. 1995)	Vietnam veterans US	cohort	1,006 Ranch Hand conceptions, 1,235 comparison group	father served in operation Ranch Hand (herbicide spraying): background, low, and high dioxin exposure groups based on serum levels.	spontaneous abortions, stillbirths, congenital malformations	increase in some subgroups of malformations in low but no high dioxin exposure categories
(Michalek et al. 1998)	Vietnam veterans, US	cohort	859 Ranch Hand children, 1,223 comparison group	father served in operation Ranch Hand (herbicide spraying): background, low, and high dioxin exposure groups based on serum levels.	preterm birth, intrauterine growth retardation, infant death	increased risk in preterm birth and infant death in background and high exposure categories
(Stellman et al. 1988)	Vietnam veterans, US	cohort	2858 Vietnam veterans, 3,933 other veterans	father served in Vietnam	spontaneous abortion, birth weight	increase risk of spontaneous abortion. No difference in birth weight
(Aschengrau and Monson 1989)	Vietnam veterans, US	case-control	201 spontaneous abortion cases, 1119 controls	father served in Vietnam	spontaneous abortion	no increase in risk of spontaneous abortion
Phenoxy Herbicides						
(Field and Kerr 1979)	Australia	ecological	annual rates of neural tube defects in New South Wales	annual usage of 2,4,5-Tin whole of Australia	neural tube defects	significant correlation between herbicide usage and NTD rates
(Nelson et al. 1979)	Arkansas, US	ecological	cleft lip and/or cleft palate rates in 75 counties	low, medium, high 2,4,5-T exposure groups on the basis of rice acreage of county	cleft lip and/or palate	no association
(Thomas 1980)	Hungary	ecological	annual rates of congenital malformations and stillbirths	annual 2,4,5-usage	stillbirths, spina bifida, anencephaly, cleft palate, cleft lip, cystic kidney	no increase in rates of congenital malformations or stillbirths with increasing use of 2,4,5-T
(Smith et al. 1981)	New Zealand	cohort	1172 births to pesticide applicators, 1122 births to other agricultural workers	father worked as applicator of pesticides including 2,4,5-T	congenital malformations, stillbirths, spontaneous abortions	no increase in risk

(Smith et al. 1982)	New Zealand	cohort	1172 births to pesticide applicators	3 exposure groups: no exposure to spraying, spraying of chemicals other than 2,4,5-T, spraying of 2,4,5-T	congenital malformations, stillbirths, spontaneous abortions	no increase in risk comparing 2,4,5-T sprayers with other exposure groups
(Arbuckle et al. 1999)	Ontario, Canada	cohort	5,853 pregnancies on Ontario farms	use of phenoxy herbicides at farm	spontaneous abortion	association between preconception exposure and early spontaneous abortions (<12 weeks gestation).

Table 7: PESTICIDES and congenital malformations

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main Findings
Occupational and residential studies						
(Kurppa et al. 1983)	Finland	case-control	cases: 289 CNS defects, 421 oral clefts, 200 skeletal defects, 137 cardiovascular defects; matched controls	interview information on occupational exposure to solvents, pesticides, decay preventing agents, disinfectants, metals, radiation	CNS defects, oral clefts, skeletal defects, cardiovascular defects	no assocation with maternal pesticide exposure
(Gordon and Shy 1981)	Iowa and Michigan	case-control	187 oral cleft cases, 985 controls	exposure index constructed from crops and pesiticide use in county of residence	cleft lip and/or palate	increased risk of cleft lip and/or palate in relation to use of pesticides (OR 2.85 (1.49-5.44) in Iowa; OR 1.68 (1.02-2.78) in Michigan)
(Roan et al. 1984)	USA	cohort	314 agricultural pilot, 178 control families	paternal occupation as agricultural pilot	SA, SB, CM	no increase in SA, SB, or CM
(Li et al. 1986)	China	cohort	6,173 exposed preganncies, 13,471 unexposed pregnancies	consumption of rice from fields where MATDA had been applied	SA, SB, CM	no difference in rates of SA, SB, CM between exposed and control populations
(Le Marchand et al. 1986)	Hawaii	ecological	island of Oahu rates compared to other islands and total US	heptachlor contamination of milk supply on island of Oahu	CM	no increased risk for all or specific malformations in Oahu.
(Kricker et al. 1986)	Australia	case-control	155 cases with limb defects, 274 controls	interview: maternal pesticide exposure in first trimester, including work, home, garden	congenital limb defects	increased risk for women reporting work/home/garden exposure : OR 3.4 (1.9-5.9)
(Schwartz et al. 1986)	California	cohort	986 exposed, 1,354 unexposed births	maternal and/or paternal work in agriculture	CM	increased risk of limb reduction defects in agricultural workers (RR 2.3); no increase in all malformations
(Grether et al. 1987)	San Fransico Bay	ecological	22,465 exposed births, 17,050(1982) and 37,858 (1981) unexposeds births	malathion application of zip-code of residence	CM, LBW	no overall increase in congenital malformations or low birth weight in exposed compared to unexposed births; increased risks for some individual anomalies but no consistent pattern

(Schwartz and LoFerfo 1988)	California	case-control	237 cases with limb reduction defects, 475 controls	maternal and/or paternal work in agriculture; agricultural productivity and pestricide use in county of maternal residence	limb reduction defects	no increase in agricultural workers (RR 0.9); increased risk in areas with high agricultural productivity (RR 1.7, 1.1-2.7) and high pesticide use (RR 1.9, 1.2-3.1)
(White et al. 1988)	New Bruswick Canada	case-control	392 cases of selected malformations; 770 controls. 298 stillbirths + controls	pesticide use in county of residence - exposure index	NTDs, cleft lip, cleft palate, renal agenesis; stillb+F23irths	significant association between spina bifida and exposure index. Significant association for stillbirths. No other significant associations.
(Whorton et al. 1989)	California	ecological	45,358 births	DBCP in drinking water of census tract of residence	LBW, CM	no relationship between low birth weight or congenital malformations and DBCP concentration
(Restrepo et al. 1990a)	Colombia	case-control	222 cases with birth defects, 443 controls	interviews: maternal and/or paternal work in floriculture	CM	increased risk of total malformations for maternal exposure (OR 1.8 1.2-2.7) mainly due to increase in haemangiomas
(Restrepo et al. 1990b)	Colombia	cohort	3,450 exposed pregnancies, 10,534 unexposed	maternal and/or paternal work in floriculture	CM, SA, SB, prematurity	increased risk of malformation for maternal (OR 1.34, 1.07-1.69) and patrernal (OR 1.53, 1.04-2.2.5) exposure. Increased risks in spontaneous abortion and prematurity
(Rupa et al. 1991)	India	cohort	1016 exposed couples, 1020 unexposed	paternal work in pesticide mixing and spraying	SB, CM, neonatal death	increased risk of SB, CM, and neonatal deaths in exposed group
(Thomas et al. 1992)	San Fransico Bay	cohort	7,450 pregnancies	residence in malathion spraying area	SA, intrauterine growth retardation, SB, CM	no association for SA, intrauterine growth retardation, SB. Total congenital malformations OR 1.20 (0.83-1.73), limb defects OR 1.73 (0.87-3.46), orofacial OR 3.35 (0.61-18.5), gastrointestinal (2nd trimester exposure) OR 4.14 (1.01-16.6)
(Zhang et al. 1992)	China	case-control	1,875 cases, 1,875 controls	maternal occupational exposures incl pesticides	perinatal death, small for gestational age, CM	pesticide exposure associated with increased risk of small for gestational age and central nervous system defects (OR1.8, 0.3-10.5)
(Spagnolo et al. 1994)	Italy	ecological	940,000 births	use of benomyl in region of residence	anophthalmia, microphthalmia	no relationship
		case-control	90 cases, 912 controls	parental occupation in agriculture	anophthalmia, microphthalmia	no association

(Kristensen and Irgens 1994)	Norway	cohort	192,417 pregnancies	exposure to benomyl classified on basis of work in greenhouses, in orchards, with field vegetables, with grain	anophthalmia, microphthalmia	no increase in risk of anophthalmia/microphthalmia but very small numbers (1 exposed case)
(Lin et al. 1994)	New York State	case-control	277 cases, 324 malformaed controls, 327 non-malformaed controls	maternal and paternal agricultural work and exposure to pesticides	limb reduction defects	no increase in total limb defects, increased risk in limb defects + associated defects for parental pesticide exposure (OR 1.4, 1.8-2.5)
(Nurminen et al. 1995)	Finland	case-control	581 orofacial clefts, 365 CNS, 360 skeletal defects; matched controls	maternal agricultural work in first trimester	orofacial clefts, CNS defects, skeletal defects	OR for orofacial clefts = 1.9 (1.1-3.5), CNS defects OR=1.3 (0.6-2.8), skeletal defects OR=0.9 (0.4-1.9)
(Goldsmith et al. 1984; Potashnik and Phillip 1988; Potashnik and Porath 1995)	Israel	cohort	30 DBCP workers	paternal occupational DBCP exposure	SA, prematurity, birth weight, CM	no increase in these outcomes at 5, 8 and 17 years follow-up
(Garcia-Rodriguez et al. 1996)	Spain	case-control	270 cryptorchidism cases, 514 controls	pesticide use of municipality	cryptorchidism	association between risk of cryptorchidism and pesticide use
(Garry et al. 1996)	Minnesota	cohort	210,723 births	paternal occupation as pesticide applicator; residence in crop spraying region	CM	paternal occupation: increased risk of total CM (OR 1.41, 1.18-1.69), circulatory / respiratory defects, gastrointestinal defects, urogenital defects, musculoskeletal defects. These groups also higher risk in crop spraying regions
(Pastore et al. 1997)	California	case-control	332 cases, 357 controls	maternal residential and occupational exposures incl pesticides	SB, SB due to CMs, SB due to other causes	occupational exposure to pesticides associated with increased risk of SB and SB due to CM (OR 2.4, 1.0-5.9); home pesticide exposure associated with increased risk of SB due to CM (OR 1.7, 1.0-2.9)
(Kristensen et al. 1997)	Norway	cohort	192,417 births to farmers, 61,351 births to non-farmers	parental work as farmer; pesticide exposure indicators	CMs	no stat sign increases in risk of total CMs or specific CMs in farmers. Increased risk of CNS defects, spina bifida, hydrocephaly, cryptorchidism, hypospadias, urinary system, and limb reduction for one or more pesticide exposure indicators

(Blatter et al. 1997)	The Netherlands	case-control	122 cases of spina bifida, 411 controls	paternal occupational exposure to range of chemicals incl pesticides	spina bifida	OR for moderate or high vs. low pesticide exposure =1.7, 0.7-4.0)
(Garcia et al. 1998)	Spain	case-control	261 cases, 261 matched controls	paternal agricultural work: from interviews and expert assessment of exposure likelihood. By chemical classes of pesticides and active ingredients	CMs	increased OR for exposure to aliphatic hydrocarbons (OR 1.05, 0.62-6.80), inorganic compounds (OR 2.02, 0.53-7.72), glufosinate (OR 2.45, 0.78-7.70), and pyridil derivates (OR 2.77, 1.19-6.44)
(Garcia et al. 1999)	Spain	case-control	261 cases, 261 matched controls	maternal and paternal agricultural work.	CMs	increased risk related to maternal agricultural activity during preconception and first trimester (OR 3.16, 1.11-9.01) and paternal handling of pesticides (OR 1.49, 0.94-2.35).
(Shaw et al. 1999)	California	case-control	1299 cases, 734 controls	maternal pesticide exposure: work, home, or residential proximity	orofacial clefts, NTDs, conotruncal defects, limb anomalies	no increased risks with occupational exposures; increased risk for pesticides applied to the home (NTD and limb) and living <1/4 mile from agricultural crop (NTDs)
(Bell et al. 2001)	California	case-control	73 cases, 611 controls	maternal residential proximity to pesticide application areas. 5 pesticide classes	fetal death due to CMs	increased ORs from 1.4 (0.8-2.4) for phosphates, carbamates and endocrine disruptors to 2.2 (1.3-3.9) for halogenated hydrocarbons
(Loffredo et al. 2001)	Maryland, District of Columbia, Northern Virginia	poulation-based case-control	1832 cases, 771 controls	maternal interview: pesticide exposure in first trimester at work or at home	TGA and non-TGA cardiac outflow tract anomalies	Increased risk of TGA associated with pesticides (OR 2.0, 1.2-3.3). Increased risk with rodenticides (OR 4.7, 1.5-14.2) and herbicides (OR 2.8, 1.2-6.9).
(Crisostomo and Molina 2002)	Nueva Ecija, the Philippines	retrospective cohort	345 conventional pesticide households, 331 integrated pest management households	interview	spontaneous abortions, preterm births, birth defects	Increased risk of birth defects in conventional pesticide households (adjusted OR 4.6, 1.2-17.1). Increased risk of spontaneous abortion (adjusted OR 6.2, 1.4-27.9).
(Brender et al. 2002)	Texas-Mexico border	case-control	184 cases, 225 controls	maternal and paternal interview	Neural tube defects	No increased risk of neural tube affected pregnancies in parents exposed to pesticides
case reports and reports of small clusters						
(Romero et al. 1989)	California	case report	1 pregnant agricultural worker	high exposure to mixture of 3 insecticides: organophosphates: oxydemeton-methyl and mevinphos; and carbamate: methomyl	congenital anomalies	baby born with multiple cardiac defects, coloboma, microphthalmia, cerebral and cerebellar atrophy, facial anomalies

(Sherman 1996)	US	case report	4 children	mothers exposed to chlorpyrifos during first trimester of pregnancy	congenital anomalies	similar and unusual pattern of defects reported: defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples and genitalia, growth retardation and mental retardation.
(Czeizel et al. 1993)	Hungary	cluster report	11 cases out of 15 livebirths	mothers consumed fish from local fish farms contaminated with trichlorfon	congenital anomalies	11 malformed cases of which 4 with Down syndrome
(Reche 1999)	Spain	cluster report	11 cases of rare dysmorphologic syndromes	residents in area with intensive farming and common pesticide noxication problems	congenital anomalies	11 cases of rare dysmorphologic syndromes

abbreviations: CNS=central nervous system, NTD=neural tube defect, SA=spontaneous abortion, SB=stillbirth, LBW=low birth weight, CM=congenital malformation

Table 8: AIR POLLUTION and adverse pregnancy outcome

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main Findings
(Williams et al. 1977) (Hemminki and Niemi 1982)	Finland 1974-77	cohort	1,792 births in one district	air pollution: regional mean concentrations of SO2, HS, CS2	spontaneous abortion	increased risk of spontaneous aortion for high exposure to HS; no association with SO2 and CS2
(Xu and Ding 1995)	4 districts in China, 1988-91	cohort				
(Wang et al. 1997)	4 districts in China, 1988-91	cohort	74,671 singleton livebirths between 37-44 weeks gestation	daily measurements of TSP and SO2; average exposure during entire pregnancy, average exposure during each trimester	low birth weight in term births (37-44 weeks)	OR 1.11 (1.06-1.16) and 1.10 (1.05-1.14) for 100 µg/m3 increase in SO2 and TSP respectively
(Bobak and Leon 1999b)	Czech Republic 1986-88	ecological	223,929 births in 85 districts	annual average levels of TSP, SO2 and Nox in districts	low birth weight, stillbirth	OR for LBW: 1.10 (1.02-1.17) for 50 µg/m^3 increase in SO_2; no association with stillbirth
(Bobak 2000)	Czech Republic 1991	ecological	126,752 births in 67 districts	average levels of SO2, TSP, NOx in each district for each trimester of pregnancy	low birth weight, prematurity, intrauterine growth retardation	ORs LBW: 1.20 (95%CI 1.11-1.30) and 1.15 (1.07-1.24) for 50ug/m3 increase in SO2 and TSP in the first trimester; ORs of prematurity : 1.27 (1.16-1.39) for SO_2 and 1.18 (1.05-1.31) for TSP in the first trimester. No association for IUGR
(Dejmek et al. 1999)	one district in Czech Republic, 1994-96	cohort	1,943 births between 37-44 weeks gestation	average levels of PM10 and PM2.5 during each month of pregnancy	intra uterine growth retardation in term births	OR : 2.64 (1.48-4.71) for high (>50 µg/m^3) vs low (=<40 µg/m^3) level of PM10 in first month of pregnancy; no association in later months
(Ritz and Yu 1999)	Los Angeles, 1989-93	cohort	125,573 births between 37-44 weeks gestation, living with 2 miles of CO monitoring station	average CO levels in last trimester of pregnancy	low birth weight in term births	OR 1.22 (1.03-1.44) for last trimester exposure to high vs low levels of CO
(Ritz and Yu 2000)	California, 1989-1993	cohort	97,518 births in Californaia	average exposure levels in periods of pregnancy for CO, NO2, ozone, PM10	pre-term birth	OR 1.20 (1.09-1.33) per 50ug/m3 PM10 during last 6 weeks. OR 1.13 (1.08-1.18 for CO exposure during last 6 weeks

(Rogers et al. 2000)	Georgia, USA, 1986-88	case-control	143 very low birth weight births; 202 control births	estimates of TSP and SO2 exposures at the birth home from environmental transport models	very low birth weight	OR 2.88 (1.16-7.13) for high vs low exposure; trend with decreasing exposure.
(Bobak 2001)	Great Britain, 1946	ecological	5,362 members of the 1946 British birth cohort	air pollution index based on domestic coal consumption per square mile	mean birth weight	strong correlation between air pollution index and birth weight. Birth weight 87 grams lower in most polluted vs least polluted areas
(Ritz et al. 2002)	California, 1987-1993	case-control	3,539 cases, 10,649 controls	average monthly exposure during first trimester pf preganncy to CO, NO2, O3, and PM10	cardiac defects, orofacial clefts	OR around 3 for cardiac anomalies comparing highest and lowest quartile of CO exposure. No association for other pollutants or orofacial clefts

Table 9: DRINKING WATER CONTAMINATION and adverse pregnancy outcome

Reference	Setting	Study type	Study subjects	Exposure Measurement	Adverse pregnancy outcomes studied	Main Findings
Solvent Contamination						
(Lagakos et al. 1986)	Woburn, Massachussets	case-control	20 leukaemia cases, 164 control children	Exposure index based on fraction of water supply from contaminated wells	Childhood leukaemia	Significant association with exposure index
		cohort	4,396 pregnancies and 5,018 children under 18	Exposure index based on fraction of water supply from contaminated wells	congenital malformations, spontaneous abortions, perinatal death, LBW; childhood disorders	Increase in congenital eye/ear anomalies, CNS/ chromosomal/ cleft anomalies; perinatal deaths; kidney/urinary tract disorders, lung/respiratory disorders
(Swan et al. 1989)	Santa Clara County California	cohort	Births in exposed census tracts compared unexposed	Residence in census tract served by contaminated water supply	Congenital heart defects	2-fold excess in cardiac anomalies
(Deane et al. 1989)	Santa Clara County California	cohort	Pregnancies in exposed census tract; pregnancies in unexposed census tract	Residence in census tract served by contaminated water supply	congenital malformation, spontaneous abortions, LBW	Increase in spontaneous abortions and congenital malformations; no excess in LBW
(Wrensch et al. 1990a)	Santa Clara County California	cohort	Pregnancies in 2 exposed census tracts; pregnancies in 2 unexposed census tracts	Residence in 2 census tracts served by contaminated water supply	congenital malformations, spontaneous abortions, LBW	No excess in spontaneous abortions or malformations in new exposed study area
(Wrensch et al. 1990b)	Santa Clara County California	cohort	Pregnancies in 2 exposed census tracts	% water in census tract from contaminated well, estimated concentration of solvents	congenital malformations, spontaneous abortions	No relation between abortion or malformation rate and estimated exposure
(Shaw et al. 1990)	Santa Clara County California	Case-control	145 cases with cardiac malformations, 176 non-malformed births	Mother's consumption of home tap water	Congenital heart defects	Elevated risk for consumption of more than 4 glasses of tap water compared to none.
(Deane et al. 1992)	Santa Clara County California	cohort	349 pregnancies in 1 exposed and 1 unexposed census tract	Mother's consumption of home tap water	congenital malformation, spontaneous abortions	Spontaneous abortions: significant trend with number of glasses tap water per day. Cogenital malformations: no trend

(Wrensch et al. 1992)	Santa Clara County California	cohort	1,016 pregnancies in exposed and unexposed areas	Mother's consumption of home tap water	congenital malformations, spontaneous abortions, LBW	Spontaneous abortions: 7-fold risk for any versus no tap water. Congenital malformations: non-significant increase. No association with LBW
(Swan et al. 1998)	3 regions in California	prospective cohort	5,342 pregnancies	Mother's consumption of tap water	spontaneous abortion	increased risk of spontaneous abortion in one region for consumption of tap water compared to bottled water.
(Goldberg et al. 1990)	Tuscon Valley, Arrizona	case control	707 cases with cardiac defects ; controls: household in general population	residence or work in contaminated area	cardiac defects	parents of cardiac cases more likely to have worked or resided in the contaminated area compared to general population survey.
(Rodenbeck et al. 2000)	Tuscon Valley, Arizona	ecological	births in exposed census tracts, births in unexposed census tracts	estimated exposure to trichloroethylene through drinking water for each household	low birth weight, very low birth weight	non-statistically significant association with very low birth weight; no association with low birth weight
(Bove et al. 1995) (see below for chlorination by-products)	New Jersey	cross-sectional	80,938 births, 594 fetal deaths	for town of residence: levels of trichloroethy, tetrachloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-dichloroethane, total dichloroethylenes, benzene, TTHMs	low birth weight, very low birth weight, small for gestational age, preterm birth, CNS defects, NTDs, oral clefts, cardiac defects, total birth defects	increased OR for TTHM and risk of all birth defects, CNS defects, NTDs, oral clefts, major cardiac defects, small for gestational age and birth weight.
(Witkowski and Johnson 1992)	Michigan	ecological	births in non-metropolitan counties of Michigan	county with documented ground or surface water contamination by benzene and chlorinated organic solvents	low birth weight	poitive association between percentage of low birth weight and water pollution index
(Sonnenfeld et al. 2001)	North Carolina	population based	11,798 births, 1968-1985	residence in area (US Marine Corps base) which received PCE contaminated drinking water -v- no PCE exposure	mean birth weight, small for gestational age, preterm birth	decrease in mean birth weight and increase in risk of small-for-gestational-age infant in older mothers and mothers with history in previous fetal loss

Chlorination by-products

(Aschengrau et al. 1993) (see also below)	Massachusetts	case-control	1039 congenital anomaly cases, 77 stillbirths, 55 neonatal deaths, 1177 controls	quality of public drinking water in area of residence: levels of metals, inorganic substances, chlorination vs. no chorination	congenital malformations, stillbirths, neonatal death	chloinated vs non-chlorinated water: OR 2.6 (0.9-7,5) for stillbirths, OR 1.5 (0.7-2.1) congenital malformation. Also increased ORs for lead and all congenital malformations, lead and cardiac defects; potassium and NTDs.
(Shaw et al. 1991)	Santa Clara County	case-control	138 cases with cardiac malformations, 168 non-malformed births	chlorinated tap water received by residence in first 3 months of pregnancy; consumption of tap water	Congenital heart defects	no increased risk for women who reported to drink tap water and lived in residences receiving chlorinated water
(Bove et al. 1995) (see also above for solvents)	New Jersey	cross-sectional	80,938 births, 594 fetal deaths	for town of residence: levels of trichloroethy, tetrachloroethylene, 1,1,1-trichloroethane, carbon tetrachloride, 1,2-dichloroethane, total dichloroethylenes, benzene, TTHMs	low birth weight, very low birth weight, small for gestational age, preterm birth, CNS defects, NTDs, oral clefts, cardiac defects, total birth defects	increased OR for TTHM and risk of all birth defects, CNS defects, NTDs, oral clefts, major cardiac defects, small for gestational age and birth weight.
(Klotz and Pyrch 1999)	New Jersey	case-control	112 NTD cases, 248 controls	levels of TTHMs in area of residence; source of drinking water	neural tube defecs	increased risk of NTDs associated with >40 vs <5 ppb TTHM (OR 1.6, 0.9-2.70) and surface water source (OR 1.5, 0.9-2.5).
(Magnus et al. 1999)	Norway	cross-sectional	141,077 births	proportion of population exposed to chlorination and colour of drinking water for each municipality. Exposed: high colour + chlorination; unexposed: low colour + no chlorination	Congenital malformation, NTDs, major cardiac defects, respiratory, urinary, oral cleft defects	increased risk of all defects (OR 1.14, 0.99-1.31), and urinar tract defects (1.99, 1.10-3.57), for exposed compared to unexposed populations. Non-significant increase in NTDs (OR 1.26, 0.61-2.66)
(Dodds et al. 1999)	Nova Scotia, Canada	retrospective cohort	50,755 births	levels of TTHMs in area of residence	small for gestational age, low birth weight, very low birth weight, preterm birth, stillbirth, NTDs, oral clefts, cardiac defects, chromosomal abnormalities	increased risk of stillbirth for TTHM >100ug/l (RR 1.66, 1.09-2.53). Non-significant increase in risk of chromosomal abnormalitties (OR 1.38, 0.73-2.59). No increase in risk of other outcomes.

(Dodds and King 2001)	Nova Scotia, Canada	retrospective cohort	49,842 births	levels of chloroform and bromodichloromethane in area of residence	NTDs, oral clefts, cardiac defects, chromosomal abnormalities	increased risk of NTDs (OR 2.5, 1.2-5.1) and decreased risk of cardiac defects (OR 0.3, 0.2-0.7) associated with >20ug/l BDCM
(Kramer et al. 1992)	Iowa	case-control	159 cases of low birth weight, 342 of prematurity, 187 of IUGR; 5 controls per case	levels of chlroform and orther THMs for municipality of residence	low birth weight, prematurity, intrauterine growth retardation	increased risk of IUGR (OR 1.8, 1.1-2.9) for chloroform >=10ug/l ; OR 1.3 (0.8-2.2) for LBW for chloroform >=10ug/l; OR 1.7 (0.9-2.9) for IUGR for dichlorobromomethane >=10 ug/l
(Savitz et al. 1995)	North-Carolina	case-control	418 cases of spontaneous abortion, 586 cases of preterm birth, 464 cases of low birth weight	levels of THM in area of residence; consumption of tap water; source of drinking water	spontaneous abortion, low birth weight, preterm birth	no association between TTHM concentration and risk of adverse pregnancy outcomes
(Gallagher et al. 1998)	Denver	retrospective cohort	1,893 births in 2 municipal water districts	TTHM levels in area of residence	low birth weight, term low birth weight, preterm delivery	increased risk of LBW (OR2.1, 1.0-4.8) and term LBW (OR 5.9, 2.0-17.0) at highest TTHM exposure level (>=61 ppb vs<=20 ppb).
(Waller et al. 1998)	California	prospective cohort	5,144 pregnancies	TTHM levels in area of residence; consumption of tap water	spontaneous abortion	inreased risk of spontaneous abortion (OR 1.8, 1.1-3.0) for women drinking >=5 glasses tap water containing >75ug/l TTHM per day.
(Jaakkola and P 2001)	Norway	cohort	137,145 births	quality of drinking water in municipality of residence: high colour and chlorination vs. low colour and no chlorination	birth weight, low birth weight, small forgestational age, preterm birth	no increased risk for exposure to water chlorination
(Tuthill et al. 1982)	Massachusetts	ecological	2,312 births	residence in community with disinfection by chlorination or by chlorine dioxide	prematurity, birth weight, fetal and neonatal mortality, birth defects	higher rates of prematurity in community iwth chlorine dioxide disinfection
(Kanitz et al. 1996)	Genoa, Italy	ecological	676 pregnancies	residence in community with disinfection by chlorine dioxide or hypochlorite compared to no disinfection	preterm birth, birth weight	no relationship between water disinfection method and birth weight or prematurity.
(Kallen and Robert 2000)	Sweden	ecological	115,777 births	residence in community with disinfection by chlorine dioxide or hypochlorite compared to no disinfection	prematurity, low birth weight, very low birth weight, perinatal death, infant death, congenital malformation subgroups	increase in prematurity (OR 1.09, 1.01-1.17) and low birth weight (OR 1.15, 1.05-1.26) in areas using sodium hypochlorite. No increase in other outcomes

(Hwang et al. 2002)	Norway	cross-sectional	285,631 births, 1993-1998	municipal level information: reference: no chlorination and low odour; exposed: chlorination and low/medium/high colour	any birth defect, NTD and hydrocephalus, cardiac, respiratory, urinary tract, oral cleft	for medium/high exposure, significantly elevated risks for any birth defect (OR 1.13, 1.01-1.25), cardiac (OR 1.37, 1.00-1.89), respiratory (OR 1.89, 1.00-3.58), urinary tract (OR 1.46, 1.00-2.13), NTD associated with high colour only (OR 2.60, 1.30-5.26)
(Shaw et al. 2003b)	California	two case-control studies 1987-1991	1) 538 NTD cases, 539 con malf controls 2) 881 cases of NTD, conotruncal heart and clefts, 431 controls	each periconceptional address linked to a water source for information on whether chlorinated quarterly THM measurements (total and four main THMs)	NTD, conotruncal heart, clefts	for TTHM as continuous measure, NTD (Study 1) OR 0.90 (0.85-0.97), NTD (Study 2) OR 1.0 (0.94-1.1), conotruncal OR 1.0 (0.93-1.0), cleft palate OR 0.96 (0.83-1.1), cleft lip OR 1.1 (0.96-1.2)
Inorganic contaminants						
(Fedrick 1970)	UK	ecological	anencepahly rates in 10 areas	area measurements of total hardness, pH, Ca, Na, Cl, and Mg	anencephaly	negative correlation with water hardness, pH, Ca, Na
(Lowe et al. 1971)	Wales	ecological	rates of central nervous system defects in 48 areas in Wales	mean total water hardness in each area	central nervous system malformations	negative correlation with water hardness
	UK	ecological	perinatal mortality from anencephalus in 58 areas in England and Wales	mean total water hardness in each area	perinantal mortality from anencephcalus	negative correlation with water hardness and Ca
(Wilson et al. 1973)	Glasgow	case-control	30 anencephalus cases, 60 controls	analysis of tap water in home of each study subject for : pH, water hardness (Ca, Mg), Pb, Cu. Zn, Fe	anencephaly	no statistically significant differences between cases and controls
(Morton et al. 1976)	Wales	ecological	rates of central nervous system defects in 48 areas in Wales	tap water analysis in 20 houss in each area for : Na, Mg, Al, K, Ca, Cr, Mn, Cu, Zn, Ba, Pb	central nervous system malformations	positive correlation with Al levels, negative correlation with Ca, Ba, Cu
(St Leger et al. 1980)	Cardiff, Wales	case-control	108 cases of neural tube defects, 108 controls	analysis of tap water in home of each study subject for : Pb, K, Mg, Na, Ca, Cu, Fe, Zn, Al, Mn	neural tube defects	no statistcially significant differences between cases and controls for most elements; lower level of Zn for cases
(Elwood 1977)	Canada	ecological	rates of infant and perinatal mortality from anencephalus in 36 Canadian sities	Mean levels of Mg, Ca, Li, Cu, Zn, pH and total hardness in water of each city	perinatal and infant mortality from anencephalus	negative correlation with magnesium levels. No correaltion with water hardness or other elements
(Elwood and Coldman 1981)	Canada	case-control	468 anencephaly deaths, 4129 live control births	water analysis in area of residence for: CA, Mg, Cu, Li, Zn, Ni, Pb, Se,	anencepahly deaths	no association with any of the 14 elements

				Hg, Cr, Si, Co, Cd, Mb		
(Zierler et al. 1988)	Massachusetts	case-control	270 cases with heart defects, 665 controls	levels of As, Ba, Cd, Cr, Pb, Hg, Se, Si, floride, nitrate, Na in community of residence	congenital heart defects; 4 subgroups of heart defects	no association between any of the 11 chemicals and risk of total heart defects. Increased risk of coarctation of aorta with increased As and decreased Se levels.
(Aschengrau et al. 1993) (see also above)	Massachusetts	case-control	1039 congenital anomaly cases, 77 stillbirths, 55 neonatal deaths, 1177 controls	quality of public drinking water in area of residence: levels of As, Ba, Cd, Cr, Pb, Hg, Se, Si, Fl, pH, hardness, Na, K, Fe, Mn, Cu, sulfate, Cl, silica, ammonia, nitrate, nitrite	congenital malformations, stillbirths, neonatal death	Statistically significant positive relationships between major malformations and Si, stillbirths and Pb, cardiac defects and Pb, central nervous system defects and K, and ear face and neck anomalies and Si. Decreased risk of major malformations with increased fluoride levels.
(Aschengrau et al. 1989)	Massachusetts	case-control	286 spontaneous abortions, 1391 livebirths	quality of public drinking water in area of residence: levels of As, Ba, Cd, Cr, Pb, Hg, Se, Si, Fl, pH, hardness, Na, K, Fe, Mn, Cu, sulfate, Cl, silica, ammonia, nitrate, nitrite	spontaneous abortion	increase in risk of spontaneous abortions with detectable levels of mercury, high levels of arsenic, potassium, silica; water hardness. Decrease in risk qith high levels of alkalinity, sulphate, and detectable levels of nitrate
(Vinceti et al. 2000)	northern Italy	ecological	353 newborns with exposed mothers -v- entire region, 1980-1988 matched to malformation register, 1128 pregnancies in single hospital identified for other outcomes	area supplied with selenium contminated drinking water	weight and length of newborn, spontaneous abortion, congenital malformation	non-significant increase in spontaneous abortion rate in exposed region. 6 exposed malformed cases -v- 4.36 expected (O/E=1.4, 0.6-2.9), Down Syndrome, two club foot, one transposition of great vessels, one horseshoe kidney. Small numbers preclude further analysis. Spontaneous abortion RR=1.73 (0.62-4.80). No effect on weight or length.
(Golding et al. 1991)	north Cornwall	ecological	92 pregnancies in exposed area during incident; 68 pregnancies in area before incident; 193 pregnancies in control area	area with aluminium sulphate contaminated drinking water	fetal and perinatal death, birth weight, preterm birth, conegntial anomalies	increased rate of taliped in exposed fetuses. No increase in other outcomes

(Dorsch et al. 1984)	Australia	case-control	258 cases of congenital anomaly, 258 controls	analysis of nitrate levels in water supply of case and control households; consumption of groundwater compared to rain water	congenital malformation	increased risk of total malformations for consumption of groundwater and for high levels of nitrate in drinking water. Increased risks for CNS and musculoskeleteal defects for consumption of groundwater
(Arbuckle et al. 1988)	Canada	case-control	130 cases of central nervous system defects	analysis of nitrate levels in water supply of case and control households; consumption of private vs public water sources	central nervous system defects	non-statistcailly significant increase in risk of CNS defects with increased nitrate levels, only for private well water sources
(Erickson 1980)	51 US cities	ecological	636,765 births	residence in city with water fluoridation	Down Syndrome	no statistically signiifcant difference in Down Syndrome rates between fluoridated and non-fluoridated cities, taking account of maternal age
(Needleman et al. 1974)	Massachusetts	ecological	2,469 Down Syndrome cases	residence in community with water fluoridation	Down Syndrome	no difference in Down Syndrome rates between fluoridated and non-fluoridated communities
(Croen et al. 2001)	California	population-based case-control	538 cases, 539 non-malformed controls	Source of water supply linked to periconceptional residential address. Nitrate values determined from water sampling at source. Maternal Nitrate exposure determined from face-to-face interview and questionnaire on beverage consumption and diet	Neural tube defects	Exposure to nitrate in drinking groundwater above the maximum contaminant level of 45 mg/litre was associated with increased risk for anencephaly (OR 4.0, 1.0-15.4) but not spina bifida. No increased risk of anencephaly was reported for mixed water drinkers with comparable high levels of nitrate. Dietary nitrate exposure was not associated with increased risk for neural tube defects.

Abbreviations: Mb: Molybdenum, Li: Lithium, Ni: Nickle, Co: Cobalt

Table 10 Disinfection by-products - Summary

	Author (year)	Exposure measure	Relative Risk	Dose-reponse
spontaneous abortion				
	(Savitz et al. 1995)	TTHM > 81 ug/l	1.2 (0.6-2.4)	yes
	(Waller et al. 1998)	TTHM > 75 ug/l + >=5 glasses tap water/day	1.8 (1.1-3.0)	N/A
stillbirth				
	(Aschengrau et al. 1993)	chlorinated surface water	2.6 (0.9-7.5)	N/A
	(Dodds et al. 1999)	TTHM > 100ug/l	1.7 (1.1-2.5)	yes
pre-term birth				
	(Tuthill et al. 1982)	chlorine dioxide	1.3 (p<0.05)	N/A
	(Kramer et al. 1992)	specific THMs	1.1 (0.7-1.6)	N/A
	(Savitz et al. 1995)	TTHM > 83 ug/l	0.9 (0.6-1.5)	no
	(Bove et al. 1995)	TTHM > 80 ug/l	1.0 (0.9-1.1)	yes
	(Kanitz et al. 1996)	chlorine dioxide	1.8 (0.7-4.7)	N/A
		sodium hypochlorite	1.1 (0.3-3.7)	N/A
	(Gallagher et al. 1998)	TTHM > 60 ug/l	1.0 (0.3-2.8)	no
	(Dodds et al. 1999)	TTHM > 100ug/l	1.0 (0.9-1.1)	no
	(Kallen and Robert 2000)	chlorine dioxide	1.0 (0.9-1.0)	N/A
		sodium hypochlorite	1.1 (1.0-1.2)	N/A
	(Jaakkola and P 2001)	chloination + high colour	0.9 (0.8-1.0)	N/A
low birth weight				
	(Kramer et al. 1992)	chloroform > 10 ug/l	1.3 (0.8-2.2)	N/A
		other specific THMs	no increase	N/A
	(Savitz et al. 1995)	TTHM > 83 ug/l	1.3 (0.8-2.1)	no
	(Bove et al. 1995)	TTHM > 100 ug/l	birth weight decrease of 70g (41g-100g)	yes
	(Kanitz et al. 1996)	chlorine dioxide	5.9 (0.8-14.9)	N/A
		sodium hypochlorite	6.0 (0.6-12.6)	N/A
		both	6.6 (0.9-14.6)	N/A
	(Gallagher et al. 1998)	TTHM > 60 ug/l	2.1 (1.0-4.8)	N/A

	(Dodds et al. 1999)	TTHM > 100ug/l	1.0 (0.9-1.2)	no
	(Kallen and Robert 2000)	chlorine dioxide	0.9 (0.8-1.0)	N/A
		sodium hypochlorite	1.2 (1.1-1.3)	N/A
	(Jaakkola and P 2001)	chlorination + high colour	1.0 (0.9-1.1)	N/A
growth retardation				
	(Kramer et al. 1992)	chloroform > 10ug/l	1.8 (1.1-2.9)	N/A
		dichlorobromomethane > 10ug/l	1.7 (0.9-2.9)	N/A
		other specific THMs	no increase	no
	(Bove et al. 1995)	TTHM > 100 ug/l	1.5 (1.2-1.9) *	yes
	(Gallagher et al. 1998)	TTHM > 60 ug/l	5.9 (2.0-17.0)	yes
	(Dodds et al. 1999)	TTHM > 100ug/l	1.1 (1-1.2)	no
	(Kallen and Robert 2000)	chlorine dioxide	1.0 (0.8-1.1)	N/A
		sodium hypochlorite	1.1 (1.0-1.2)	N/A
	(Jaakkola and P 2001)	chlorination + high colour	1.0 (0.9-1.1)	N/A
all anomalies				
	(Aschengrau et al. 1993)	chlorinated surface water	1.5 (0.7-2.1)	N/A
	(Bove et al. 1995)	TTHM > 80 ug/l	1.6 (1.2-2.0)*	yes
	(Magnus et al. 1999)	chlorination + high colour	1.1 (1.0-1.3)	N/A
	(Hwang et al. 2002)	chlorination + high colour	1.2 (1.0-1.4)	N/A
neural tube defects				
	(Bove et al. 1995)	TTHM > 80 ug/l	3.0 (1.3-6.6)*	yes
	(Dodds et al. 1999)	TTHM > 100ug/l	1.2 (0.7-2.1)	no
	(Klotz and Pyrch 1999)	TTHM > 40 ppb	1.6 (0.9-2.7)	no
		TTHM > 80 ppb	1.6 (0.7-3.6)	no
	(Magnus et al. 1999)	chlorination + high colour	1.3 (0.6-2.6)	N/A
	(Dodds and King 2001)	bromodichloromethane > 20ug/l	2.5 (1.2-5.1)	N/A
		chloroform >100ug/l	1.2 (0.7-2.3)	N/A
	(Shaw et al. 2003b)	TTHM continual per 10 ppb (study 1)	0.9 (0.85-0.97)	N/A
		TTHM continual per 10 ppb (study 2)	1.0 (0.94-1.1)	N/A
	(Hwang et al. 2002)	chlorination + high colour	Increase for colour but not chlorination	N/A
oral cleft defects				
	(Bove et al. 1995)	TTHM > 100 ug/l	3.2 (1.2-7.3)*	no
	(Dodds et al. 1999)	TTHM > 100ug/l	1.0 (0.6-1.9)	no

	(Magnus et al. 1999)	chlorination + high colour	0.9 (0.6-1.4)	N/A
	(Dodds and King 2001)	bromodichloromethane > 20ug/l	0.6 (0.2-1.9)	N/A
		chloroform >100ug/l	1.5 (0.8-2.8)	N/A
	(Shaw et al. 2003b)	cleft lip per 10ppb TTHM	1.1 (0.96-1.2)	N/A
		cleft palate per 10ppb TTHM	0.96 (0.83-1.1)	N/A
	(Hwang et al. 2002)	chlorination + high colour	0.9 (0.5-1.6)	N/A
cardiac defects				
	(Shaw et al. 1991)	chlorinated tap water	1.0 (0.64-1.6)	N/A
	(Bove et al. 1995)	TTHM > 80 ug/l	1.8 (1.0-3.3)*	no
	(Dodds et al. 1999)	TTHM > 100ug/l	0.8 (0.6-1.0)	no
	(Magnus et al. 1999)	chlorination + high colour	1.0 (0.8-1.5)	N/A
	(Dodds and King 2001)	bromodichloromethane > 20ug/l	0.3 (0.2-0.7)	N/A
		chloroform >100ug/l	0.7 (0.5-1.0)	N/A
	(Shaw et al. 2003b)	conotruncal heart per 10ppb TTHM	1.0 (0.93-1.10)	N/A
	(Hwang et al. 2002)	chlorination + medium/high colour	1.4 (1.0-1.9)	no
respiratory system				
	(Hwang et al. 2002)	chlorination + medium/high colour	1.9 (1.0-3.6)	no
urinary tract				
	(Hwang et al. 2002)	chlorination + medium/high colour	1.5 (1.0-2.1)	no
chromosomal defects				
	(Dodds et al. 1999)	TTHM>100ug/l	1.4 (0.7-2.6)	N/A
	(Dodds and King 2001)	bromodichloromethane > 20ug/l	0.9 (0.4-2.3)	N/A
		chloroform >100ug/l	1.4 (0.8-2.8)	N/A

* 90% CI

Table 11: HAZARDOUS WASTE SITES and adverse pregnancy outcome

Reference	Setting	Study Type	Study Subjects	Exposure Measure	Adverse pregnancy outcomes studied	Main findings
Single Site Studies						
(Vianna and Polan 1984)	Love Canal, NY.	Retrospective follow-up	174 births near site; 443 live births in rest of Love Canal area; all births in New York State	Residence in Love Canal area	Low birth weight (LBW)	Higher percentage of LBW in exposed area; excess in period of active dumping.
(Goldman et al. 1985)	Love Canal, NY.	Retrospective follow-up	239 exposed children, 707 unexposed controls	Residence in Love Canal area during pregnancy	LBW, birth defects	Three-fold risk of LBW (homeowners only); increased risk for birth defects (homeowners and renters).
(Berry and Bove 1997)	Lipari Landfill, New Jersey	Retrospective follow-up	2,092 births in proximate area; 6,840 births in control area	Residence at birth in area closest to landfill	Average birth weight, LBW, preterm birth.	Significantly lower average birth weight, higher proportion of LBW and prematurity during the time of heaviest pollution.
(Kharrazi et al. 1997)	BKK Landfill, California	Retrospective follow-up	25,216 births	Residence in census tract, proximate zone, and frequency of odour complaints.	LBW, fetal mortality, infant mortality, prematurity	No difference over entire study period; moderate decrease in birth weight in high odour complaint zone in period of highest exposure.
(Goldberg et al. 1995b)	Miron Quarry Landfill, Quebec, Canada	Case-control	7,977 LBW cases and 7,856 control births	Residence in areas adjacent to landfill and level of estimated exposure to biogas	LBW, very-LBW, preterm birth, small for gestational age	Excess in LBW and small for gestational age births, no excess in very-LBW or preterm birth.
(Budnick et al. 1984)	Drake, Clinton County, PA	Geographical comparison	cancer deaths and birth defects compared to Pennsylvania and US.	Residence in Clinton and 3 other counties surrounding waste site	Bladder cancer and cancers of other organ sites; birth defects.	Increase in bladder cancer deaths in Clinton, increase in number of other cancers in Clinton and 3 surrounding counties. No excess in birth defects.

(Fielder et al. 2000)	Nant-y-Gwyddon, Wales	ecological	rates of low birth weight and congenital malformations	residence in 5 wards near landfill compared to 22 wards further away	congenital malformations; low birth weight' spontaneous abortion	increased risk of congenital malformation both before and after opening of site. Confirmed cluster of gastroschisis. No increase in other outcomes
(Fielder et al. 2001)	Merthyr Tydfil, Wales	ecological	comparison of routinely collected population-based health data	residence in 3 wards near landfill compared to 26 other wards in region	LBW, spontaneous abortion, congenital malformations	Increased risk of congenital malformation after site opened. No increase in LBW babies.
(Dodds and Seviour 2001)	Nova Scotia	Geographical comparison	4,128 births in exposed area, 11,620 births in unexposed area. 109,437 births in remaining areas of Nova Scotia	Maternal residence at time of delivery	Major congenital anomalies	Increased risk for all major anomalies in exposed area (25%) compared to whole region. Significant increase of Neural tube defects. Non-significant increase in cardiovascular, genito-urinary, ENT, and chromosomal anomalies.
Multi-Site Studies						
(Shaw et al. 1992)	300 sites in 1,072 census tracts in California	Geographical comparison	5,046 birth defects cases and 28,085 control births. 190,4000 births for birthweight analysis	Residence in census tract with site and potential for human exposure	Birth defects, LBW	1.5-fold increased in risk of heart defects. Other malformations and birth weight not associated.
(Sosniak et al. 1994)	1281 NPL sites in US	Case-control	17,407 births	Residence within 1 mile	Birth weight, birth defects, foetal deaths, infant deaths	No association between adverse pregnancy outcomes and living near a NPL site.
(Geschwind et al. 1992)	590 waste sites in New York State	Case-control	9,313 live births with birth defects and 17,802 normal control births	Residence within 1 mile and hazard score of site	Birth defects	Increased risk for all malformations (12%), integument system, nervous system, musculoskeletal. Indications for dose response relation with exposure risk

(Marshall et al. 1995)	643 waste sites in New York State	Case-control	473 cases with central nervous system defects; 3,305 musculo-skeletal cases; 12,436 control births	Ratings of exposure probability within 1 mile of each site.	Birth defects of central nervous system and musculoskeletal defects	No association between two types of defects and proximity to waste sites.
(Croen et al. 1997)	105 NPL and 659 non-NPL sites in California	Case-control	507 NTD cases and 517 controls; 210 heart defects, 439 oral clefts, and 455 controls.	Census tracts: no site, non-NPL site, NPL site. residence within 1 and within 1/4 mile from site	Birth defects: NTD, heart defects and oral clefts	No increased risks relating to residence in census tract with site. Small, non-significant increase in risk of NTD and heart defects for living within 1/4 mile.
(Dolk et al. 1998b)	21 hazardous waste landfill sites in 5 European countries	Case-control	1089 cases, 2366 controls	residence within 3 km of a landfill	non-chromosomal congenital malformations	OR 1.33 (1.11-1.59) for all malformations combined. Significantly increased risks of neural tube defects, malformations of cardiac septa, and malformations of great areteries and veins
(Vrijheid et al. 2002)	23 hazardous waste landfills sites in 5 European countries	Case-control	245 cases, 2412 controls	residence within 3 km of a landfill	chromosomal congenital malformations	OR 1.41 (1.00-1.99) for chromosomal anomalies
(Elliott et al. 2001)	over 9,000 landfill sites in Great Britain	Geographical comparison	over 8 million births	residence within 2 km of a landfill	congenital malformations, low birth weight, very low birth weight	small, but significant, increases in risk of all malformations, neural tube defects, hypospadias, abdominal wall defects, LBW and very LBW
(Kuehl and Loffredo 2003)	Maryland, District of Columbia, Northern Virginia	Case-control	36 cases, 3495 controls	post-hoc identification of hazardous waste sites near clusters	L-transposition of great arteries	identified two spatial clusters and found hazardous waste sites in vicinity

Abbreviations: LBW, low birthweight; NTD, neural tube defects; NPL, national Priority List sites

Table 12: OTHER INDUSTRIAL POINT SOURCES and adverse pregnancy outcome

Reference	Setting	Study Type	Study Subjects	Exposure Measure	Adverse pregnancy outcomes studied	Main Findings
Smelters						
(Nordstrom et al. 1978b)	smelter in Sweden	ecological	pregnancies in 4 areas near smelter and in employees	residence in area near smelter or work in smelter compared to residence in area further away	mean birth weight	decreased birth weight in offspring of employees and in two areas closest to the smelter
(Nordstrom et al. 1978a)	smelter in Sweden	ecological	pregnancies in 4 areas near smelter	residence in area near smelter compared to residence in area further away	spontaneous abortion	highest frequency of spontaneous abortion in area closest to smelter
(Nordstrom et al. 1979a)	smelter in Sweden	cohort	pregnancies amongst smetler employees	work at smelter compared to control population; employment before, during, after pregnancy	mean birth weight and spontaneous abortion	decrease in birth weight in employees; highest frequency of spontaneous abortion if employed during pregnancy
(Nordstrom et al. 1979b)	smelter in Sweden	ecological	pregnancies in 6 areas near smelter	residence in area near smelter compared to residence in area further away; work in smelter during pregnancy	congenital malformations	no difference between areas. Higher rate in employees who worked during pregnancy
(Wulff et al. 1995)	smelter in Sweden	cohort	pregnancies near smelter	work in smelter or residence near smelter compared to residence in reference area	birth weight, perinatal death	no difference in birthweight or perinatal death
(Wulff et al. 1996)	smelter in Sweden	cohort	2,724 children in exposed area; 15,191 in control area	residence in area <20 km from smelter	congenital malformations	non-significant increase in exposed area: OR 1.15 (95%CI 0.95-1.39)
(Saric 1984)	lead smelter in Croatia	ecological	births in smelter community and control community	residence in community where smelter is located	spontaneous abortion, twinning rate	spontaneous abortion rate higher in smelter community compared to control community. No difference in twinning rate

(McMichael et al. 1986)	pregnancies in Port-Pieri smelter community, Australia	cohort	831 pregnant women in smelter and control community	maternal blood lead levels measured at 14-20 weeks gestation, 32 weeks, and at delivery. Cord blood lead levels.	spontaneous abortion, pre-term delivery, late fetal death, LBW, congenital malformation	increased risk of pre-term birth with increased lead levels. No association for congenital malformation, spontaneous abortion, or stillbirth
(Murphy et al. 1990)	lead smelter in Kosovo	cohort	639 pregnant women in smelter and control community	residence in smelter town compared to residence in comparison town	spontaneous abortion	no difference in spontaneous abortion rate
(Factor-Litvak et al. 1991)	lead smelter in Kosovo	cohort	901 pregnant women in smelter and control community	residence in smelter town compared to residence in comparison town; blood lead levels	mean birthweight, mean lenght of gestation, preterm delivery	no difference between exposed and unexposed town; no association with blood lead level
(Loiacono et al. 1992)	lead smelter in Kosovo	cohort	161 pregnant women in smelter and control community	placental samples of cadmium	mean birth weight	no association between cadmium level and mean birth weight
(Philion et al. 1997)	lead smelter in Canada	ecological	births in smelter city and control city	residence in smelter city	intrauterine growth retardation	no significant difference
Incinerators						
(Scottish Home and Health Department 1988)	incinerators in Forth Valley, Scotland		births in 6 health board areas in Scotland	residence in area where incinerator is located	microphthalmia	no increase in area where incinerator is located but incomplete case ascertainment likely
(Jansson and Voog 1989)	incinerators in Sweden	ecological	births in boroughs with incinerator	residence in borough with incinerator before and after start of incinerator	cleft lip and palate	no increase since start of incineration
(ten Tusscher et al. 2000)	incinerators in Amsterdam, The Netherlands	ecological	births in two maternity clinics in Amsterdam	location of the maternity clinic near the incinerator compared to elsewhere in city	cleft lip and palate	increased rate in maternity clinic located near incinerator
Other industrial point sources						
(Dolgner et al. 1983)	cement factory in Germany	ecological	297 births	residence in exposed town	congenital malformation	malformation rate higher than for entire state

(Kallen and Thorbert 1985)	chemical factory in Sweden	ecological	449 in 3 parishes near factory	residence in parish near factory compared to rates in whole county	spontaneous abortion, congenital malformaiton, perinatal death	no increase in spontanesou aborion or congenital malformation. Increase in preinatal deaths among twins
(Axelsson and Molin 1988)	Petrochemical industries in Sweden	cohort	2,673 pregnancies	residence near plant comapred to residence in conrtol community	spontaneous abortion	non-significant increase in spontaneous abortion rate in exposed community. Signifincat increase in risk for women working in the industries
(Bell et al. 1991)	Kodak plant in New York State	ecological	91,302 births	census tract of residence classified into high, moderate, low, no exposure to methylene chloride	mean birth weight, low birth weight	very small, non-significant reduction of birth weight in high exposure areas. No difference in low birthweight
(Czeizel et al. 1999)	acrylonitrile factory in Hungary	ecological	46,326 births in study region	residence in region <25km from acrylonitrile factory compared to national baseline rate	congenital malformation	no increase in risk of total malformations in study region. Increase only in skeletal anomalies, decrease in risk of 14 anomalies.
(Bhopal et al. 1999)	steel and petrochemical industries in UK	ecological	births in 27 neighbourhoods	residence in areas near compared to further away from industry	low birth weight, stillbirth, sex ratio, congenital malformation	no trends of increasing risk with decreasing distance to industry
(Oliveira et al. 2002)	petrochemical plant in Brazil, 1983-1998	case-control	160 cases, 160 controls.	distance of maternal residence from plant	major congenital malformations, LBW, stillborns	No increase in risk of congenital anomalies reported (OR=0.37, 0.07-1.72). Increase in LBW babies living near plant (OR 1.5, 0.9-2.5)
(Dummer et al. 2003)	Cumbria, UK	retrospective cohort	287,993 births	maternal residence grid-referenced, exposure measure computed using proximity to sites	stillbirth, neonatal death, lethal congenital anomaly	No significantly increased risks for stillbirth or neonatal death associated with proximity to industrial sites. Increased risk of death from congenital heart defects in one time period which is likely to be due to chance.
Residence in polluted areas						
(Hansteen et al. 1998)	Norway	cohort	3,331 livebirths	residence in indutrial area vs residence in other urban or rural area	mean birth weight. Length and head circumference	significantly lower mean birth weight, length and head circumference in industrial areas compared to urban and rural

(Castilla et al. 2000)	Argentina	ecological	614,796 births in 21 counties	classification of counties into 80 industrial activities	congenital malformations	significant associations found between textile industry and anencephaly and manufacture of engines and microcephaly
(Monteleone Neto and Castilla 1994)	Cubatao, Brazil	ecological	10,378 births from Cubatao, 869,750 births in reference population	residence in polluted town of Cubatao	congenital malformations	significant increase in prevalence of polydactyly, decrease in congenital hip dislocation, multiple congenital anomalies, etiologic syndromes, pathogenic syndromes

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