

Solvents: summary of epidemiologic evidence

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1. Overall summary

Solvents include aliphatic hydrocarbons (mineral spirits, varnish, kerosene), aromatic hydrocarbons (benzene, toluene, xylene), halogenated hydrocarbons (carbon tetrachloride, trichloroethylene), aliphatic alcohols (methanol, ethanol), glycols (ethylene glycol) and glycol ethers (methoxyethanol) (McMartin et al 1998). This section summarizes epidemiologic evidence cited in the tables below and will be updated as new evidence becomes available. I would appreciate feedback on any errors or omissions. don.wigle@sympatico.ca

Health effect	Level of evidence ^a	Comments
Early fetal deaths (spontaneous abortions)	Maternal exposure Limited (? Sufficient)	<p>A cohort study in Montreal found a weak association between early fetal deaths and maternal 1st trimester occupational exposure to solvents (McDonald et al 1988). A Finnish case-control study nested within a cohort of men monitored for solvent exposure found no association between early fetal deaths and maternal 1st trimester occupational exposure to organic solvents (Taskinen et al 1989). Another Finnish case-control study, nested within a cohort of women employed as dry cleaning or laundry workers, found associations between early fetal deaths and frequent 1st trimester maternal occupational use of tetrachloroethylene (but not other solvents) and with frequent maternal 1st trimester alcohol intake (Kyrronen et al 1989). Similarly, a nested case-control study within a cohort of dry cleaning and laundry workers in Denmark, Sweden and Finland found an association between early fetal deaths and maternal 1st trimester occupational exposure to tetrachloroethylene (Olsen et al 1990). However, the Swedish component of this study found no association between early fetal deaths and maternal 1st trimester occupational exposure to tetrachloroethylene (Ahlborg et al 1990). A case-control study in California found an association between early fetal deaths and maternal 1st trimester occupational exposure to aliphatic solvents, paint thinners, trichloroethylene and tetrachloroethylene (Windham et al 1991). A nested case-control study among female laboratory workers in Finland found an association between early fetal deaths and 1st trimester maternal occupational solvent exposure; the association held for aromatic and halogenated but not aliphatic solvents (Taskinen et al 1994). A national cohort study of women employed in semiconductor manufacturing in the USA found an association between early fetal deaths and work in a fabrication room in the historic but not in the prospective cohort; there was also an exposure-risk relationship between early fetal death and maternal 1st trimester exposure to any photoresist chemical (glycol ethers, butyl acetate, xylene) (Schenker et al 1995, Swan et al 1995). A retrospective cohort study of US semiconductor workers found an association between early fetal death and maternal occupational exposure to ethylene glycol ethers during the month of conception (Correa et al 1996). A review of epidemiologic studies of early fetal death and occupational exposures concluded that there was limited evidence for an association between early fetal deaths and maternal occupational exposure to ethylene glycol ethers (Paul 1997). A small Italian case-control study in a shoe manufacturing region found an association between early fetal death and maternal 1st trimester occupational solvent exposure (Agnesi et al 1997). A UK retrospective cohort study of women working in dry cleaning and laundry found an association between early fetal death and maternal occupation as a dry cleaning operator during early pregnancy, an indicator of tetrachloroethylene exposure (Doyle et al 1997). A meta-analysis of five epidemiologic studies found a borderline association between early fetal deaths and maternal organic solvent exposure during early pregnancy (McMartin et al 1998). A very small cohort study in Canada found no association between early fetal death and maternal 1st trimester occupational solvent exposure (Khattak et al 1999). A nested case-control study among a</p>

	Paternal exposure (Inadequate)	<p>cohort of female employees in the UK semiconductor manufacturing industry found no association between early fetal death and maternal 1st trimester employment or exposure to ethylene glycol ethers (Elliott et al 1999). A cohort study of Swedish female employees in biomedical research laboratories found an association (of borderline statistical significance) between early fetal deaths and occupational chloroform exposure (Wennborg et al 2000).</p> <p>A retrospective cohort study of US workers found no association between fetal death (at any gestation length) and paternal occupations likely exposed to solvents (Daniell and Vaughan 1988). A Finnish case-control study nested within a cohort of men monitored for solvent exposure found an association between early fetal deaths and paternal preconceptual occupational exposure to organic solvents and with specific occupations including painting; when analyzed by type of solvent, early fetal deaths were associated with paternal preconceptual occupational exposure to toluene and xylene (the latter was not statistically significant) (Taskinen et al 1989). A Norwegian cohort study of male printers found an association between early fetal deaths and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A retrospective cohort study of US semiconductor workers found no association between early fetal death and paternal occupational exposure to ethylene glycol ethers during the month of conception (Correa et al 1996). A cohort study of men employed as car mechanics, on offshore oil rigs or as carpenters found no association between early fetal deaths and likely exposure to solvents or other oil products (Bull et al 1999).</p>
Late fetal deaths (stillbirths)	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure (Inadequate)</p>	<p>A cohort study in Montreal found an association between late fetal deaths and maternal 1st trimester occupational exposure to solvents (McDonald et al 1988). A large population-based US case-control study found a borderline association between late fetal deaths and maternal occupational benzene exposure during the year before delivery (Savitz et al 1989). A case-control study in the region of a petrochemical plant in Brazil found no association between late fetal deaths and maternal residential proximity to the plant (Oliveira et al 2002).</p> <p>A retrospective cohort study of US workers found no association between fetal death (at any gestation length) and paternal occupations likely exposed to solvents (Daniell and Vaughan 1988). A large population-based US case-control study found no association between late fetal deaths and paternal occupational benzene exposure during the year before delivery (Savitz et al 1989). A Norwegian cohort study of male printers found no association between late fetal deaths and paternal occupational exposure to solvents with or without concurrent lead exposure (Kristensen et al 1993).</p>
Low birth weight (not adjusted for gestation length)	Maternal exposure (Inadequate)	<p>A hospital-based case-control study in California found no association between low birth weight and maternal 1st trimester occupational solvent exposure (Windham et al 1991). A retrospective cohort study in Wisconsin found no association between low birth weight and maternal occupations likely exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association of borderline statistical significance between low birth weight and self-reported maternal 1st trimester occupational exposure to organic solvents (Khattak et al 1999). A cohort study in Brazil found a marginally increased risk of low birth weight for mothers living within 10 kilometres of a petrochemical plant (Oliveira et al 2002).</p>
Low birth weight (at term or adjusted for gestation length)	Maternal exposure (Limited)	<p>A retrospective cohort study in New Jersey found an association between term low birth weight and drinking water carbon tetrachloride levels in the public water system serving the maternal residence (Bove et al 1995). A retrospective cohort study in Sweden found a borderline inverse association between term birth weight and maternal occupational exposure before or during pregnancy to diethylether but not other solvents (Wennborg et al</p>

	Paternal exposure (Inadequate)	<p>2000). A retrospective cohort study in China found an inverse association between birth weight (adjusted for gestation length) and maternal occupational organic solvent exposure (Ha et al 2002). A large retrospective cohort study in Singapore found no association between term low birth weight and maternal occupations likely exposed to solvents (Chia et al 2004).</p> <p>A retrospective cohort study found borderline associations between term low birth weight and paternal employment as auto body workers or painters (Daniell and Vaughan 1988). A Norwegian cohort study of men in printing industries found no association between low birth weight adjusted for gestation length and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993). A retrospective cohort study in China found no association between birth weight (adjusted for gestation length) and paternal occupational organic solvent exposure (Ha et al 2002). A large retrospective cohort study in Singapore found weak associations between term low birth weight and paternal occupations likely exposed to solvents (Chia et al 2004).</p>
Intrauterine growth retardation	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure (Inadequate)</p>	<p>A large population-based case-control study in the USA found no association between intrauterine growth retardation and maternal occupational benzene exposure (Savitz et al 1989). A hospital-based case-control study in California found no association between intrauterine growth retardation and maternal 1st trimester occupational solvent exposure (Windham et al 1991). A retrospective cohort study in New Jersey found an association between small for gestational age infants and drinking water carbon tetrachloride levels in the public water system serving the maternal residence (Bove et al 1995). A German birth cohort study found no association between small for gestational age infants and maternal occupational exposure to carbon tetrachloride or a broad category of organic solvents (Seidler et al 1999). A retrospective cohort study in Sweden found no association between term birth weight and maternal occupational exposure before or during pregnancy to solvents (Wennborg et al 2000). A literature review noted that two of five epidemiologic studies found associations between small for gestational age infants and maternal residence in a region served by trichloroethylene-contaminated drinking water (Bove et al 2002).</p> <p>A large population-based case-control study in the USA found no association between intrauterine growth retardation and paternal occupational benzene exposure (Savitz et al 1989). A Norwegian cohort study of men in printing industries found no association between small for gestational age infants and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993).</p>
Preterm birth	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure (Inadequate)</p>	<p>A retrospective cohort study found borderline associations between preterm birth and paternal employment as auto body workers or painters (Daniell and Vaughan 1988). A large population-based case-control study in the USA found no association between preterm birth and maternal or paternal occupational benzene exposure (Savitz et al 1989). A retrospective cohort study in Wisconsin found no association between preterm birth and maternal occupations likely exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association of borderline statistical significance between preterm birth and self-reported maternal 1st trimester occupational exposure to organic solvents (Khattak et al 1999). A literature review noted that none of five epidemiologic studies found an association between preterm birth and maternal residence in regions served by trichloroethylene-contaminated drinking water (Bove et al 2002).</p> <p>A large population-based case-control study in the USA found no association between preterm birth and maternal or paternal occupational benzene exposure (Savitz et al 1989). A Norwegian cohort study of men in printing</p>

		industries found associations between early preterm birth (gestation weeks 16-27) and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993).
Total birth defects	Maternal exposure Limited Paternal exposure Inadequate	<p>A hospital-based birth cohort study found no association between birth defects and maternal occupational solvent exposure (McDonald et al 1988b). A small case-control study within a cohort of Finnish women employed as dry cleaning or laundry workers found an association (imprecise odds ratio) between birth defects and frequent maternal occupational use of solvents other than tetrachloroethylene (Kyrönen et al 1989). A case-control study in Atlanta found an association between total birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found an association between birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). A meta-analysis of five epidemiologic studies found an overall association between major birth defects and maternal organic solvent exposure (McMartin et al 1998). A small retrospective cohort study in Wisconsin found no association between birth defects and maternal occupations likely to be exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association between major birth defects and maternal 1st trimester occupational organic solvent exposure (Khattak et al 1999). A case-control study in Brazil found a marginally <i>decreased</i> risk of birth defects among mothers living closest to a petrochemical plant (Oliveira et al 2002). A retrospective cohort study in Singapore found no association between non-chromosomal single birth defects and maternal occupation as cleaners; there was a borderline association with maternal occupation as plant and machine operators/assemblers (Chia et al 2003).</p> <p>A Norwegian cohort study of male workers in printing industries found no association between total birth defects and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A review of ten epidemiologic literature of birth defects and paternal occupation published during 1989-1999 concluded that methodologic limitations and inconsistent findings precluded definitive statements on observed associations; however, paternal occupations most consistently associated with birth defects included janitors, painters, printers and other occupations exposed to solvents (Chia and Shi 2002). A retrospective cohort study in Singapore found that non-chromosomal single birth defects were associated with paternal occupations potentially exposed to solvents including plant and machine operators/assemblers and cleaners (Chia et al 2003).</p>
Multiple birth defects	Maternal exposure (Inadequate)	A hospital-based case-control study in France found a non-significant association between multiple birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A hospital-based case-control study in Spain found a borderline association between multiple birth defects and maternal occupation as assembler in the leather industry, a proxy for organic solvent exposure (Garcia and Fletcher 1998).
Central nervous system defects	Maternal exposure Limited	A hospital-based case-control study in France found no association between CNS birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between neural tube birth defects and maternal occupation in nursing (Matte et al 1993). A retrospective cohort study in New Jersey found no association between CNS defects and trichloroethylene levels in public water supplies serving the 1 st trimester maternal residence (Bove et al 1995). A case-control study in the Netherlands found no association between spina bifida and maternal occupational exposure to alcohol or other organic solvents (Blatter et al 1996). A large population-based case-control study in New York State found no association between CNS birth defects and likelihood of maternal exposure to solvents

Cardiac defects	<p>Maternal exposure Limited</p> <p>Paternal exposure (Inadequate)</p>	<p>A population-based case-control study in Arizona found an association between cardiac birth defects and maternal 1st trimester residence in a region served by a water supply contaminated by trichloroethylene, dichloroethylene and chromium (Goldberg et al 1990). A small case-control study within the Baltimore-Washington Infant Study found associations between total anomalous pulmonary venous return and maternal periconceptual occupational exposure to solvents (non-significant, based on only 3 exposed case mothers) and to paint or paint stripping (Correa-Villasenor et al 1991). A large population-based case-control study in Finland found borderline or significant associations between several types of cardiac birth defects and maternal occupational exposure to chemicals including organic solvents and dyes, lacquers or paints (Tikkanen and Heinonen 1992a, 1992b, 1992c). A hospital-based case-control study in France found no association between cardiac birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between cardiac birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found an association between cardiac defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). The Baltimore-Washington Infant Study found associations between several types of cardiac defects and self-reported maternal exposure to solvents, degreasing agents or paint (Wilson et al 1998). A review noted that three epidemiologic studies had found associations between cardiovascular birth defects and maternal 1st trimester occupations likely exposed to lacquers, paints or organic solvents (Shi and Chia 2001). The Baltimore-Washington Infant Study found associations between cardiac birth defects and 1st trimester maternal exposure to miscellaneous solvents (paint thinners, photographic chemicals, glue, varnish removers) (Wollins et al 2001). A review of five epidemiologic studies of pregnancy outcome and drinking water solvent levels noted that one study found an association between cardiac defects and trichloroethylene-contaminated drinking water (Bove et al 2002). A large case-control study in California found a borderline association between certain cardiac defects and maternal prenatal occupational exposure to aliphatic hydrocarbons; this association was stronger among infants with the GSTM1 polymorphism (Shaw et al 2003). A population-based case-control study within the Baltimore-Washington Infant Study found an association between certain cardiac defects and maternal residential proximity to hazardous waste disposal sites known to release solvents including trichloroethene, tetrachloroethene and 1,2-dichloroethene as well as vinyl chloride (Kuehl and Loffredo 2003).</p> <p>A Norwegian cohort study of male workers in printing industries found no association between cardiac defects and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). The Baltimore-Washington Infant Study found associations between certain cardiac birth defects and paternal occupational exposure to paint strippers (Correa-Villasenor et al 1993). A case-control study in Texas found an association between certain cardiac defects and paternal occupational exposure to laboratory chemicals (Sakamoto et al 2004).</p>
Urinary tract defects	Maternal exposure (Inadequate)	<p>A hospital-based case-control study in France found no association between urinary tract defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between urinary tract birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found no association between genitourinary birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997).</p>
Reproductive tract defects	Paternal exposure (Inadequate)	<p>A Norwegian cohort study of male workers in printing industries found no association between hypospadias or cryptorchidism and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A case-control study in Atlanta found an association between genital tract birth defects and maternal occupation in nursing</p>

		(Matte et al 1993). A multicentre European case-control study found no association between genitourinary birth defects and maternal 1 st trimester occupational exposure to glycol ethers (Cordier et al 1997).
Musculoskeletal defects	Maternal exposure (Inadequate) Paternal exposure (Inadequate)	A large population-based case-control study in New York State found no association between musculoskeletal birth defects and likelihood of maternal exposure to solvents from hazardous waste sites by routes other than drinking water or maternal residential proximity to industrial facilities emitting solvents (Marshall et al 1997). A multicentre European case-control study found a borderline association between musculoskeletal birth defects and maternal 1 st trimester occupational exposure to glycol ethers (Cordier et al 1997). A Norwegian cohort study of male workers in printing industries found no association between limb defects other than clubfoot and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993).
Chromosomal abnormalities	Maternal exposure (Inadequate)	A hospital-based case-control study in France found no association between chromosomal abnormalities and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992).
Total childhood cancers	Maternal exposure (Inadequate) Paternal exposure (Inadequate)	A population-based case-control study in Denver found no association between childhood cancers and maternal or paternal occupational exposure to solvents including benzene and aliphatic hydrocarbons (Feingold et al 1992). A cohort study of male Norwegian printers found no excess cancer risk among their children (Kristensen and Andersen 1992).
Childhood leukemia	Maternal exposure Limited Paternal exposure Limited (Linet et al	A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found a dose-response relationship between childhood acute nonlymphoblastic leukemia and frequency of maternal occupational solvent exposure (Buckley et al 1989a). A recent large case-control study by the Children's Cancer Study Group (USA and Canada) found that childhood acute lymphocytic leukemia was associated with preconceptual or prenatal (but not postnatal) maternal occupational exposures to solvents, degreasers or cleaning agents or to paints or paint thinners (Shu et al 1999). A pooled analysis of three German population-based case-control studies found no association between acute lymphocytic leukemia and maternal occupations likely exposed to solvents; however, there was an association with preconceptual or prenatal but not postnatal maternal occupational exposure to paints or lacquers (Schuz et al 2000). A review of epidemiologic studies concluded that there is suggestive epidemiologic evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene and suggestive evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene and limited evidence for associations between childhood acute lymphoblastic leukemia and maternal or paternal occupational exposure to hydrocarbons, paints or motor vehicle exhaust (Linet et al 2003). A large case-control study by the US Children's Oncology Group found an association between those childhood acute lymphocytic leukemia cases with <i>K-ras</i> but not those with <i>N-ras</i> mutation and preconceptual or prenatal maternal occupational exposure to solvents, degreasers or cleaning agents; cases with the <i>K-ras</i> or <i>N-ras</i> mutation were not associated with preconceptual or prenatal maternal occupational exposure to paints or paint thinners (Shu et al 2004). A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found dose-response relationships between childhood acute nonlymphoblastic leukemia and frequencies of paternal

	<p>2003) Inadequate (Olshan and van Wijngaarden 2003)</p> <p>Childhood exposure (Limited)</p>	<p>occupational exposure to solvents and petroleum products; the association with solvents occurred for preconceptual and prenatal but not postnatal exposures (Buckley et al 1989a). A population-based case-control study in the UK found an association between childhood leukemia or non-Hodgkin's lymphoma and paternal preconceptual occupational solvent exposure; there were too few exposed mothers for meaningful analysis of maternal exposure (McKinney et al 1991). A population-based case-control study in Denver found no association between childhood acute lymphatic leukemia and paternal occupational exposure to solvents including benzene and aliphatic hydrocarbons (Feingold et al 1992). A review of 48 epidemiologic studies of childhood cancer and parental occupational exposures concluded that the strongest associations with childhood leukemia related to paternal occupational exposure to solvents and paints and employment in motor vehicle-related occupations; all five reviewed studies of childhood leukemia/lymphoma and paternal occupational solvent exposure reported odds ratios exceeding 2 (Colt and Blair 1998). A recent large case-control study by the Children's Cancer Study Group (USA and Canada) found that childhood acute lymphocytic leukemia was not associated with paternal preconceptual, prenatal or postnatal occupational exposure to solvents, degreasers or cleaning agents or to paints or paint thinners (Shu et al 1999). A pooled analysis of three German population-based case-control studies found no association between acute lymphocytic leukemia and paternal occupations likely exposed to solvents or to paints or lacquers (Schuz et al 2000). A review of epidemiologic studies concluded that there is suggestive evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene and limited evidence for associations between childhood acute lymphoblastic leukemia and maternal or paternal occupational exposure to hydrocarbons, paints or motor vehicle exhaust (Linert et al 2003). A large case-control study by the US Children's Oncology Group found no association between those childhood acute lymphocytic leukemia cases with <i>K-ras</i> or <i>N-ras</i> mutations and preconceptual or prenatal paternal occupational exposure to solvents, degreasers or cleaning agents or exposure to paints or paint thinners (Shu et al 2004). A recent review noted that studies published since the 1998 Colt and Blair review generally did not support an association between childhood leukemia/lymphoma and paternal occupational solvent exposure (Olshan and van Wijngaarden 2003).</p> <p>A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found a dose-response relationship between childhood acute nonlymphoblastic leukemia and frequency of household use of petroleum products (Buckley et al 1989a). A cluster investigation found a 4-fold increased risk of childhood leukemia in Woburn (Massachusetts), a town where drinking water from wells had likely been contaminated by hazardous wastes including solvents, arsenic, chromium, pesticides and plasticizers (Durant et al 1995). A subsequent case-control study in Woburn found a borderline association between childhood leukemia and ever-exposure to Woburn's public drinking water supply; the association was stronger for prenatal than childhood exposure (Costas et al 2002). A record-based case-control study in the UK found borderline associations between childhood leukemia and residential proximity to main roads and gasoline stations (Harrison et al 1999). A risk assessment concluded that infant and child environmental benzene exposures yield an average daily absorbed dose (per unit body weight) about three orders of magnitude below that for adults occupationally exposed to airborne benzene at the LOAEL for adult acute non-lymphocytic leukemia (32-80 mg/m³) (Duarte-Davidson et al 2001). A Swedish birth cohort study found no association between childhood leukemia and paternal occupations likely exposed to solvents (Feychting et al 2001). A large US case-control study found associations between childhood acute lymphatic leukemia and childhood artwork using solvents but not model building (during the year before diagnosis) and with indoor painting but not home furniture stripping (since year before child's birth) (Freedman et al 2001).</p>
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Brain cancer	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure Limited (Linet et al 2003)</p> <p>Inadequate (Olshan and van Wijngaarden 2003)</p>	<p>A population-based case-control study in France found an association between childhood astroglial and primitive neuroectodermal brain tumours and maternal occupations likely exposed to solvents (Cordier et al 1997).</p> <p>A population-based case-control study in Denver found no association between childhood brain cancer and paternal occupational exposure to aliphatic hydrocarbons; there were too few exposed case fathers to assess other solvents (Feingold et al 1992). A review of 48 epidemiologic studies of childhood cancer and parental occupational exposures concluded that the strongest association with childhood brain cancer was paternal occupational exposure to paints (a proxy for solvent exposure) with 4 of the 5 reviewed studies reported odds ratios exceeding 2 (Colt and Blair 1998). A Swedish birth cohort study found no association between childhood brain tumours and paternal occupations likely exposed to solvents (Feychting et al 2001). A review of epidemiologic studies concluded that there is limited evidence for associations between childhood brain tumours and paternal occupational exposure to paint or solvents (Linet et al 2003). A recent review noted that two studies published since the 1998 Colt and Blair review found no association between childhood brain cancer and paternal occupational solvent exposure).</p>
Neuroblastoma	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure (Inadequate)</p>	<p>A large case-control study of neuroblastoma in the USA and Canada found associations with paternal occupations likely exposed to solvents including alcohols, lacquer or paint thinner, mineral spirits or turpentine (De Roos et al 2001).</p> <p>A large case-control study of neuroblastoma in the USA and Canada found no association with maternal occupations likely exposed to solvents including halogenated hydrocarbons (De Roos et al 2001).</p>
Wilms' tumour	Paternal exposure (Inadequate)	A US case-control study found no association between Wilms' tumour and paternal preconceptual, prenatal or postnatal employment in occupations likely exposed to solvents and other hydrocarbons (Olshan et al 1990).
Liver cancer	<p>Maternal exposure (Inadequate)</p> <p>Paternal exposure (Inadequate)</p>	A case-control study by the Children's Cancer Study Group (USA and Canada) found that hepatoblastoma was associated with maternal or paternal occupational exposure to paints but not solvents (Buckley et al 1989b).
Ewing's sarcoma	Paternal exposure (Inadequate)	A population-based case-control study in Australia found a borderline association between Ewing's sarcoma and paternal occupational exposure to solvents and glues during the periconceptual period (Valery et al 2002).
Germ cell tumours	Maternal exposure (Inadequate)	A review of epidemiologic studies concluded that there is limited evidence for associations between childhood germ cell tumours and maternal occupational exposure to solvents (Linet et al 2003).
Visual function	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found higher error scores on red-green and blue-yellow colour discrimination tests and lower visual acuity scores among children of women prenatally exposed to organic solvents (Till et al 2001).
Developmental milestones	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1 st trimester with respect to developmental milestones (age at first

		smile, lifted head, sat, crawled, stood, first word, walked) (Laslo-Baker et al 2004).
Cognitive function	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1 st trimester with respect to full-scale, verbal or performance IQ scores at ages 6-8 years (Laslo-Baker et al 2004).
Language	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found an inverse association between grooved pegboard scores (a measure of dexterity and visual-motor coordination) at ages up to 8 years and maternal 1 st trimester occupational exposure to organic solvents (Laslo-Baker et al 2004).
Visual-motor coordination	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1 st trimester with respect to total language scores at ages 3-8 years (Laslo-Baker et al 2004).
Hyperactivity	Maternal exposure (Inadequate)	A small retrospective cohort study in Canada found associations between Connor hyperactivity/impulsivity scores and diagnosis of DSM-IV hyperactivity at ages up to 8 years and maternal 1 st trimester occupational exposure to organic solvents (Laslo-Baker et al 2004).
Reduced female fertility	Limited	A cohort study of women employed in the California semiconductor industry found the likelihood of conception during a 5-month period of attempting to conceive was inversely associated with work in the fabrication room and with exposure to ethylene glycol ethers (Eskenazi et al 1995). In a retrospective cohort study of Finnish women monitored for occupational organic solvent exposure, likelihood of conception was inversely associated with maternal occupational exposure at the beginning of unprotected intercourse to halogenated hydrocarbons but not with exposure to other solvents (Sallmen et al 1995). A retrospective cohort study of semiconductor workers in the eastern USA found a dose-response relationship between female subfertility (required at least 12 months of unprotected intercourse to conceive) and estimated intensity of occupational exposure to ethylene glycol ethers during the year before conception (Correa et al 1996). A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced female fertility and occupational exposure to solvents in the semiconductor industry (Paul 1997). An Italian retrospective cohort study found no association between likelihood of conception and maternal preconceptional occupational solvent exposure (Spinelli et al 1997). A US case-control study found an association between female infertility and occupations likely exposed to solvents (Smith et al 1997). A retrospective cohort study of persons employed in printing found an inverse association between likelihood of conception and maternal occupational toluene exposure during the period of attempting conception (Plenge-Bonig and Karmaus 1999). A retrospective cohort study of Finnish women employed in wood fabrication found an inverse association between likelihood of conception and high maternal occupational formaldehyde exposure but not with high organic solvent exposure (Taskinen et al 1999). In a cohort study of couples seeking <i>in vitro</i> fertilization in the Netherlands, the embryo implantation success rate was not associated with maternal occupational exposure to organic solvents, metal dust/fumes, welding fumes or pesticides (Tielemans et al 2000). A retrospective cohort study of women in Swedish biomedical research laboratories found inverse associations between likelihood of conception and maternal preconceptional occupational exposure to organic solvents in general and acetone in particular (Wennborg et al 2001). A retrospective cohort study of non-smoking, non-alcohol-using female workers in semiconductor manufacturing in Taiwan found that likelihood of conception was inversely associated with work in

		<p>photolithography and with exposure to ethylene glycol ethers (Chen et al 2002). A review of epidemiologic studies of developmental and reproductive health outcomes and occupational exposures concluded that there is limited evidence of an association between reduced female fertility and occupational organic solvent exposure (Kumar 2004).</p>
Reduced male fertility	Limited (less consistent than evidence for reduced female fertility)	<p>A retrospective cohort study of semiconductor workers in the eastern USA found no association between male subfertility (required at least 12 months of unprotected intercourse to conceive) and estimated intensity of occupational exposure to ethylene glycol ethers during the year before conception (Correa et al 1996). An Italian retrospective cohort study found no association between likelihood of conception and paternal preconceptional occupational solvent exposure (Spinelli et al 1997). A retrospective cohort study of Finnish men monitored for occupational organic solvent exposure found a borderline inverse association between likelihood of conception and paternal occupational organic solvent exposure; the association was stronger among couples attempting their first pregnancy (Sallmen et al 1998). A cohort of married men employed on offshore oil rigs or as car mechanics or carpenters found no association between likelihood of conception and occupational exposure to oil or oil products (Bull et al 1999). A retrospective cohort study of German males employed in printing found no association between likelihood of conception and intensity of paternal occupational toluene exposure during the period of attempting conception (Plenge-Bonig and Karmaus 1999). In a cross-sectional study of couples seeking <i>in vitro</i> fertilization treatment in the Netherlands, reported in a letter to the editor, the <i>in vitro</i> fertilization success rate was not associated with male partner exposure to organic solvents (Tielemans et al 1999). In a cohort study of couples seeking <i>in vitro</i> fertilization in the Netherlands, the embryo implantation success rate was inversely associated with high paternal occupational exposure to organic solvents (Tielemans et al 2000). A review of epidemiologic studies of male fertility and occupational exposures concluded that reduced male fertility is associated with occupational exposures to solvents, heavy metals, pesticides and other agricultural materials, radiation, heat and welding (Sheiner et al 2003). A review of epidemiologic studies of developmental and reproductive health outcomes and occupational exposures concluded that there is limited evidence of an association between reduced male fertility and occupational organic solvent exposure (Kumar 2004).</p>
Semen quality	Limited (? Sufficient)	<p>A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced semen quality and occupational exposure to solvents including ethylene glycol ethers, chloropropene and carbon disulphide (Paul 1997). A case-control study in the Netherlands found no overall association between low semen quality and occupational solvent exposure; among the subgroup of men with primary infertility, however, there were borderline associations between low semen quality and occupational exposure to aromatic solvents and urinary solvent metabolite levels (Tielemans et al 1999). The latter study also found a significant association between azoospermia and occupational organic solvent exposure. A cohort study of married workers found inverse associations between sperm vitality, sperm activity and semen acrosin levels (an indicator of sperm ability to penetrate the zona pellucida and achieve fertilization) and occupation in jobs exposed to organic solvents; there was also an association between semen liquefaction time and blood benzene levels (Xiao et al 1999). Further investigation of this cohort showed that workers exposed to organic solvents had lower sperm activity and lower levels of semen enzymes including acrosin (reflects ability of sperm to penetrate the zona pellucida and achieve fertilization), LDH-C4 (reflects ability of sperm to generate energy) and γ-GT levels (reflects prostate function) (Xiao et al 2001). The latter study also showed that sperm vitality and activity and semen acrosin levels were inversely associated with duration of organic solvent exposure while semen γ-GT levels were inversely associated with blood benzene levels. A cross-sectional study of couples at fertility clinics</p>

		in Argentina found associations between low sperm concentration, low total sperm count, low percent of motile sperm and high percent of morphologically abnormal sperm and occupational solvent exposure (Oliva et al 2001). A fertility clinic-based case-control study in Canada found a dose-response relationship between low sperm counts and intensity of occupational solvent exposure (Cherry et al 2001). A review of epidemiologic studies of male fertility and occupational exposures concluded that there is a clear association between reduced semen quality and occupational solvent exposure (Sheiner et al 2003).
Asthma	(Inadequate)	A cross-sectional study in Australia found a dose-response relationship between positive reactions to one or more skin prick allergen tests and home indoor air formaldehyde levels (Garrett et al 1999).
Allergies	(Inadequate)	A cross-sectional study in Australia found a dose-response relationship between childhood asthma and home indoor air formaldehyde levels (Garrett et al 1999).
Poisonings	(Inadequate)	A study of US national mortality data found that there were 4129 suicidal and 3807 accidental poisoning deaths among children and youth age 10-19 years; volatile solvents and gases played important roles in accidental deaths among those age 10-14 years and in suicidal deaths among those age 15-19 years (Shepherd and Klein-Schwartz 1998).

^a Sufficient evidence = based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed; limited evidence = relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders; inadequate evidence = relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

2. Fetal death

Reference, location	Design	Exposure	Results	Association ¹	DR ²	Covariates
(McDonald et al. 1988a), Montreal	Retrospective cohort study, 22,613 previous pregnancies of 56,067 women employed for at least 30 hr/wk at the time of conception, 5010 early and 210 late fetal deaths	Self-reported maternal 1 st trimester occupational exposures; expert assessment of likely chemical exposures	Early fetal deaths associated with maternal 1 st trimester occupational exposure to solvents in manufacturing industries (relative risk)	1.2 (1.0-1.4)		Maternal age, gravidity, parity, abortion, ethnicity, education, smoking, alcohol
			Late fetal deaths associated with maternal 1 st trimester occupational exposure to solvents (relative risk)	2.8 (1.4-4.4)		As above
(Daniell and Vaughan 1988), Seattle, USA	Retrospective cohort study, men employed in solvent-exposed occupations as auto body workers (n=1122), painters (n=1299), printers (n=799), fiberglass workers (n=648), comparison cohorts of men in unexposed occupations (n=1469) and electricians (n=2529)	Live birth record information on paternal occupation	Fetal death (any gestation length) not associated with paternal employment in solvent-exposed occupations (relative risk compared to men in occupations not exposed to solvents)	auto body workers 1.0 (0.8-1.2) painters 0.9 (0.8-1.1) fiberglass workers 0.9 (0.7-1.2) printers 1.1 (0.8-1.3)		Maternal age, gravidity
(Savitz et al. 1989), USA	Case-control study nested within surveys of national probability samples of live births (with 4-fold oversampling of low birth weight infants) and stillbirths (gestational age ≥ 28 wk or weight ≥ 1000g) in 1980; numbers of live births and stillbirths for analysis of maternal occupation were respectively 3,668 and 2,096 and for paternal occupation were 5,669 and 3,170	Self-reported information on parental occupational exposures during 12 mos before delivery; note – more fathers than mothers were employed during the 12 mos before delivery	Borderline association between stillbirths and maternal but not paternal occupational benzene exposure (odds ratios)	maternal 1.3 (1.0-1.8) paternal 1.0 (0.8-1.3)		Race, previous miscarriage; parity; to women who received prenatal care, age < 40, smoking, alcohol consumption, previous stillbirth

¹ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

² 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

(Taskinen et al. 1989), Finland	Case-control study nested within cohort of men monitored for exposure to styrene, toluene, xylene, tetrachloroethylene, trichloroethylene and 1,1,1-trichloroethane during 1965-1983, 120 early fetal deaths, 251 healthy infant controls	Maternal and paternal self-reported information on occupational and other exposures during 1 st trimester (women) and 80 days before conception (men)	Early fetal loss associated with paternal preconceptual but not maternal 1 st trimester occupational exposure to organic solvents (odds ratio)	paternal solvent exp 2.3 (1.1-5.0) maternal solvent exp 1.2 (0.5-2.7)	Paternal dust exposure, sp organic solv exposure, he lifting, prev loss
			Early fetal loss associated with paternal occupation as painter, woodworker or plastics worker (odds ratios)	painter 3.3 (1.6-6.8) woodworker 3.8 (1.2-12) plastics worker 1.9 (0.9-4.3)	As above
			Early fetal loss associated with paternal preconceptual occupational exposure to toluene but not other solvent categories (odds ratios, frequent vs rare use)	styrene 0.7 (0.4-1.5) toluene 2.3 (1.1-4.7) xylene 1.6 (0.8-3.2) halogenated hydrocarbons 0.8 (0.3-2.2) aliphatic hydrocarbons 1.3 (0.6-2.6)	As above pl paternal exp solvents oth the one indic
(Kyyronen et al. 1989), Finland	Nested case-control study of early fetal death among 1,108 women employed as dry cleaning or laundry workers during 1973-1983 (see also Olsen et al 1990); 130 early fetal death cases, 289 healthy infant controls, 24 birth defect cases, 93 controls	Self-reported maternal exposures in dry cleaning and laundry establishments during 1 st trimester	Early fetal death associated with frequent maternal occupational use of tetrachloroethylene but not other solvents during 1 st trimester (odds ratios)	tetrachloroethylene 3.4 (1.0-11) other solvents 1.5 (0.4-5.4)	Heavy lifting, frequent alco intake
			Early fetal death associated with frequent maternal alcohol intake	2.0 (1.0-4.0)	As above

			during 1 st trimester (odds ratio)		
(Olsen et al. 1990), Denmark, Sweden, Finland	Nested case-control study of early fetal death within cohort of women employed in Scandinavian dry cleaning and laundry establishments for at least 1 month during 1973-1983; 159 cases early fetal deaths, 436 healthy infant controls	Self-reported maternal exposures in dry cleaning and laundry establishments during 1 st trimester or later pregnancy	Early fetal death associated with maternal tetrachloroethylene exposure during early pregnancy (odds ratio, high vs low exposure)	2.9 (1.0-8.4)	Maternal sm parity, alcohol
(Ahlborg 1990), Sweden	Case-control studies nested within 2 cohorts; cohort 1 comprised 2181 women employed in workplaces where dry-cleaning comprised at least 10% of total production during 1973-1983, cohort 2 comprised 5176 women for which census record indicated employment as washers/cleaners; in the 2 cohorts combined, there totals of 98 early fetal deaths, 17 perinatal deaths, 26 birth defects and 7 very low birth weight infants (<1500 g) among 1710 pregnancies	Self-reported 1 st trimester maternal occupational exposures; dry-cleaning used tetrachloroethylene (perchloroethylene)	Any adverse pregnancy outcome not associated with maternal 1 st trimester occupational exposure to tetrachloroethylene (odds ratios by exposure category vs unexposed)	low 1.1 (0.6-2.2) high 1.1 (0.5-2.2)	Maternal sm alcohol, med complication of adverse p outcomes
			Early fetal death not associated with maternal 1 st trimester occupational exposure to tetrachloroethylene (odds ratios by exposure category vs unexposed)	low 1.0 (0.4-2.2) high 0.9 (0.4-2.1)	As above
(Windham et al. 1991), Santa Clara County, California	Hospital-based case-control study, 361 early fetal deaths, 735 healthy infant controls, 1986-1987	Self-reported maternal prenatal occupational and household exposure to solvents	Early fetal deaths associated with maternal 1 st trimester occupational exposure to aliphatic solvents (odds ratios by solvent type)	halogenated 1.0 (0.7-1.6) aromatic 1.2 (0.6-2.4) aliphatic 1.8 (1.1-3.0) glycol ethers 0.9 (0.5-1.7) other 1.3 (0.7-2.4)	Maternal ag education, p fetal loss, sm hours worke response qua occupation c

			Early fetal deaths associated with maternal 1 st trimester occupational exposure to paint thinners, perchloroethylene or trichloroethylene (crude odds ratios)	<p>paint thinners 2.3 (1.0-5.1)</p> <p>perchloroethylene 4.7 (1.1-21)</p> <p>trichloroethylene 3.1 (0.9-10)</p>	
			Early fetal deaths not associated with maternal 1 st trimester exposure to household products containing solvents (odds ratios by product type)	1.1 (0.8-1.4)	Maternal age, education, parity, fetal loss, smoking, alcohol, marijuana
			Borderline association between early fetal deaths and maternal 1 st trimester exposure to household use of automotive engine cleaners (odds ratios by product type)	1.7 (0.8-3.7)	As above
(Kristensen et al. 1993), Norway	Cohort study, 10,992 men in printing industry; identified 6,251 infants (incl 60 late fetal deaths at gestational age ≥ 28 wk) of workers during 1967-1986 by linking union membership and Norwegian birth registry records	Organic solvent and lead exposure based on job title at time of conception	Early fetal deaths (gestation length < 28 wk) associated with paternal occupational solvent exposure (odds ratios)	solvents \pm lead 5.5 (1.8-17)	Twin birth, birth weight
			Late fetal deaths (gestation length ≥ 28 wk) not associated with paternal occupational solvent exposure (odds ratios)	<p>solvents only 0.9 (0.4-2.2)</p> <p>solvents and lead 1.1 (0.5-2.6)</p>	Birth weight, birth length
			Borderline associations between all fetal and neonatal deaths and paternal occupational solvent exposure (odds ratios)	<p>solvents only 1.8 (0.6-5.4)</p> <p>solvents and lead 2.4 (0.9-6.3)</p>	Father's occupation, maternal age, gestational length, birth length, maternal age
(Taskinen et al. 1994),	Case-control study nested within cohort of 9186 women working in laboratories,	Self-reported occupational exposures during 1 st trimester	Early fetal death associated with 1 st trimester maternal occupational	2.3 (1.1-4.3)	Employment, smoking, alcohol

Finland	206 early fetal deaths, 329 healthy infant controls (matched for maternal age)		exposure to solvents (odds ratio, high vs low exposure)		parity, previous miscarriage, birth control, illness during pregnancy
			Early fetal death associated with 1 st trimester maternal occupational exposure to aromatic and halogenated but not aliphatic solvents (odds ratio, high vs low exposure)	aliphatic 1.0 (0.4-2.5) aromatic 2.7 (1.3-5.6) halogenated 1.8 (0.9-3.7)	As above
(Schenker et al. 1995), USA	Nation-wide cohort study, women employed in semiconductor manufacturing; 904 women in historical cohort who became pregnant while working during 1986-1989, 403 women in prospective cohort who were monitored for pregnancy using daily urine pregnancy tests	Self-reported 1 st trimester occupational exposures	Early fetal death associated with maternal employment in semiconductor fabrication room in historic but not in prospective cohort (relative risk, yes vs no)	historic cohort 1.4 (1.0-2.1) prospective cohort 1.3 (0.6-1.8)	Maternal age, smoking, previous early fetal death, work-related, race
			Early fetal death associated with maternal employment in mask group within semiconductor fabrication room in historic but not in prospective cohort (relative risk, yes vs no)	historic cohort 1.8 (1.2-2.6) prospective cohort 1.3 (0.6-1.8)	As above
			Early fetal death associated with maternal exposure to any photoresist chemical (glycol ethers, butyl acetate, xylene) within the semiconductor fabrication room in the historic cohort (relative risks)	exposed vs not 1.4 (0.9-2.0) highly exposed vs not 2.2 (1.3-3.4)	
(Swan et al. 1995), USA	Nation-wide cohort study, women employed in semiconductor manufacturing (see Schenker et al 1995 above); assessed chemical-specific risks of early fetal death in historic cohort (904	Exposures inferred from job at conception; exposure intensity estimated from self-reported work activities and hours of work during 1 st trimester	Early fetal death associated with intensity of maternal 1 st trimester occupational exposure to any photoresist or developer solvent (glycol ethers, butyl acetate,	0.9 (0.5-1.6) 1.7 (0.8-3.2) 2.7 (1.4-4.6)	Maternal age, smoking, ethnicity, pregnancy history, education, income, stress, year of

	women)		xylene) within the semiconductor fabrication room in the historic cohort (relative risks for increasing exposure levels vs none)			conception
(Correa et al. 1996), Baltimore	Retrospective cohort study, semiconductor workers (females and married males), 1980-1989; self-reported reproductive history, 1150 pregnancies and 177 early fetal deaths among 3007 female employees and wives of male employees	Estimated exposure to ethylene glycol ethers and self-reported occupational histories and job-exposure matrix based on plant records; main exposure occurred during chemical mixing and photolithography processes	Early fetal death associated with maternal occupational exposure to ethylene glycol ethers during the month of conception (relative risks, low, medium and high vs no exposure)	1.0 (0.6-1.7) 1.4 (0.8-2.6) 2.8 (1.4-5.6)		Maternal age, education, parity, fetal loss, parity at conception, plant
			Early fetal death not associated with paternal occupational exposure to ethylene glycol ethers during the month of conception (relative risks, low, medium and high vs no exposure)	0.8 (0.4-1.5) 1.1 (0.6-2.0) 0.7 (0.3-1.6)		As above
(Paul 1997), USA	Review of literature on developmental and reproductive outcomes and occupational exposures		Limited evidence of associations between early fetal death and maternal occupational exposure to ethylene glycol ethers and waste anesthetic gases			
(Agnesi et al. 1997), Italy	Hospital-based case-control study in region with shoe manufacturing, 108 early fetal deaths, 108 healthy infant controls	Self-reported information on occupation and working conditions during pregnancy		Early fetal deaths associated with maternal 1 st trimester occupational solvent exposure (odds ratios, low and high vs no exposure)	low 1.6 (0.6-4.1) high 3.9 (1.2-12)	Gravidity, parity, smoking, alcohol, coffee, medication, marital status
(Doyle et al. 1997), UK	Retrospective cohort study, 7,305 women employed in dry cleaning and laundry, age 16-45 yr; assessed fetal loss before gestation wk 28	Self-reported maternal occupational exposures in dry cleaning or laundry before and after conception; machine operator vs non-operator used as a proxy for tetrachloroethylene exposure	Early fetal death associated with maternal occupational tetrachloroethylene exposure during early pregnancy (odds ratio, dry-cleaning operator vs non-operator)	1.6 (1.0-2.7)		Maternal age, parity, gravidity, year of birth

			Early fetal death associated with maternal occupational tetrachloroethylene exposure during early pregnancy (odds ratio, dry-cleaning operator, exposed vs unexposed pregnancies)	1.7 (1.2-2.4)		As above
(McMartin et al. 1998), Toronto, Canada	Meta-analysis, 5 epidemiologic studies each of early fetal deaths in relation to maternal organic solvent exposure, published during 1988-1992 (including Windham et al 1991 above); Mantel-Haenszel summary odds ratios		Borderline association between early fetal deaths and maternal organic solvent exposure (summary odds ratio)	1.3 (1.0-1.6)		
(Khattak et al. 1999), Toronto	Cohort study, 125 pregnant women, 1987-1996; comparison cohort of women not exposed to solvents	Occupationally exposed to organic solvents including phenols, trichloroethylene, xylene, vinyl chloride, acetone	Early fetal deaths not associated with maternal 1 st trimester occupational solvent exposure (odds ratio – calculated from data in paper)	1.4 (0.4-4.9)		Matched for age, gravidity, smoking, alcohol
(Elliott et al. 1999), UK	Case-control study nested within cohort of 2,207 female workers in semiconductor industry, 36 cases early fetal deaths, 80 healthy live birth controls	Self-reported information on job title, department, work group, hours of work; known hazards included several solvents (glycol ethers, butyl acetate, xylene, acetone, methanol, isopropanol, MEK)	Early fetal death not associated with maternal 1 st trimester employment in semiconductor fabrication (odds ratio, yes vs no)	0.6 (0.3-1.5) (16 exposed case mothers)	Maternal 1 st trimester smoking, alcohol, lifting, bending, stress	
			Early fetal death not associated with maternal 1 st trimester exposure to ethylene glycol ethers (odds ratio, yes vs no)	0.5 (0.1-2.1) (2 exposed case mothers)		As above
(Bull et al. 1999), Norway	Cohort study, 741 married men employed on offshore oil rigs, car mechanics or carpenters; 301 pregnancies analyzed for time to conceive and 580 for early fetal death	Maternal and paternal self-reported information on occupation	Early fetal deaths not associated with exposure to oil and oil products (odds ratio)	1.1 (0.6-2.0)		Maternal age, prenatal smoking
(Wennborg et al. 2000),	Cohort study, 1417 births among 419 women employed in Swedish biomedical	Self-reported maternal prenatal occupational exposures	Borderline association between early fetal deaths and maternal	chloroform 2.3 (0.9-5.9)		Maternal age, previous fetal loss

Sweden	research laboratories and 278 female university employees who had never worked in a laboratory, 1990-1995; self-reported early fetal deaths, record-based information on birth weight, gestation length and birth defects		occupational exposure to chloroform but not other solvents during or before pregnancy (odds ratios)	other solvents 0.9 (0.5-1.9)	
(Oliveira et al. 2002), Brazil	Hospital-based case-control study, 990 low birth weight infants (<2500 g), 230 late fetal deaths and 160 infants with birth defects among a total of 17113 births, 1983-1998	Maternal residential proximity to petrochemical plant: region 1 = <10 km, region 2 = 10-20 km, referent region = 30+ km	Risk of late fetal deaths not increased for mothers living closest to petrochemical plant (odds ratio, maternal residence <10 vs 30+ km)	0.7 (0.2-2.6) p=0.60	Maternal age, smoking, his chronic dise

Fetal death: summary

Early fetal deaths (spontaneous abortions)

Maternal exposure A cohort study in Montreal found a weak association between early fetal deaths and maternal 1st trimester occupational exposure to solvents (McDonald et al 1988). A Finnish case-control study nested within a cohort of men monitored for solvent exposure found no association between early fetal deaths and maternal 1st trimester occupational exposure to organic solvents (Taskinen et al 1989). Another Finnish case-control study, nested within a cohort of women employed as dry cleaning or laundry workers, found associations between early fetal deaths and frequent 1st trimester maternal occupational use of tetrachloroethylene (but not other solvents) and with frequent maternal 1st trimester alcohol intake (Kyrronen et al 1989). Similarly, a nested case-control study within a cohort of dry cleaning and laundry workers in Denmark, Sweden and Finland found an association between early fetal deaths and maternal 1st trimester occupational exposure to tetrachloroethylene (Olsen et al 1990). However, the Swedish component of this study found no association between early fetal deaths and maternal 1st trimester occupational exposure to tetrachloroethylene (Ahlborg et al 1990). A case-control study in California found an association between early fetal deaths and maternal 1st trimester occupational exposure to aliphatic solvents, paint thinners, trichloroethylene and tetrachloroethylene (Windham et al 1991). A nested case-control study among female laboratory workers in Finland found an association between early fetal deaths and 1st trimester maternal occupational solvent exposure; the association held for aromatic and halogenated but not aliphatic solvents (Taskinen et al 1994). A national cohort study of women employed in semiconductor manufacturing in the USA found an association between early fetal deaths and work in a fabrication room in the historic but not in the prospective cohort; there was also an exposure-risk relationship between early fetal death and maternal 1st trimester exposure to any photoresist chemical (glycol ethers, butyl acetate, xylene) (Schenker et al 1995, Swan et al 1995). A retrospective cohort study of US semiconductor workers found an association between early fetal death and maternal occupational exposure to ethylene glycol ethers during the month of conception (Correa et al 1996). A review of epidemiologic studies of early fetal death and occupational exposures concluded that there was limited evidence for an association between early fetal deaths and maternal occupational exposure to ethylene glycol ethers (Paul 1997). A small Italian case-control study in a shoe manufacturing region found an association between early fetal death and maternal 1st trimester occupational solvent exposure (Agnesi et al 1997). A UK retrospective cohort study of women working in dry cleaning and laundry found an association between early fetal death and maternal occupation as a dry cleaning operator during early pregnancy, an indicator of tetrachloroethylene exposure (Doyle et al 1997). A meta-analysis of five epidemiologic studies found a borderline association between early fetal deaths and maternal organic solvent exposure during early pregnancy (McMartin et al 1998). A small cohort study in Canada found no association between early fetal death and maternal 1st trimester occupational solvent exposure; the low statistical power of this study precludes any strong inferences (Khattak et al 1999). A nested case-control study among a cohort of female employees in the UK semiconductor manufacturing industry found no association between early fetal death and maternal 1st trimester employment or exposure to ethylene glycol ethers (Elliott et al 1999). A cohort study of Swedish female employees in biomedical research laboratories found an association (of borderline statistical significance) between early fetal deaths and occupational chloroform exposure (Wennborg et al 2000).

Paternal exposure A retrospective cohort study of US workers found no association between fetal death (at any gestation length) and paternal occupations likely exposed to solvents (Daniell and Vaughan 1988). A Finnish case-control study nested within a cohort of men monitored for solvent exposure found an association

between early fetal deaths and paternal preconceptual occupational exposure to organic solvents and with specific occupations including painting; when analyzed by type of solvent, early fetal deaths were associated with paternal preconceptual occupational exposure to toluene and xylene (the latter was not statistically significant) (Taskinen et al 1989). A Norwegian cohort study of male printers found an association between early fetal deaths and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A retrospective cohort study of US semiconductor workers found no association between early fetal death and paternal occupational exposure to ethylene glycol ethers during the month of conception (Correa et al 1996). A cohort study of men employed as car mechanics, on offshore oil rigs or as carpenters found no association between early fetal deaths and likely exposure to solvents or other oil products (Bull et al 1999).

Late fetal deaths (stillbirths)

Maternal exposure A cohort study in Montreal found an association between late fetal deaths and maternal 1st trimester occupational exposure to solvents (McDonald et al 1988). A large population-based US case-control study found a borderline association between late fetal deaths and maternal occupational benzene exposure during the year before delivery (Savitz et al 1989). A case-control study in the region of a petrochemical plant in Brazil found no association between late fetal deaths and maternal residential proximity to the plant (Oliveira et al 2002).

Paternal exposure A retrospective cohort study of US workers found no association between fetal death (at any gestation length) and paternal occupations likely exposed to solvents (Daniell and Vaughan 1988). A large population-based US case-control study found no association between late fetal deaths and paternal occupational benzene exposure during the year before delivery (Savitz et al 1989). A Norwegian cohort study of male printers found no association between late fetal deaths and paternal occupational exposure to solvents with or without concurrent lead exposure (Kristensen et al 1993).

	2,096 and for paternal occupation were 5,669 and 3,170		No association between IUGR and maternal but association between IUGR and paternal occupational benzene exposure (respective odds ratios)	0.6 (CI 0.3-1.3) 1.5 (CI 1.1-2.3)	Child's race, sex, maternal smoking; restricted maternal age ≥ 20 y
(Windham et al. 1991), Santa Clara County, California	Hospital-based case-control study, 55 IUGR infants, 44 low birth weight infants, 735 healthy infant controls, 1986-1987	Self-reported maternal prenatal occupational and household exposure to solvents	IUGR not associated with maternal 1 st trimester occupational solvent exposure (crude odds ratio)	1.4 (0.7-2.6)	Maternal age, race, education, previous smoking, hours worked, response quality on occupation question
			Low birth weight not associated with maternal 1 st trimester occupational solvent exposure (crude odds ratio)	0.5 (0.2-1.3)	As above
(Kristensen et al. 1993), Norway	Cohort study, 10,992 men in printing industry; identified 6,251 infants (incl 60 late fetal deaths at gestational age ≥ 28 wk) of workers during 1967-1986 by linking union membership and Norwegian birth registry records	Organic solvent and lead exposure based on job title at time of conception	Early preterm birth (16-27 wk) associated with paternal occupational solvent exposure (odds ratios)	solvents only 5.4 (1.7-17) solvents and lead 8.6 (2.7-27)	Father's occupation, year of birth, twin birth, maternal age, birth order
			SGA not associated with paternal occupational solvent exposure (odds ratios)	solvents only 1.0 (0.8-1.3) solvents and lead 0.9 (0.6-1.2)	Father's occupation, maternal chronic disease, previous fetal loss, birth order
			Low birth weight not associated with paternal occupational solvent exposure (odds ratios)	solvents only 1.0 (0.7-1.3) solvents and lead 1.2 (0.9-1.6)	Gestation length, birth sex, previous fetal loss, birth, parental consanguinity
(Bove et al. 1995), New Jersey	Retrospective cohort study, 80,938 live births, 594 fetal deaths among residents of 75 towns, 1985-1988; live births included 1853 term low birth weight, 4082 small for gestational age and 7167	75 towns served by 49 public water systems; used twice-yearly measures of several organochlorines to estimate monthly levels; assessed avg levels during 1 st trimester for	Term low birth weight associated with carbon tetrachloride levels (odds ratio, >1 vs <1 $\mu\text{g/L}$)	2.3 (1.2-4.2)	Maternal age, race, education, primiparous, previous pregnancy, infant sex, prenatal

	preterm infants and 118 CNS, 56 NTD, 83 oral cleft and 346 cardiac birth defects (the latter included 108 major cardiac defects of which 87 were VSDs)	birth defect and fetal death outcomes and throughout pregnancy for fetal growth outcomes			
			Small for gestational age (<5 th percentile weight for race, sex, gestational age) associated with carbon tetrachloride levels (odds ratio, >1 vs <1 µg/L)	1.8 (1.1-2.7)	As above
(Hewitt and Tellier 1998), Wisconsin	Retrospective cohort study, 118 pregnant women seen by occupational health nurse, 226 women randomly selected from state-wide birth record	Information on occupation and expert opinion on likelihood of solvent exposure	Preterm birth not associated with maternal occupations likely to have solvent exposure (relative risk)	1.2 (0.4-3.1)	Adjusted for age; analysis based on white women without gestational smoking was not a confounder
			Low birth weight not associated with maternal occupations likely to have solvent exposure (relative risk)	1.2 (0.3-3.7)	As above
(Khattak et al. 1999), Toronto	Cohort study, 125 pregnant women, 1987-1996; comparison cohort of women not exposed to solvents	Occupationally exposed to organic solvents including phenols, trichloroethylene, xylene, vinyl chloride, acetone	Non-significant association between preterm births and maternal 1 st trimester occupational exposure to organic solvents (odds ratio); note – 9 cases among exposed women and 3 among unexposed women	3.3 (0.8-19)	Matched for maternal gravidity, smoking,
			Non-significant association between birth weight <2500 g and maternal 1 st trimester occupational solvent exposure (odds ratio); note – 8 cases among exposed women and 3 among unexposed women	2.9 (0.8-14)	As above
(Seidler et al. 1999), Germany	Birth cohort study, 3216 pregnant women, enrolled during gestation wk 15-28, 1987-1988; physician-reported pregnancy outcome history, 194 SGA	Self-reported maternal occupational history; job-exposure matrix to assess exposure to organic solvents, carbon tetrachloride, herbicides,	SGA infants not associated with maternal occupational organic solvent exposure (odds ratios, low and moderate exposure vs	low 1.4 moderate 1.2	Maternal age, smoking, alcohol, BMI, parity

	infants	chlorophenols, polychlorinated biphenyls, aromatic amines, lead and lead compounds, mercury and mercury115 compounds	unexposed)	p-trend=0.21	
			SGA infants not associated with maternal occupational exposure to carbon tetrachloride(odds ratios, low and moderate exposure vs unexposed)	low 1.0 moderate 1.4 p-trend=0.74	As above
(Wennborg et al. 2000), Sweden	Cohort study, 1417 births among 419 women employed in Swedish biomedical research laboratories and 278 female university employees who had never worked in a laboratory, 1990-1995; self-reported early fetal deaths, record-based information on birth weight, gestation length and birth defects	Self-reported maternal prenatal occupational exposures	Borderline inverse association between term birth weight and maternal occupational exposure to diethylether but not other solvents during or before pregnancy (birth weight difference, exposed vs unexposed)	chloroform 27g (-136, 190) diethylether -155g (-356, 46) toluene 42g (-99, 183)	Maternal age, smok gravidity, gestation infant sex, paternal laboratory work
			Small for gestational age not associated with maternal occupational solvent exposure during or before pregnancy (odds ratio)	1.1 (0.3-4.0)	As above
(Oliveira et al. 2002), Brazil	Nested case-control study within cohort of 17,113 births in main hospital of Montenegro during 1983-1998; 990 low birth weight infants (<2500 g), 230 late fetal deaths, 160 infants with birth defects	Maternal residential proximity to petrochemical plant: region 1 = <10 km, region 2 = 10-20 km, referent region = 30+ km	Marginally increased risk of low birth weight for mothers living closest to petrochemical plant (odds ratio, maternal residence <10 vs 30+ km)	1.5 (0.9-2.5) p=0.12	Maternal age, smok history of chronic d
(Bove et al. 2002), USA	Review of literature on adverse pregnancy outcomes and drinking water solvent levels; included 5 studies published during 1990-2000	Assessed pregnancy outcomes in relation to tap water solvent levels; most studies did not assess maternal tap water consumption	Small for gestational age was associated with drinking water trichloroethylene in Camp LeJeune and Woburn		
			Preterm birth was not associated with drinking water trichloroethylene in any of the studies		

(Ha et al. 2002), Beijing, China	Retrospective cohort study, 1,222 non-smoking female employees of a large petrochemical industry who had a singleton live birth infant with no major birth defects during 1996-1998; assessed birth weight	Parent-reported exposure to aromatic solvents including benzene, toluene, styrene, xylene	Birth weight inversely associated with maternal occupational organic solvent exposure (birth weight deficit, exposed vs unexposed mothers)	-82g (-106, -3) p=0.04	Gestation length, maternal prepregnancy weight, maternal height, paternal height, education
			Birth weight not associated with paternal occupational organic solvent exposure (birth weight excess, exposed vs unexposed fathers)	13g (-62, 87) p=0.74	As above
(Chia et al. 2004), Singapore	Retrospective birth cohort study, 186,064 singleton term live births, 1994-1998; assessed term low birth weight (<2500 g)	Parental occupation indicated on birth records	Term low birth weight not associated with any maternal occupation category (odds ratio for cleaners, labourers and related workers vs managers, senior officers and legislators)	0.9 (0.7-1.2)	Paternal occupation, maternal education, maternal height, age, gestation length, sex, birth order, information on maternal smoking and alcohol consumption. Prevalence of these factors was very low in this region
			Term low birth weight associated with paternal occupations potentially exposed to solvents (odds ratios for stated categories vs managers, senior officers and legislators)	production and related 1.2 (1.1-1.4) plant and machine operators/assemblers 1.2 (1.0-1.4) cleaners, labourers, related 1.3 (1.1-1.6)	As above except adjusted for maternal occupation

Birth weight, gestation length: summary

Low birth weight (not adjusted for gestation length)

Maternal exposure A hospital-based case-control study in California found no association between low birth weight and maternal 1st trimester occupational solvent exposure (Windham et al 1991). A retrospective cohort study in Wisconsin found no association between low birth weight and maternal occupations likely exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association of borderline statistical significance between low birth weight and self-reported maternal 1st trimester occupational exposure to organic solvents (Khattak et al 1999). A cohort study in Brazil found a marginally increased risk of low birth weight for mothers living within 10 kilometres of a petrochemical plant (Oliveira et al 2002).

Low birth weight (at term or adjusted for gestation length)

Maternal exposure A retrospective cohort study in New Jersey found an association between term low birth weight and drinking water carbon tetrachloride levels in the public water system serving the maternal residence (Bove et al 1995). A retrospective cohort study in Sweden found a borderline inverse association between term birth weight and maternal occupational exposure before or during pregnancy to diethylether but not other solvents (Wennborg et al 2000). A retrospective cohort study in China found an inverse association between birth weight (adjusted for gestation length) and maternal occupational organic solvent exposure (Ha et al 2002). A large retrospective cohort study in Singapore found no association between term low birth weight and maternal occupations likely exposed to solvents (Chia et al 2004).

Paternal exposure A retrospective cohort study found borderline associations between term low birth weight and paternal employment as auto body workers or painters (Daniell and Vaughan 1988). A Norwegian cohort study of men in printing industries found no association between low birth weight adjusted for gestation length and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993). A retrospective cohort study in China found no association between birth weight (adjusted for gestation length) and paternal occupational organic solvent exposure (Ha et al 2002). A large retrospective cohort study in Singapore found weak associations between term low birth weight and paternal occupations likely exposed to solvents (Chia et al 2004).

Intrauterine growth retardation

Maternal exposure A large population-based case-control study in the USA found no association between intrauterine growth retardation and maternal or paternal occupational benzene exposure (Savitz et al 1989). A hospital-based case-control study in California found no association between intrauterine growth retardation and maternal 1st trimester occupational solvent exposure (Windham et al 1991). A retrospective cohort study in New Jersey found an association between small for gestational age infants and drinking water carbon tetrachloride levels in the public water system serving the maternal residence (Bove et al 1995). A German birth cohort study found no association between small for gestational age infants and maternal occupational exposure to carbon tetrachloride or a broad category of organic solvents (Seidler et al 1999). A retrospective cohort study in Sweden found no association between term birth weight and maternal occupational exposure before or during pregnancy to solvents (Wennborg et al 2000). A literature review noted that two of five epidemiologic studies found associations between small for gestational age infants and maternal residence in a region served by trichloroethylene-contaminated drinking water (Bove et al 2002).

Paternal exposure A large population-based case-control study in the USA found no association between intrauterine growth retardation and maternal or paternal occupational benzene exposure (Savitz et al 1989). A Norwegian cohort study of men in printing industries found no association between small for gestational age infants and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993).

Preterm birth

Maternal exposure A retrospective cohort study found borderline associations between preterm birth and paternal employment as auto body workers or painters (Daniell and Vaughan 1988). A large population-based case-control study in the USA found no association between preterm birth and maternal or paternal occupational benzene exposure (Savitz et al 1989). A retrospective cohort study in Wisconsin found no association between preterm birth and maternal occupations likely exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association of borderline statistical significance between preterm birth and self-reported maternal 1st trimester occupational exposure to organic solvents (Khattak et al 1999). A literature review noted that none of five epidemiologic studies found an association between preterm birth and maternal residence in a region served by trichloroethylene-contaminated drinking water (Bove et al 2002).

Paternal exposure A large population-based case-control study in the USA found no association between preterm birth and maternal or paternal occupational benzene exposure (Savitz et al 1989). A Norwegian cohort study of men in printing industries found associations between early preterm birth (gestation weeks 16-27) and paternal occupational exposure to solvents or to solvents and lead (Kristensen et al 1993).

4. Birth defects

Reference, location	Design	Exposure	Results	Association ⁵	DR ⁶	Covariate
(McDonald et al. 1988b), Montreal	Hospital-based cohort study, 51,885 term live births, self-reported information on 48,582 previous pregnancies, 1202 birth defects	Self-reported exposure information including occupational history for women employed at time of conception; expert assessment of likely exposures	Birth defects not associated with maternal occupational solvent exposure (relative risk)	1.1 (0.8-1.4)		
(Kyyronen et al. 1989), Finland	Nested case-control study of early fetal death among 1,108 women employed as dry cleaning or laundry workers during 1973-1983 (see also Olsen et al 1990); 130 early fetal death cases, 289 healthy infant controls, 24 birth defect cases, 93 controls	Self-reported maternal exposures in dry cleaning and laundry establishments during 1 st trimester	Birth defects associated with frequent maternal occupational use of solvents other than tetrachloroethylene during 1 st trimester (odds ratios)	tetrachloroethylene 0.8 (0.2-3.5) other solvents 5.9 (1.0-36)		Heavy lifting at work frequent alcohol intake
(Goldberg et al. 1990), Tucson, Arizona	Population-based case-control study in region with known drinking water contamination, 246 cardiovascular birth defects (confirmed by pediatric cardiologists), 461 controls in 3 sets: 1) randomly selected from same region, 2) matched for telephone prefix, 3) other cases of cardiovascular birth defects with no parental occupational or residential contact with contaminated water, 1969-1987	Parent-reported residential history during and before 1 st trimester; water supply for one region of Tucson was contaminated with trichloroethylene, dichloroethylene and chromium from about 1950 to 1981 when contaminated wells were closed	Cardiovascular birth defects associated with parental exposure to drinking water in contaminated region (odds ratio stated without supporting data or CI); no association between CVD birth defects among infants of persons moving into the formerly contaminated region after the well was closed (odds ratio)	3		
(Correa-Villasenor et al. 1991), Baltimore-	Case-control study, 41 cases total anomalous pulmonary venous return, 1981-1987, 2801 healthy infant controls	Self-reported maternal occupational exposures during 3 mos before and 1 st month after conception	Non-significant association between total anomalous pulmonary venous return and maternal periconceptual	3.4 (99% CI 0.7-16)		

⁵ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

⁶ 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

Washington Infant Study			occupational solvent exposure (crude odds ratio); note – only 3 exposed case mothers		
			Total anomalous pulmonary venous return associated with maternal periconceptual occupational exposure to paint/paint stripping (odds ratio)	3.0 (99% CI 1.1-7.7)	Soldering, pesticide exposure
(Tikkanen and Heinonen 1992a), Finland	Population-based case-control study, 406 cardiac birth defect cases, 755 healthy infant controls, 1982-1983	Self-reported maternal prenatal occupational exposures	Ventricular septal defects associated with maternal prenatal occupational exposure to certain chemicals (odds ratios – computed from data in paper)	any chemical 1.5 (1.0-2.2) dyes, lacquers or paint 5.4 (1.7-17)	
			Conus arteriosus syndrome associated with maternal prenatal occupational exposure to certain chemicals (odds ratios – computed from data in paper)	any chemical 2.2 (1.4-3.5) dyes, lacquers or paint 6.7 (1.8-24)	
			Atrial septal defect and hypoplastic left ventricle associated with maternal prenatal occupational exposure to any chemical (odds ratio – computed from data in paper)	atrial septal defect 1.9 (1.0-3.5) hypoplastic left ventricle 2.5 (1.2-5.3)	
(Tikkanen and Heinonen 1992c), Finland	Population-based case-control study, 50 cases atrial septal defect, 756 healthy infant controls, 1982-1983	Self-reported maternal prenatal occupational exposures	Atrial septal defects associated with maternal 1 st trimester occupational exposure to certain chemicals (odds ratios)	any chemical 1.9 (1.1-3.4) organic solvents 2.6 (0.7-9.1) dyes, lacquers or paint 2.2 (0.3-18)	
(Tikkanen and Heinonen 1992b), Finland	Population-based case-control study, 90 cases cardiac conal defects, 756 healthy infant controls, 1982-1983	Self-reported maternal prenatal occupational exposures	Cardiac conal defects associated with maternal 1 st trimester occupational exposure to certain chemicals (odds ratios)	any chemical 1.9 (1.2-3.2) organic solvents	Maternal age, alcohol respiratory infection chemicals other than category of interest

				0.6 (0.2-1.4)	
				dyes, lacquers or paint 2.9 (1.2-7.5)	
(Cordier et al. 1992), France	Hospital-based case-control study, 325 major birth defect cases, 325 healthy infant controls, 1984-1987	Self-reported maternal and paternal occupational history during and before pregnancy; expert assessment of work-related exposures	CNS, urinary tract and cardiac birth defects and chromosomal abnormalities not associated with maternal prenatal occupational exposure to solvents or products containing solvents (odds ratios); note that the numbers of exposed case mothers were 15, 6, 6 and 7	CNS 1.4 (0.6-3.2) urinary tract 1.1 (0.2-5.2) cardiac 1.3 (0.3-6.2) chromosomal abnormalities 0.7 (0.2-1.7)	Residential area, maternal age, SES
			Non-significant associations between oral cleft, musculoskeletal and multiple birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (odds ratios); note that the numbers of exposed case mothers were 8, 12 and 8	oral clefts 6.8 (0.7-128) musculoskeletal 1.7 (0.7-4.2) multiple birth defects 2.8 (0.8-11)	As above
			Borderline or significant associations between oral cleft and multiple birth defects and maternal prenatal occupational exposure to pure solvents (odds ratios); note that the numbers of exposed case mothers were 8 and 12	oral cleft 3.3 (0.8-18) multiple birth defects 4.5 (1.4-17)	As above
(Kristensen et al. 1993), Norway	Cohort study, 10,992 men in printing industry; identified 6,251 infants (incl 60 late fetal deaths at gestational age \geq 28 wk) of workers during 1967-1986 by linking union membership and Norwegian birth registry records	Organic solvent and lead exposure based on job title at time of conception	Total birth defects not associated with paternal occupational solvent exposure (odds ratio)	solvents \pm lead 0.9 (0.8-1.0)	Maternal age, infant birth, sex, birth order

			Borderline association between cleft lip/palate and paternal occupational solvent and/or lead exposure (odds ratio)	1.6 (1.0-2.5)		As above
			CNS, cardiac, genital and limb defects not associated with paternal occupational solvent and/or lead exposure (odds ratios)	CNS 1.1 (0.5-2.0) cardiac 0.7 (0.3-1.2) cryptorchidism 0.6 (0.4-1.0) hypospadias 1.0 (0.5-1.7) limb defects other than clubfoot 1.0 (0.7-1.3)		As above
(Correa-Villasenor et al. 1993), Baltimore-Washington Infant Study	Population-based case-control study, 3377 cardiac birth defects in Maryland during 1981-1989, 3572 control infants	Self-reported parental occupational exposures (case mothers and 21% of case fathers were interviewed)	Among offspring of fathers who participated in interviews, coarctation of aorta and ventricular septal defect were associated with prenatal paternal occupational exposure to paint strippers (odds ratios)	coarctation of aorta 3.5 (1.5-8.0) ventricular septal defect 3.5 (1.5-8.5)	+	Maternal age, year infant's birth, SES, history of cardiac b defects, infant gene disorder
(Matte et al. 1993), Metropolitan Atlanta Congenital Defects Program [citation on order]	Case-control study, 4915 infants with birth defects, 3027 healthy infant controls	Record-based parental occupation as nurses; health care workers may be exposed to known and suspected teratogens including viruses, anesthetic gases, sterilants, mercury and ionizing radiation.	Total, neural tube, cardiac, genital and urinary birth defects associated with maternal occupation in nursing	total defects 1.4 (1.1- 1.9) neural tube 2.0 (1.0-4.3) coarctation of aorta 2.1 (1.1-3.8) genital defects 1.6 (1.0-2.5) urinary tract		Not confounded by age, education or alcohol consumption

				3.4 (1.4-8.3)	
(Bove et al. 1995), New Jersey	Retrospective cohort study, 80,938 live births, 594 fetal deaths among residents of 75 towns, 1985-1988; live births included 1853 term low birth weight, 4082 small for gestational age and 7167 preterm infants and 118 CNS, 56 NTD, 83 oral cleft and 346 cardiac birth defects (the latter included 108 major cardiac defects of which 87 were VSDs)	75 towns served by 49 public water systems; used twice-yearly measures of several organochlorines to estimate monthly levels; assessed avg levels during 1 st trimester for birth defect and fetal death outcomes and throughout pregnancy for fetal growth outcomes	No association between CNS birth defects and trichloroethylene levels (odds ratios, 2-5, 6-10 and >10 vs ≤1 µg/L)(8, 0, 6 and 104 cases in these exposure categories)	0.9 (0.3-2.4) na 1.7 (0.5-5.0)	Maternal age, race, education, primiparous, previous pregnancy, infant sex, prenatal
			No association between oral cleft birth defects and trichloroethylene levels (odds ratios, 2-5, 6-10 and >10 vs ≤1 µg/L)(7, 6, 3 and 67 cases in these exposure categories)	1.3 (0.4-3.6) 3.5 (1.1-11) 1.3 (0.2-5.7)	As above
(Laumon et al. 1996), France	Case-control study, 200 cases oral cleft birth defects, 400 healthy infant controls, 1985-1989	Self-reported maternal 1 st trimester occupational exposures	Oral clefts associated with maternal 1 st trimester occupational exposure to any solvent (odds ratio)	1.6 (1.0-2.5)	
			Oral clefts associated with maternal 1 st trimester occupational exposure to halogenated aliphatic solvents (odds ratio)	4.4 (1.3-15)	Maternal epilepsy, viral disease, infant treatment, alcohol, education, stress, family history of oral cleft
(Blatter et al. 1996), The Netherlands	Case-control study, 349 cases spina bifida (from hospitals and rehabilitation centres), 314 controls (mainly population-based)	Self-reported occupational exposures	Spina bifida not associated with maternal occupational exposure to alcohol or organic solvents other than alcohol (odds ratio for other organic solvents)	1.5 (0.6-4.0)	Population controls for municipality size; region; adjusted for family history of neural defects and maternal fertility drugs
(Blatter et al. 1997), Holland	Case-control study, 222 spina bifida cases (hospital-based), 764 controls (hospital- and community-based)	Self-reported paternal occupational exposures from 3 mos before conception until 1 month after conception including duration of exposure (hr/wk)	No association between spina bifida and moderate or high paternal occupational solvent exposure	0.9 (0.4-2.0)	Excluded infants with maternal use of anticonvulsants, homocysteinemia, consanguinity; adjusted for fertility drugs, oral

					contraceptives, parity, history of NTDs, passive smoking, alcohol
(Marshall et al. 1997), New York State	Population-based case-control study, 473 CNS and 3,305 musculoskeletal birth defects, 12,436 normal births, 1983-1986	Defined exposure based on residence at delivery within 1 mile of hazardous waste sites; assessed potential for exposure via air, water or soil/dust to pesticides, metals and solvents based on information about each of 643 hazardous waste sites; included data on industrial air emissions and drinking water THM levels $\geq 100 \mu\text{g/L}$	No association between CNS birth defects and likelihood of maternal exposure to solvents from hazardous waste sites by routes other than drinking water (odds ratio, likelihood >low vs low)	0.8 (0.4-1.6)	Adjusted as necessary for maternal age, race, education, population density, parity, delay in prenatal care, infant
			Borderline association between CNS birth defects and maternal residential proximity to industrial facilities emitting solvents (odds ratio for distance 0.67-1.0, 0.34-0.66 and ≤ 0.33 vs >1 mile)	1.1 (0.8-1.5) 1.4 (1.0-1.8) 1.4 (1.0-2.0)	As above
			Musculoskeletal birth defects not associated with likelihood of maternal exposure to solvents from hazardous waste sites (odds ratio, likelihood >low vs low)	1.0 (0.8-1.3)	As above
			Musculoskeletal birth defects not associated with maternal residential proximity to industrial facilities emitting solvents (odds ratio, ≤ 1 vs ≥ 1 mile)	1.0 (0.9-1.1)	As above
(Cordier et al. 1997), Europe	Multicentre case-control study, 984 major birth defect cases, 1,134 healthy infant controls	Self-reported information on occupation during month before conception and by trimester during pregnancy; expert evaluation of potential for exposure to glycol ethers	Birth defects associated with maternal 1 st trimester occupational exposure to glycol ethers (odds ratio)	1.4 (1.1-1.9)	Subjects matched for sex and date of birth; adjusted for maternal age, SES, urban/rural, country of origin, study centre
			Cardiac birth defects associated with maternal 1 st trimester occupational exposure to glycol	1.5 (1.0-2.1)	As above

			ethers (odds ratio)		
			Borderline association between musculoskeletal birth defects and maternal 1 st trimester occupational exposure to glycol ethers (odds ratio)	1.3 (0.9-2.1)	As above
			CNS birth defects associated with maternal 1 st trimester occupational exposure to glycol ethers (odds ratio)	1.9 (1.2-3.0)	As above
			Cleft lip and/or palate associated with maternal 1 st trimester occupational exposure to glycol ethers (odds ratio)	2.0 (1.2-3.3)	As above
			Digestive system and genitourinary tract birth defects not associated with maternal 1 st trimester occupational exposure to glycol ethers (odds ratios)	Digestive 1.4 (0.7-2.6) Genitourinary 1.3 (0.7-2.6)	As above
(McMartin et al. 1998), Toronto, Canada	Meta-analysis, 5 epidemiologic studies of major birth defects in relation to maternal organic solvent exposure, published during 1983-1992 (incl Cordier et al 1992 above); Mantel-Haenszel summary odds ratios		Major birth defects associated with maternal organic solvent exposure (summary odds ratio)	1.6 (1.2-2.3)	As above
(Wilson et al. 1998), Baltimore-Washington Infant Study	Case-control study, 1585 cases of heart birth defects, 3572 healthy live birth controls	Self-reported information on various exposures	Transposition of great arteries associated with maternal solvent exposure (odds ratio)	3.2 (p < 0.01)	Adjusted as necessary for family history of congenital heart disease, maternal diabetes, age, smoking, alcohol, ionizing radiation exposure, race, SES.
			Hypoplastic left heart syndrome associated with maternal exposure to solvents/degreasing agents	3.4 (p < 0.01)	As above

			Tetralogy of Fallot associated with exposure of both parents to paint	1.8 (p < 0.05)	As above
			Atrial septal defect with Down syndrome associated with maternal painting (odds ratio)	1.5 (p < 0.05)	As above
(Hewitt and Tellier 1998), Wisconsin	Retrospective cohort study, 118 pregnant women seen by occupational health nurse, 226 women randomly selected from state-wide birth record	Information on occupation and expert opinion on likelihood of solvent exposure	Birth defects not associated with maternal occupations likely to have solvent exposure (relative risk)	0.5 (0.03-2.8)	Adjusted for age; a based on white women without gestational smoking was not a confounder
(Garcia and Fletcher 1998), Spain	Hospital-based case-control study, 261 infants with birth defects, 261 healthy infant controls, 1993-1994	Self-reported parental occupational exposures; occupation in leather industry a proxy for organic solvent exposure	Oral clefts associated with maternal occupation as assembler in leather industry (odds ratio, only 3 exposed case mothers)	6.2 (1.5-26)	
			Multiple birth defects associated with maternal occupation as assembler in leather industry (odds ratio, only 4 exposed case mothers)	3.1 (0.8-12)	Previous fetal loss, smoking, paternal occupation in industry
(Khattak et al. 1999), Toronto	Cohort study, 125 pregnant women, 1987-1996; comparison cohort of women not exposed to solvents	Occupationally exposed to organic solvents including phenols, trichloroethylene, xylene, vinyl chloride, acetone	Major birth defects associated with maternal 1 st trimester occupational organic solvent exposure (odds ratio); note – 13 cases among exposed women and 1 among unexposed women	13 (1.8-100)	Matched for maternal gravidity, smoking
(Lorente et al. 2000), Europe	Multicentre case-control study, 100 mothers of infants with oral clefts, 751 mothers of healthy infants, enrolled during 1989-1992	All subjects were employed during the 1 st trimester; self-reported exposures	Isolated cleft palate (but not cleft lip and palate combined) associated with maternal occupation in housekeeping (odds ratios)	isolated CP 2.8 (1.1-7.2) cleft lip & palate 1.2 (0.5-3.0)	Maternal age, SES, centre, degree of urbanization, country of origin
			Isolated cleft palate associated with 1 st trimester maternal occupational exposure to aliphatic	isolated CP 2.5 (1.1-5.6)	As above

			alcohols; borderline association between combined cleft lip and palate and such exposure (odds ratios)	cleft lip & palate 1.7 (0.9-3.3)	
			Combined cleft lip and palate associated with 1 st trimester maternal occupational exposure to glycol ethers; borderline association between isolated cleft palate and such exposure (odds ratios)	isolated CP 1.8 (0.8-4.0) cleft lip & palate 2.1 (1.1-3.9)	As above
			Combined cleft lip and palate, but not isolated cleft palate, associated with 1 st trimester maternal occupational exposure to cleaning agents (odds ratios)	isolated CP 1.5 (0.7-3.4) cleft lip & palate 1.9 (1.1-3.5)	As above
			Borderline associations between isolated cleft palate and combined cleft lip and palate and 1 st trimester maternal occupational exposure to ethanol (odds ratios)	isolated CP 2.1 (0.9-5.0) cleft lip & palate 1.8 (0.9-3.5)	As above
(Shi and Chia 2001), Singapore	Review of literature on epidemiologic studies of birth defects and maternal occupational exposures		Maternal occupational solvent exposure during 1 st trimester associated with increased risk of major birth defects including cardiovascular (lacquers, paints, organic solvents), oral clefts (halogenated aliphatic solvents, glycol ethers), urinary tract (aromatic solvents, esp. toluene), neural tube (glycol ethers)		
(Wollins et al. 2001), Baltimore-Washington Infant Study	Population-based case-control study, 126 cases coarctation of aorta only, 67 cases coarctation and ventricular septal defect, 3,572 healthy live birth controls, enrolled during 1981-1989	Parent (mainly mother) reported information on parental occupational solvent exposure during critical windows: conception date \pm 3 mos for mother, conception date minus 6 mos for father	Coarctation of aorta associated with maternal 1 st trimester exposure to miscellaneous solvents (paint thinners, photographic chemicals, glue, varnish removers) (odds ratio, daily vs no solvent exposure)	Isolated coarctation of aorta 3.2 (1.3-7.9)	Family history of c heart disease, mater epilepsy, clomiphe macrodantin, sympathomimetics

			Coarctation of aorta combined with ventricular septal defect associated with maternal 1 st trimester exposure to miscellaneous solvents (odds ratio)	Coarctation of aorta and VSD 3.7 (1.3-11)	
(Brender et al. 2002), Texas	Case-control study, Mexican-American mothers of infants with neural tube birth defects (n=184) or healthy infant controls (n=225)	Self-reported parental occupational exposures from 1 yr before to 3 mos after conception	Neural tube birth defects associated with maternal periconceptual solvent exposure at work or home (odds ratio)	2.5 (1.3-4.7)	Maternal age, education, BMI
			Neural tube birth defects associated with maternal periconceptual occupational exposure to glycol ethers and solvents (odds ratios) – note: no control mothers exposed to glycol ethers or solvents	glycol ethers ∞ (1.8- ∞) solvents ∞ (2.4- ∞)	As above
			Neural tube birth defects not associated with paternal periconceptual occupational exposure to glycol ethers or solvents (odds ratio)	glycol ethers 0.7 (0.4-1.3) solvents 0.8 (0.5-1.4)	Household income
(Oliveira et al. 2002), Brazil	Nested case-control study within cohort of 17,113 births in main hospital of Montenegro during 1983-1998; 990 low birth weight infants (<2500 g), 230 late fetal deaths, 160 infants with birth defects	Maternal residential proximity to petrochemical plant: region 1 = <10 km, region 2 = 10-20 km, referent region = 30+ km	Marginally decreased risk of birth defects among mothers living closest to petrochemical plant (odds ratio, maternal residence <10 vs 30+ km)	0.3 (0.7-1.3) p=0.10	Maternal age, smoking, history of chronic disease
(Bove et al. 2002), USA	Review of literature on adverse pregnancy outcomes and drinking water solvent levels; included 5 studies published during 1990-2000	Assessed pregnancy outcomes in relation to tap water solvent levels; most studies did not assess maternal tap water consumption	Studies in Woburn and Camp LeJeune found associations between neural tube defects and cleft lip and drinking water trichloroethylene levels		
			Drinking water trichloroethylene was associated with cardiac		

			defects in one study (Goldberg et al. 1990) and with choanal atresia and eye defects in another study (Woburn)		
			One study (Bove et al. 1995) assessed several other solvents and found associations between neural tube and oral cleft birth defects and drinking water carbon tetrachloride levels		
(Chia and Shi 2002), Singapore	Review of epidemiologic literature on paternal occupation and birth defects; included 10 studies published during 1989-1999	Exposure status usually based on occupational title; statistical power usually insufficient to assess specific types of birth defects	Methodologic limitations and inconsistent findings preclude definitive statements on observed associations		
			Paternal occupations most consistently associated with birth defects included janitors, painters, printers and other occupations exposed to solvents		
(Chia et al. 2003), Singapore	Retrospective cohort study, 3276 birth defect cases among 237,755 live births	Parental occupation stated on birth records	Birth defects (non-chromosomal, single defects) were associated with certain paternal occupations (odds ratio of given category vs manager, senior officer or legislator)	production and related 1.4 (1.1-1.8) plant and machine operators/assemblers 1.5 (1.1-2.0) cleaners, labourers, related 1.4 (1.1-1.9)	Maternal age, education, ethnicity, maternal occupation
			Birth defects (non-chromosomal, single defects) not associated with maternal occupations (odds ratio of given category vs manager, senior officer or legislator)	production and related 1.3 (0.8-2.0) plant and machine operators/assemblers 1.4 (0.8-2.3) cleaners, labourers, related	Paternal age, education, ethnicity, maternal occupation

				1.1 (0.6-2.0)	
(Shaw et al. 2003), California	Case-control study, 662 cleft lip and/or cleft palate cases, 207 conotruncal defect cases, 165 limb reduction cases, 734 healthy infant controls, 1987-1989; identified infant genetic variants for glutathione-S-transferase M1, glutathione-S-transferase T1 and N-acetyltransferases 1 and 2	Self-reported maternal prenatal (1 month before and 3 mos after conception) occupational exposures; expert assessment of potential chemical exposures	Borderline associations between cleft palate &/or lip and maternal prenatal occupational exposure to certain chemicals (odds ratios); note – multiple cleft palate refers to infants with cleft palate and multiple other major birth defects	isolated cleft lip&/or palate vs organic dyes 2.7 (0.9-7.7) isolated cleft palate vs aliphatic hydrocarbons (C ₁₋₄) 2.2 (0.9-5.7) multiple cleft palate vs glycol ethers & derivatives 2.2 (0.8-7.0)	Assessed maternal race/ethnicity, education, folic acid supplementation during periconception
			Borderline associations between conotruncal cardiac defects and maternal prenatal occupational exposure to certain chemicals (odds ratios)	aliphatic hydrocarbons (C ₅₋₁₂) 1.6 (0.8-3.3) organic dyes 5.0 (1.3-17) phenol compounds 3.1 (0.9-9.9) dyes and pigments 2.0 (1.0-4.1)	As above
			Association between conotruncal cardiac defects and maternal prenatal occupational exposure to aliphatic hydrocarbons (C ₁₋₄) stronger among infants with GSTM1 polymorphism (odds ratio)	4.6 (1.0-19)	As above
(Kuehl and Loffredo 2003), Baltimore-Washington Infant Study	Population-based case-control study, 36 cases left transposition of great arteries, 3495 healthy live birth controls; Maryland, District of Columbia and northern Virginia, 1981-1989; assessed geographic case	Maternal residential proximity to National Priority List (NPL) hazardous waste sites, maternal housing characteristics, Maryland toxic release inventory (air emissions of toxic chemicals) for	Two spatial clusters of cases identified (1 in Baltimore, 1 in DC); cases associated with maternal residence in either of 2 geographic clusters (odds ratio, yes vs no); the cluster areas	13 (4.7-38)	

	clustering	1987-1989; 2 of the NPL sites in Baltimore released large amounts of vinyl chloride and chlorinated solvents incl trichloroethene, tetrachloroethene and 1,2-dichloroethene	contained 4 NPL hazardous waste sites (1 in DC, 3 in Baltimore)		
				l-transposition of great arteries associated with paternal occupational exposure to laboratory chemicals (odds ratio, yes vs no)	8.2 (1.7-40)
(Sakamoto et al. 2004), Texas	Case-control study, 184 mothers of infants with neural tube birth defects, 225 controls (mothers of normal infants)	Maternal-reported information about parental occupational exposures during periconceptual period (conception±3 mos for mother, conception -6 mos to +1 month for father); self-reported maternal solvent use at home or with hobbies	Neural tube birth defects associated with maternal occupational solvent exposure (odds ratio)		∞ (2.4-∞) (9 exposed case mothers, 0 exposed control mothers)
			Neural tube birth defects associated with maternal home use of solvents (odds ratio)		2.5 (1.3-4.7)
			Neural tube birth defects associated with maternal occupation as cleaner (odds ratio)		9.5 (1.1-82) (6 exposed case mothers, 1 exposed control mother)
			Neural tube birth defects not associated with paternal occupational solvent exposure (odds ratio)		0.8 (0.5-1.4)

Birth defects: summary

Total birth defects

Maternal exposure A hospital-based birth cohort study found no association between birth defects and maternal occupational solvent exposure (McDonald et al 1988b). A small case-control study within a cohort of Finnish women employed as dry cleaning or laundry workers found an association (imprecise odds ratio) between birth defects and frequent maternal occupational use of solvents other than tetrachloroethylene (Kyrronen et al 1989). A case-control study in Atlanta found an association between total birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found an association between birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). A meta-analysis of five epidemiologic studies found an overall association between major birth defects and maternal organic solvent exposure (McMartin et al 1998). A small retrospective cohort study in Wisconsin found no association between birth defects and maternal occupations likely to be exposed to solvents (Hewitt and Tellier 1998). A very small cohort study in Canada found an association between major

birth defects and maternal 1st trimester occupational organic solvent exposure (Khattak et al 1999). A case-control study in Brazil found a marginally *decreased* risk of birth defects among mothers living closest to a petrochemical plant (Oliveira et al 2002). A retrospective cohort study in Singapore found no association between non-chromosomal single birth defects and maternal occupation as cleaners; there was a borderline association with maternal occupation as plant and machine operators/assemblers (Chia et al 2003).

Paternal exposure A Norwegian cohort study of male workers in printing industries found no association between total birth defects and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A review of ten epidemiologic literature of birth defects and paternal occupation published during 1989-1999 concluded that methodologic limitations and inconsistent findings precluded definitive statements on observed associations; however, paternal occupations most consistently associated with birth defects included janitors, painters, printers and other occupations exposed to solvents (Chia and Shi 2002). A retrospective cohort study in Singapore found that non-chromosomal single birth defects were associated with paternal occupations potentially exposed to solvents including plant and machine operators/assemblers and cleaners (Chia et al 2003).

Multiple birth defects

Maternal exposure

A hospital-based case-control study in France found a non-significant association between multiple birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A hospital-based case-control study in Spain found a borderline association between multiple birth defects and maternal occupation as assembler in the leather industry, a proxy for organic solvent exposure (Garcia and Fletcher 1998).

Central nervous system defects

Maternal exposure

A hospital-based case-control study in France found no association between CNS birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between neural tube birth defects and maternal occupation in nursing (Matte et al 1993). A retrospective cohort study in New Jersey found no association between CNS defects and trichloroethylene levels in public water supplies serving the 1st trimester maternal residence (Bove et al 1995). A case-control study in the Netherlands found no association between spina bifida and maternal occupational exposure to alcohol or other organic solvents (Blatter et al 1996). A large population-based case-control study in New York State found no association between CNS birth defects and likelihood of maternal exposure to solvents from hazardous waste sites by routes other than drinking water; there was, however, an association between CNS defects and maternal residential proximity to industrial facilities emitting solvents (Marshall et al 1997). A multicentre European case-control study found an association between CNS defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). A review of epidemiologic studies concluded that neural tube defects were associated with maternal 1st trimester occupational exposure to glycol ethers (Shi and Chia 2001). A case-control study among Mexican-American mothers in Texas found associations between neural tube birth defects and maternal periconceptual exposure at work or home to solvents and to glycol ethers in particular (Brender et al 2002). A review of five epidemiologic studies of pregnancy outcome and drinking water solvent levels noted that two studies found associations between neural tube defects and drinking water trichloroethylene levels; one study also found an association between neural tube defects and drinking water carbon tetrachloride levels (Bove et al 2002). A case-control study in Texas found associations between neural tube birth defects and maternal use of solvents at work and with their use at home (Sakamoto et al 2004).

Paternal exposure

A Norwegian cohort study of male workers in printing industries found no association between CNS defects and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A case-control study in the Netherlands found no association between spina bifida and paternal occupational solvent exposure (Blatter et al 1997). Two case-control studies in Texas found no associations between neural tube birth defects and paternal periconceptual occupational exposure to glycol ethers or other solvents (Brender et al 2002, Sakamoto et al 2004).

Oral cleft defects

Maternal exposure

A hospital-based case-control study in France found a non-significant association between oral cleft defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A retrospective cohort study in New Jersey found no association between oral cleft defects and trichloroethylene levels in public water supplies serving the 1st trimester maternal residence (Bove et al 1995). A case-control study in France found associations between

oral clefts and self-reported 1st trimester occupational exposure to any solvent and to halogenated aliphatic solvents in particular (Laumon et al 1996). A multicentre European case-control study found an association between cleft lip and/or palate and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). A hospital-based case-control study in Spain found an association (imprecise odds ratio based on 3 exposed case mothers) between oral cleft defects and maternal occupation as assembler in the leather industry, a proxy for organic solvent exposure (Garcia and Fletcher 1998). A multicentre European case-control study found borderline or significant associations between isolated cleft palate and combined cleft lip and palate and 1st trimester maternal occupational exposure to aliphatic alcohols, glycol ethers or ethyl alcohol (Lorente et al 2000). A review noted that six epidemiologic studies had found associations between oral cleft defects and maternal 1st trimester occupations likely exposed to halogenated aliphatic solvents or glycol ethers (Shi and Chia 2001). A review of five epidemiologic studies of pregnancy outcome and drinking water solvent levels noted that two studies found associations between cleft lip and drinking water trichloroethylene levels; one study also found an association between oral cleft defects and drinking water carbon tetrachloride levels (Bove et al 2002). A large case-control study in California found borderline associations between cleft palate and/or lip and maternal prenatal occupational exposure to aliphatic hydrocarbons, glycol ethers or organic dyes (Shaw et al 2003).

Paternal exposure A Norwegian cohort study of male workers in printing industries found a borderline association between cleft lip and/or cleft palate and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993).

Cardiac defects

Maternal exposure A population-based case-control study in Arizona found an association between cardiac birth defects and maternal 1st trimester residence in a region served by a water supply contaminated by trichloroethylene, dichloroethylene and chromium (Goldberg et al 1990). A small case-control study within the Baltimore-Washington Infant Study found associations between total anomalous pulmonary venous return and maternal periconceptual occupational exposure to solvents (non-significant, based on only 3 exposed case mothers) and to paint or paint stripping (Correa-Villasenor et al 1991). A large population-based case-control study in Finland found borderline or significant associations between several types of cardiac birth defects and maternal occupational exposure to chemicals including organic solvents and dyes, lacquers or paints (Tikkanen and Heinonen 1992a, 1992b, 1992c). A hospital-based case-control study in France found no association between cardiac birth defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between cardiac birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found an association between cardiac defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997). The Baltimore-Washington Infant Study found associations between several types of cardiac defects and self-reported maternal exposure to solvents, degreasing agents or paint (Wilson et al 1998). A review noted that three epidemiologic studies had found associations between cardiovascular birth defects and maternal 1st trimester occupations likely exposed to lacquers, paints or organic solvents (Shi and Chia 2001). The Baltimore-Washington Infant Study found associations between cardiac birth defects and 1st trimester maternal exposure to miscellaneous solvents (paint thinners, photographic chemicals, glue, varnish removers) (Wollins et al 2001). A review of five epidemiologic studies of pregnancy outcome and drinking water solvent levels noted that one study found an association between cardiac defects and trichloroethylene-contaminated drinking water (Bove et al 2002). A large case-control study in California found a borderline association between certain cardiac defects and maternal prenatal occupational exposure to aliphatic hydrocarbons; this association was stronger among infants with the GSTM1 polymorphism (Shaw et al 2003). A population-based case-control study within the Baltimore-Washington Infant Study found an association between certain cardiac defects and maternal residential proximity to hazardous waste disposal sites known to release solvents including trichloroethene, tetrachloroethene and 1,2-dichloroethene as well as vinyl chloride (Kuehl and Loffredo 2003).

Paternal exposure A Norwegian cohort study of male workers in printing industries found no association between cardiac defects and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). The Baltimore-Washington Infant Study found associations between certain cardiac birth defects and paternal occupational exposure to paint strippers (Correa-Villasenor et al 1993). A case-control study in Texas found an association between certain cardiac defects and paternal occupational exposure to laboratory chemicals (Sakamoto et al 2004).

Urinary tract defects

Maternal exposure A hospital-based case-control study in France found no association between urinary tract defects and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992). A case-control study in Atlanta found an association between urinary tract birth defects and maternal

occupation in nursing (Matte et al 1993). A multicentre European case-control study found no association between genitourinary birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997).

Reproductive tract defects

Paternal exposure A Norwegian cohort study of male workers in printing industries found no association between hypospadias or cryptorchidism and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993). A case-control study in Atlanta found an association between genital tract birth defects and maternal occupation in nursing (Matte et al 1993). A multicentre European case-control study found no association between genitourinary birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997).

Musculoskeletal defects

Maternal exposure A large population-based case-control study in New York State found no association between musculoskeletal birth defects and likelihood of maternal exposure to solvents from hazardous waste sites by routes other than drinking water or maternal residential proximity to industrial facilities emitting solvents (Marshall et al 1997). A multicentre European case-control study found a borderline association between musculoskeletal birth defects and maternal 1st trimester occupational exposure to glycol ethers (Cordier et al 1997).

Paternal exposure A Norwegian cohort study of male workers in printing industries found no association between limb defects other than clubfoot and paternal occupational exposure to solvents and/or lead (Kristensen et al 1993).

Chromosomal abnormalities

Maternal exposure A hospital-based case-control study in France found no association between chromosomal abnormalities and maternal prenatal occupational exposure to solvents or products containing solvents (Cordier et al 1992).

5. Childhood cancer

Reference, location	Design	Exposure	Results	Association ⁷	DR ⁸	Covariates
(Buckley et al. 1989a), Children's Cancer Study Group, USA, Canada	Population-based case-control study, 178 case-control pairs, acute nonlymphoblastic leukemia (ANLL), healthy controls, age < 18 yr, 1980- 1984	Self-reported parental occupational histories; job- exposure matrix	Childhood ANLL associated with paternal or maternal occupational exposure to solvents (odds ratios, 1- 1000 and >1000 vs 0 days)	paternal exp 2.6 (1.3-5.5) 2.0 (1.2-3.8) p-trend=0.003		
				maternal exp 1.5 (0.6-3.3) 2.2 (0.9-5.4) p-trend=0.05		
			Childhood ANLL associated with paternal occupational exposure to solvents before or during but not after pregnancy (odds ratios)	preconceptual 2.2, p<0.05		
				prenatal 2.1, p<0.05		
				postnatal 1.5, p>0.05		
			Childhood ANLL associated with paternal occupational exposure to petroleum products (odds ratios, 1- 1000 and >1000 vs 0 days)	1.4 (0.8-2.5) 2.4 (1.3-4.1) p-trend=0.002		
			Childhood ANLL associated with postnatal household use of petroleum products (odds ratios, <1, 1-3 and 4+ vs 0 times/month)	1.7 (0.6-4.8) 4.7 (1.3-17) 1.8 (0.7-4.3) p-trend=0.02		
(Buckley et al. 1989b), Children's	Case-control study, 75 cases hepatoblastoma, matched controls, 91% of cases age <	Self-reported parental occupational exposures	Childhood hepatoblastoma not associated with parental occupations likely exposed to	maternal 1.0		

⁷ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

⁸ 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

Cancer Study Group, USA	5yr		solvents (odds ratios, exposed vs unexposed parents; CI's not stated)	paternal 1.1	
			Childhood hepatoblastoma associated with maternal but not paternal occupations exposed to paints or pigments (odds ratios, exposed vs unexposed parents; CI's not stated)	maternal 3.7 (p<0.05) paternal 1.5	
(Olshan et al. 1990), USA	Case-control study, 200 cases of Wilms' tumour, 1984-1986, 233 controls	Self-reported parental occupational histories since age 18 yr	Wilms' tumour not associated with paternal occupations likely exposed to solvents and other hydrocarbons (odds ratios, exposed vs unexposed by period of exposure)	preconceptual 1.4 (0.8-2.7) pregnancy 1.2 (0.6-2.4) postnatal 1.4 (0.7-2.8)	Adjustment for household income made little difference in odds ratios
(McKinney et al. 1991), UK	Population-based case-control study, 109 cases leukemia or non-Hodgkin's lymphoma, 218 controls, age < 15 yr, living in 3 regions with known high childhood leukemia incidence rates	Self-reported parental lifetime occupational and other exposures	Childhood leukemia associated with paternal preconceptional occupational solvent exposure (odds ratios, exposed vs unexposed); there were too few exposed mothers for meaningful analysis of maternal exposure	CCl ₄ 2.9 (1.1-7.4) benzene 5.8 (1.7-26)	Matched for region of residence; odds ratios changed only slightly when adjusted for potential confounders
(Feingold et al. 1992), Denver	Population-based case-control study, 252 cases cancer, age < 15 yr, 222 controls, 1976-1983	Self-reported parental occupational histories (usually reported by mother) for period from year before birth to diagnosis; job-exposure matrix	Childhood cancers not associated with paternal occupational exposure to selected solvents (odds ratios, exposed vs unexposed)	benzene 1.3 (0.6-2.9) solvents 1.5 (0.5-4.8) aliphatic hydrocarbons 1.1 (0.6-2.0)	Paternal education
			Childhood cancers not associated with maternal occupational exposure to selected solvents (odds ratios, exposed vs unexposed)	benzene 1.9 (0.5-6.8) aliphatic hydrocarbons	

				0.9 (0.4-1.9)	
			Childhood acute lymphatic leukemia not associated with paternal occupational exposure to selected solvents (odds ratios, exposed vs unexposed)	benzene 1.6 (0.5-5.8) aliphatic hydrocarbons 1.2 (0.5-3.0)	Paternal education
			Childhood brain cancer not associated with paternal occupational exposure to aliphatic hydrocarbons (odds ratios, exposed vs unexposed)(too few exposed case fathers to assess other solvents)	aliphatic hydrocarbons 0.8 (0.3-2.2)	Paternal education
(Kristensen and Andersen 1992), Norway	Cohort study, 12440 children of men employed as printers, during 1965-1987; linked to cancer registry and computed observed vs expected numbers of childhood cancers	Hygiene surveys during 1947-1980 showed that printers were exposed to solvents and lead	No excess cancer among children age 0-14 yr (8 cases observed, 13.9 expected based on national incidence rates)	SIR=0.6 (0.3-1.1)	
(Durant et al. 1995), Woburn, Massachusetts	Cluster investigation, 28 cases childhood leukemia, 1966-1986; assessed potential exposure to contaminated drinking water	Two new wells in mid-1960's may have been contaminated by hazardous wastes including arsenic, chromium, solvents, pesticides and plasticizers; water contaminant measurements included arsenic (70 µg/L) and chromium (240 µg/L); no direct exposure measurements or estimates for individual cases (see Rogers et al., 1997, below)	The childhood leukemia rate in Woburn during 1966-1986 was about four times the national average	SIR = 4.7 (p < 0.05)	
(Cordier et al. 1997), France	Population-based case-control study, 251 cases brain tumours, 601 controls, age < 16 yr	Parent-reported occupational history for 5 yr before child's birth; coded occupations and industries and applied a job-exposure matrix	Borderline association between astroglial tumors and maternal occupational exposure to solvents	2.3 (0.9-5.8)	Child's age, sex, environmental tobacco smoke and ionizing radiation exposure; maternal age,

			education, centre		
			Primitive neuroectodermal tumors associated with maternal occupational exposure to solvents	3.2 (1.0- 10)	As above
(Colt and Blair 1998), USA	Review of literature, 48 epidemiologic studies (mostly case-control studies) of childhood cancer and parental occupational exposures; limitations included quality of exposure assessment, small numbers of exposed cases, multiple comparisons, and possible bias toward reporting of positive results	Noted that paternal occupations and exposures had been investigated much more frequently than maternal; potential occupational exposure usually based on interviews, birth certificates or other administrative records; some specific exposures estimated by industrial hygienists or self-reports	Concluded that: (1) certain parental occupational exposures may cause childhood cancer and deserve further study, (2) strongest associations were childhood leukemia vs paternal occupational exposure to solvents and paints and employment in motor vehicle-related occupations and childhood CNS cancers vs paternal occupational exposure to paints		
(Harrison et al. 1999), West Midlands, U.K.	Record-based case-control study, 130 leukemia cases, age 0-15 yr, 1990-1994, 251 solid cancer cases used as controls; also assessed observed and expected leukemia cases based on incidence rates for each of 6 regional health authorities	Residence at diagnosis within 100 m of a main road or gas station, traffic flow data; these are crude proxies for outdoor air benzene exposure levels	Case-control analysis: borderline associations between childhood leukemia and residential proximity to a main road or gas station (odds ratios, <100 vs ≥100m)	main road 1.6 (0.9-2.9) gas station 2.0 (0.7-5.4)	(+)
			Ecologic analysis: observed number of childhood leukemia cases with residence <100m from a main road or gas station not significantly increased compared to expected number (ratios of observed to expected cases)	main road 1.2 (0.7-1.7) gas station 1.5 (0.7-2.9)	Population at risk
(Shu et al. 1999), Children's Cancer Group, USA, Canada	Case-control study, 1,842 acute lymphocytic leukemia (ALL) cases, 1986 matched controls, age <15 yr, 1989-1993	Self-reported parental occupational exposures including specific solvents, plastics, paints and oil or coal products	ALL associated with preconceptional or prenatal but not postnatal maternal occupational exposure to solvents, degreasers or cleaning agents (odds ratios, exposed vs unexposed)	preconceptional 1.8 (1.3-2.5) pregnancy 1.6 (1.1-2.3) postnatal 1.1 (0.8-1.4)	Matched for age, race, telephone area code; adjusted for maternal education, race, family income

ALL not associated with paternal occupational exposure to solvents, degreasers or cleaning agents (odds ratios, exposed vs unexposed)	preconceptional 1.1 (0.9-1.3) pregnancy 1.0 (0.8-1.2) postnatal 0.9 (0.8-1.1)	As above
ALL associated with maternal but not paternal preconceptional occupational exposure to solvents, degreasers or cleaning agents (odds ratios, \leq median and $>$ median vs unexposed); also borderline association with prenatal maternal but not paternal exposure (results not shown)	maternal 2.1 (1.3-3.4) 1.4 (0.8-2.3) p-trend<0.01 paternal 1.0 (0.8-1.3) 1.2 (0.5-1.5) p-trend=0.14	As above
ALL associated with preconceptional or prenatal but not postnatal maternal occupational exposure to paints or thinners (odds ratios, exposed vs unexposed)	preconceptional 1.6 (1.2-2.2) pregnancy 1.7 (1.2-2.3) postnatal 1.1 (0.8-1.5)	As above
ALL not associated with paternal occupational exposure to paints or thinners (odds ratios, exposed vs unexposed)	preconceptional 1.0 (0.8-1.2) pregnancy 0.9 (0.8-1.1) postnatal 0.9 (0.7-1.1)	As above
ALL associated with maternal but not paternal preconceptional occupational exposure to paints or thinners (odds ratios, \leq median and $>$ median vs unexposed); also associated with prenatal maternal	maternal 1.8 (1.2-2.9) 1.4 (0.9-2.2) p-trend=0.02 paternal	

			but not paternal exposure (results not shown)	1.0 (0.8-1.2) 1.0 (0.8-1.2) p-trend=0.80	
(Schuz et al. 2000), Germany	Pooled analysis of 3 population-based case-control studies during 1992-1997, 1138 cases acute lymphocytic leukemia (ALL), 2962 controls	Self-reported parental occupational exposures	ALL not associated with maternal occupational exposure to solvents (odds ratios by time period, exposed vs unexposed)	preconceptional 1.2 (0.9-1.7) pregnancy 1.3 (0.8-1.9) postnatal 1.1 (0.6-1.8)	Child sex, age, year of birth, SES, degree of urbanization
			ALL not associated with paternal occupational exposure to solvents (odds ratios by time period, exposed vs unexposed)	preconceptional 1.0 (0.8-1.2) pregnancy 1.0 (0.8-1.3) postnatal 1.0 (0.8-1.2)	As above
			ALL associated with maternal occupational exposure to paints or lacquers before or during pregnancy but not later (odds ratios by time period, exposed vs unexposed)	preconceptional 1.6 (1.1-2.4) pregnancy 2.0 (1.2-3.3) postnatal 1.0 (0.6-1.8)	As above
			ALL not associated with paternal occupational exposure to paints or lacquers before or during pregnancy or postnatally (odds ratios by time period, exposed vs unexposed)	preconceptional 1.1 (0.9-1.4) pregnancy 1.1 (0.9-1.4) postnatal 1.0 (0.8-1.3)	As above
(De Roos et al. 2001), USA, Canada	Case-control study based in 139 hospitals, 538 cases neuroblastoma age <19 yr,	Self-reported parental occupational exposures during 2 yr before child's birth; expert	Neuroblastomas not associated with expert-assessed maternal occupational exposure to	halogenated hydrocarbons 0.7 (0.2-2.1)	Child's age, maternal race, age, education

1992-1994, 538 controls matched for date of birth	assessment of likely exposures including nonvolatile (diesel fuel, lubricating oils) and volatile hydrocarbons (acetone, alcohols, gasoline, lacquer thinner, paint thinner)	hydrocarbons (odds ratios)	nonvolatile hydrocarbons 1.1 (0.5-2.5)	volatile hydrocarbons 1.2 (0.7-2.1)
(Duarte-Davidson et al. 2001), UK	Risk assessment of environmental airborne benzene exposure	Avg urban and rural outdoor air benzene levels were 4 and 1.3 $\mu\text{g}/\text{m}^3$; avg indoor air benzene levels were 8 $\mu\text{g}/\text{m}^3$; indoor levels higher if smokers in home or car in attached garage; avg levels in cars in traffic about 44 $\mu\text{g}/\text{m}^3$; estimated total daily doses were infants (15-20 $\mu\text{g}/\text{m}^3$), children (29-38 $\mu\text{g}/\text{m}^3$),	Neuroblastomas associated with expert-assessed paternal occupational exposure to several hydrocarbons (odds ratios)	As above halogenated hydrocarbons 0.9 (0.5-1.5) nonvolatile hydrocarbons 1.5 (1.0-2.2) alcohols 1.8 (0.9-3.3) lacquer thinner 3.5 (1.6-7.8) mineral spirits 2.2 (1.0-4.9) paint thinner 1.9 (1.0-3.4) turpentine 10 (2.4-45)

		ETS-exposed infants (26 $\mu\text{g}/\text{m}^3$) and ETS-exposed children (49 $\mu\text{g}/\text{m}^3$)	(32-80 mg/m^3)		
(Feychting et al. 2001), Sweden	Birth cohort study, 235,635 children of married couples followed from birth by linking national databases including cancer registry and census; identified cancer cases age < 15 yr (161 leukemia, 162 nervous system tumours, 40 lymphomas, 522 total cases)	Census information on father's occupation/industry and job exposure matrix	Leukemia not associated with paternal occupational solvent exposure	1.3 (CI 0.8-2.0)	Census year, sex, maternal age
			Nervous system tumours not associated with paternal occupational solvent exposure	1.2 (CI 0.7-1.9)	As above
(Freedman et al. 2001), USA	Case-control study, 640 cases acute lymphatic leukemia (ALL), 640 controls, age < 15 yr, enrolled during 1989-1993	Mother-reported information on children's hobbies (during year before diagnosis), indoor painting (since 3 mos before child's conception)	ALL associated with childhood artwork using solvents but not with childhood model building or home furniture stripping (odds ratios for low, medium and high frequency vs never exposed)	artwork using solvents 1.1, 1.2, 4.1 p-trend=0.07 model building 0.9, 1.5, 1.9 p-trend=0.21 furniture stripping 0.9, 1.8, 1.0 p-trend=0.33	Child's age, sex, household income, maternal education
			ALL associated with indoor painting in the year before the child's birth (odds ratios for 1-2, 3-4 and 5+ vs 0 rooms)	1.0 (0.8-1.3) 1.4 (0.9-2.1) 1.7 (1.1-2.7) p-trend=0.01	As above
(Valery et al. 2002), Australia	Population-based case-control study, 106 Ewing's sarcoma cases, 344 controls	Self- or parent-reported exposures from 6 mos before pregnancy to age at diagnosis	Borderline association between Ewing's sarcoma and paternal occupational exposure to solvents and glues at time of conception	2.5 (CI 0.9-6.7)	Matched for age and state of residence; adjusted for sex, maternal

				education, state of residence	
(Costas et al. 2002), Woburn, Massachusetts	Case-control study, 19 cases leukemia, age 0-18 yr, 37 controls, 1969-1989	Potential for exposure to public water supply contaminated with trichloroethylene and other solvents from two wells	Borderline association between childhood leukemia and ever-exposure to Woburn's public drinking water supply (odds ratio, yes vs no)(15 exposed cases)	3.0 (0.8-11)	
			Association between childhood leukemia and exposure to Woburn's public drinking water supply stronger for prenatal than childhood exposure (respective odds ratios, yes vs no)	prenatal 8.3 (0.7-95) childhood 1.2 (0.3-5.1)	Composite covariate for SES, maternal age, prenatal smoking and breast-feeding
(Linnet et al. 2003), USA	Review of epidemiologic literature on childhood cancer		Concluded that there is suggestive epidemiologic evidence for associations between childhood acute myeloid leukemia and parental occupational exposure to benzene		
			Concluded that there is limited epidemiologic evidence for associations between childhood acute lymphoblastic leukemia (ALL) and parental occupational exposure to hydrocarbons, paints or motor vehicle exhaust; brain tumours and paternal occupational exposure to paint or solvents; and between germ cell tumours and maternal occupational exposure to solvents		
(Olshan and van Wijngaarden 2003), USA	Review of epidemiologic literature on childhood cancer and paternal occupation; included reviews by Savitz and Chen (1990) and by Colt and Blair (1998) plus studies published since the latter review including 15 reports on		Leukemia/lymphoma: Colt and Blair (1998) noted that all 5 studies of childhood leukemia/lymphoma and paternal occupational solvent exposure had reported odds ratios exceeding 2; subsequent studies have generally not supported this association (Feychting et al 2001,		

leukemia/lymphoma and 7 reports on brain cancer		Schuz et al 2000, Shu et al 1999)			
		Brain cancer: Colt and Blair (1998) concluded that there was suggestive evidence for an association between childhood brain cancer and paternal occupational exposure to paints (4 of 5 studies reported odds ratios exceeding 2); two recent studies distinguished between paint and solvent exposure and found no association between childhood brain cancer and paternal occupational solvent exposure (Cordier et al 1997, Feychting et al 2001)			
(Shu et al. 2004), Children's Oncology Group, USA	Case-control study, 1,842 acute lymphoblastic leukemia (ALL) cases, 1986 matched controls, age <15 yr, 1989-1993; tested bone marrow samples from 837 cases for mutations in <i>K-ras</i> and <i>N-ras</i> genes at codons 12, 13 and 61 (15% of cases had mutations)	Self-reported parental occupational exposures including specific solvents, plastics, paints and oil or coal products	ALL cases with <i>K-ras</i> but not <i>N-ras</i> mutation were associated with prenatal maternal occupational exposure to solvents, degreasers or cleaning agents (odds ratios, exposed vs non-exposed case mothers); similar results for preconceptual maternal exposure (results not shown)	<i>K-ras</i> +ve 3.1 (1.0-9.7) <i>N-ras</i> +ve 1.0 (0.4-3.1)	Maternal age, race, education, child's age, sex, family income
		ALL cases with <i>K-ras</i> or <i>N-ras</i> mutation were not associated with preconceptual paternal occupational exposure to solvents, degreasers or cleaning agents (odds ratios, exposed vs non-exposed case mothers); similar results for prenatal paternal exposure (results not shown)		<i>K-ras</i> +ve 0.6 (0.3-1.5) <i>N-ras</i> +ve 0.9 (0.5-1.5)	As above
		ALL cases with <i>K-ras</i> or <i>N-ras</i> mutation not associated with prenatal maternal occupational exposure to paints or thinners (odds ratios, exposed vs non-exposed case mothers); similar results for		<i>K-ras</i> +ve 1.0 (0.2-4.4) <i>N-ras</i> +ve 1.5 (0.6-3.6)	Maternal age, race, education, child's age, sex, family income

preconceptual maternal exposure
(results not shown)

ALL cases with <i>K-ras</i> or <i>N-ras</i> mutation were not associated with preconceptual paternal occupational exposure to paints or thinners (odds ratios, exposed vs non-exposed case mothers); similar results for prenatal paternal exposure (results not shown)	<i>K-ras</i> +ve 1.2 (0.6-2.7)	As above
	<i>N-ras</i> +ve 1.0 (0.6-1.7)	

Childhood cancer: summary

Total childhood cancers

Maternal exposure A population-based case-control study in Denver found no association between childhood cancers and maternal occupational exposure to solvents including benzene and aliphatic hydrocarbons (Feingold et al 1992).

Paternal exposure A population-based case-control study in Denver found no association between childhood cancers and paternal occupational exposure to solvents including benzene and aliphatic hydrocarbons (Feingold et al 1992). A cohort study of male Norwegian printers found no excess cancer risk among their children (Kristensen and Andersen 1992).

Leukemia

Maternal exposure A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found a dose-response relationship between childhood acute nonlymphoblastic leukemia and frequency of maternal occupational solvent exposure (Buckley et al 1989a). A recent large case-control study by the Children's Cancer Study Group (USA and Canada) found that childhood acute lymphocytic leukemia was associated with preconceptual or prenatal (but not postnatal) maternal occupational exposures to solvents, degreasers or cleaning agents or to paints or paint thinners (Shu et al 1999). A pooled analysis of three German population-based case-control studies found no association between acute lymphocytic leukemia and maternal occupations likely exposed to solvents; however, there was an association with preconceptual or prenatal but not postnatal maternal occupational exposure to paints or lacquers (Schuz et al 2000). A review of epidemiologic studies concluded that there is suggestive epidemiologic evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene (Linet et al 2003). A review of epidemiologic studies concluded that there is suggestive evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene and limited evidence for associations between childhood acute lymphoblastic leukemia and maternal or paternal occupational exposure to hydrocarbons, paints or motor vehicle exhaust (Linet et al 2003). A large case-control study by the US Children's Oncology Group found an association between those childhood acute lymphocytic leukemia cases with *K-ras* but not those with *N-ras* mutation and preconceptual or prenatal maternal occupational exposure to solvents, degreasers or cleaning agents; cases with the *K-ras* or *N-ras* mutation were not associated with preconceptual or prenatal maternal occupational exposure to paints or paint thinners (Shu et al 2004).

Paternal exposure A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found dose-response relationships between childhood acute nonlymphoblastic leukemia and frequencies of paternal occupational exposure to solvents and petroleum products; the association with solvents occurred for preconceptual and prenatal but not postnatal exposures (Buckley et al 1989a). A population-based case-control study in the UK found an association between childhood leukemia or non-Hodgkin's lymphoma and paternal preconceptual occupational solvent exposure; there were too few exposed mothers for meaningful analysis of maternal exposure (McKinney et al 1991). A population-based case-control study in Denver found no association between childhood acute lymphatic leukemia and paternal occupational exposure to solvents including benzene and aliphatic hydrocarbons (Feingold et al 1992). A review of 48 epidemiologic studies of childhood cancer and parental occupational exposures concluded that the strongest associations with childhood leukemia related to paternal occupational exposure to solvents and paints and

employment in motor vehicle-related occupations paints; all five reviewed studies of childhood leukemia/lymphoma and paternal occupational solvent exposure reported odds ratios exceeding 2 (Colt and Blair 1998). A recent large case-control study by the Children's Cancer Study Group (USA and Canada) found that childhood acute lymphocytic leukemia was not associated with paternal preconceptual, prenatal or postnatal occupational exposure to solvents, degreasers or cleaning agents or to paints or paint thinners (Shu et al 1999). A pooled analysis of three German population-based case-control studies found no association between acute lymphocytic leukemia and paternal occupations likely exposed to solvents or to paints or lacquers (Schuz et al 2000). A review of epidemiologic studies concluded that there is suggestive evidence for associations between childhood acute myeloid leukemia and maternal or paternal occupational exposure to benzene and limited evidence for associations between childhood acute lymphoblastic leukemia and maternal or paternal occupational exposure to hydrocarbons, paints or motor vehicle exhaust (Linnet et al 2003). A large case-control study by the US Children's Oncology Group found no association between those childhood acute lymphocytic leukemia cases with *K-ras* or *N-ras* mutations and preconceptual or prenatal paternal occupational exposure to solvents, degreasers or cleaning agents or exposure to paints or paint thinners (Shu et al 2004).

Childhood exposure A population-based case-control study by the Children's Cancer Study Group (USA and Canada) found a dose-response relationship between childhood acute nonlymphoblastic leukemia and frequency of household use of petroleum products (Buckley et al 1989a). A cluster investigation found a 4-fold increased risk of childhood leukemia in Woburn (Massachusetts), a town where drinking water from wells had likely been contaminated by hazardous wastes including solvents, arsenic, chromium, pesticides and plasticizers (Durant et al 1995). A subsequent case-control study in Woburn found a borderline association between childhood leukemia and ever-exposure to Woburn's public drinking water supply; the association was stronger for prenatal than childhood exposure (Costas et al 2002). A record-based case-control study in the UK found borderline associations between childhood leukemia and residential proximity to main roads and gasoline stations (Harrison et al 1999). A risk assessment concluded that infant and child environmental benzene exposures yield an average daily absorbed dose (per unit body weight) about three orders of magnitude below that for adults occupationally exposed to airborne benzene at the LOAEL for adult acute non-lymphocytic leukemia (32-80 mg/m³) (Duarte-Davidson et al 2001). A Swedish birth cohort study found no association between childhood leukemia and paternal occupations likely exposed to solvents (Feychting et al 2001). A large US case-control study found associations between childhood acute lymphatic leukemia and childhood artwork using solvents but not model building (during the year before diagnosis) and with indoor painting but not home furniture stripping (since year before child's birth) (Freedman et al 2001). A recent review noted that studies published since the 1998 Colt and Blair review generally did not support an association between childhood leukemia/lymphoma and paternal occupational solvent exposure (Olshan and van Wijngaarden 2003).

Brain cancer

Maternal exposure A population-based case-control study in France found an association between childhood astroglial and primitive neuroectodermal brain tumours and maternal occupations likely exposed to solvents (Cordier et al 1997).

Paternal exposure A population-based case-control study in Denver found no association between childhood brain cancer and paternal occupational exposure to aliphatic hydrocarbons; there were too few exposed case fathers to assess other solvents (Feingold et al 1992). A review of 48 epidemiologic studies of childhood cancer and parental occupational exposures concluded that the strongest association with childhood brain cancer was paternal occupational exposure to paints (a proxy for solvent exposure) with 4 of the 5 reviewed studies reported odds ratios exceeding 2 (Colt and Blair 1998). A Swedish birth cohort study found no association between childhood brain tumours and paternal occupations likely exposed to solvents (Feychting et al 2001). A review of epidemiologic studies concluded that there is limited evidence for associations between childhood brain tumours and paternal occupational exposure to paint or solvents (Linnet et al 2003). A recent review noted that two studies published since the 1998 Colt and Blair review found no association between childhood brain cancer and paternal occupational solvent exposure (Olshan and van Wijngaarden 2003).

Neuroblastoma

Maternal exposure A large case-control study of neuroblastoma in the USA and Canada found associations with paternal occupations likely exposed to solvents including alcohols, lacquer or paint thinner, mineral spirits or turpentine (De Roos et al 2001).

Paternal exposure A large case-control study of neuroblastoma in the USA and Canada found no association with maternal occupations likely exposed to solvents including halogenated hydrocarbons (De Roos et al 2001).

Wilms' tumour

Paternal exposure A US case-control study found no association between Wilms' tumour and paternal preconceptual, prenatal or postnatal employment in occupations likely exposed to solvents and other hydrocarbons (Olshan et al 1990).

Liver cancer

Maternal exposure A case-control study by the Children's Cancer Study Group (USA and Canada) found that hepatoblastoma was associated with maternal occupational exposure to paints but not solvents (Buckley et al 1989b).

Paternal exposure A case-control study by the Children's Cancer Study Group (USA and Canada) found that hepatoblastoma was not associated with paternal occupational exposure to paints or solvents (Buckley et al 1989b).

Ewing's sarcoma

Paternal exposure A population-based case-control study in Australia found a borderline association between Ewing's sarcoma and paternal occupational exposure to solvents and glues during the periconceptual period (Valery et al 2002).

Germ cell tumours

Maternal exposure A review of epidemiologic studies concluded that that there is limited evidence for associations between childhood germ cell tumours and maternal occupational exposure to solvents (Linnet et al 2003).

6. Neurotoxicity

Reference, location	Design	Exposure	Results	Association ⁹	DR ¹⁰	Covariates
(Till et al. 2001), Toronto, Canada	Retrospective cohort study, 32 children of women occupationally exposed to organic solvents during 1 st trimester or longer, comparison group of 27 mother-child pairs involving unexposed women; excluded women exposed to illicit or teratogenic drugs from both groups; assessed vision of offspring using Minimalist Test of colour vision and Cardiff Cards test of acuity	Self-reported 1 st gestation occupational exposure to organic solvents including benzene, toluene, methanol, ethanol, trichloroethylene, methyl chloride, methyl ethyl ketone, glycols, ethers, petroleum fuels	Higher error scores on red-green and blue-yellow colour discrimination tests and lower visual acuity scores among children of women prenatally exposed to organic solvents			
(Laslo-Baker et al. 2004), Toronto, Canada	Retrospective cohort study, 32 mother-child pairs involving women occupationally exposed to organic solvents during 1 st trimester or longer, comparison group of 32 mother-child pairs involving unexposed women; excluded women exposed to lead, mercury, alcohol, illicit drugs, teratogenic drugs or heavy lifting from both groups; conducted Wechsler Preschool and Primary Scale of Intelligence at ages 3-5 yr, WISC at ages 6 and 8 yr, language tests at ages 3, 5, 6 and 8 yr and several other neuropsychologic tests	Self-reported occupational exposures solicited prenatally and twice postnatally	No difference between children of women occupationally exposed or not to organic solvents during the 1 st trimester with respect to developmental milestones (age at first smile, lifted head, sat, crawled, stood, first word, walked)	Full-scale, verbal and performance IQ scores at ages 6-8 yr not associated with maternal 1 st trimester occupational exposure to organic solvents (β -coefficient)	full-scale IQ -0.15, p=0.23 verbal IQ -0.17, p=0.16	Maternal IQ, education

⁹ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

¹⁰ 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

		performance IQ 0.03, p=0.85	
	Total language scores at ages 3-8 yr not associated with maternal 1 st trimester occupational exposure to organic solvents (β -coefficient)	-0.18, p=0.14	As above
	Grooved pegboard scores (measure of dexterity and visual-motor coordination) inversely associated with maternal 1 st trimester occupational exposure to organic solvents (β -coefficients)	dominant hand 0.32, p=0.08 non-dom hand 0.45, p=0.01	As above
	Connor hyperactivity/impulsivity score associated with maternal 1 st trimester occupational exposure to organic solvents (β -coefficient)	0.27, p=0.05	As above
	Connor DSM-IV hyperactivity diagnosis associated with maternal 1 st trimester occupational exposure to organic solvents (β -coefficient)	0.63, p<0.001	As above

Neurotoxicity: summary

Visual function

A small retrospective cohort study in Canada found higher error scores on red-green and blue-yellow colour discrimination tests and lower visual acuity scores among children of women prenatally exposed to organic solvents (Till et al 2001).

Developmental milestones

A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1st trimester with respect to developmental milestones (age at first smile, lifted head, sat, crawled, stood, first word, walked) (Laslo-Baker et al 2004).

Cognitive function

A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1st trimester with respect to full-scale, verbal or performance IQ scores at ages 6-8 years (Laslo-Baker et al 2004).

Language

A small retrospective cohort study in Canada found an inverse association between grooved pegboard scores (a measure of dexterity and visual-motor coordination) at ages up to 8 years and maternal 1st trimester occupational exposure to organic solvents (Laslo-Baker et al 2004).

Visual-motor coordination

A small retrospective cohort study in Canada found no difference between children of women occupationally exposed or not to organic solvents during the 1st trimester with respect to total language scores at ages 3-8 years (Laslo-Baker et al 2004).

Behaviour

A small retrospective cohort study in Canada found associations between Connor hyperactivity/impulsivity scores and diagnosis of DSM-IV hyperactivity at ages up to 8 years and maternal 1st trimester occupational exposure to organic solvents (Laslo-Baker et al 2004).

7. Reproductive health effects

Reference, location	Design	Exposure	Results	Association ¹¹	DR ¹²	Covariates
(Eskenazi et al. 1995), California	Cohort study, 152 women employed fabrication room and 251 employed elsewhere in semiconductor industry; assessed time to conception during avg follow-up of 5 mos, daily urine samples for pregnancy tests, daily diary on menstrual bleeding, contraceptive use, intercourse	Daily diary of work activities, other self-reported information, expert assessment of likely exposures	Likelihood of conception lower among exposed workers (fecundability ratio, exposed vs unexposed workers)	0.4 (0.2-1.0)		Opportunity to conceive, maternal age, recent oral contraceptive use, recent pregnancy or lactation, ethnicity
			Likelihood of conception lower among women occupationally exposed to ethylene glycol ethers (fecundability ratio, exposed vs unexposed workers)	0.4 (0.1-1.2)		As above
(Sallmen et al. 1995), Finland	Retrospective cohort study, 105 pregnancies among women monitored for occupational organic solvent exposure, 92 among unexposed women, 1973-1983; assessed time to conception	Self-reported occupational exposure to organic solvents during year before conception: styrene, toluene, trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane; expert assessment of likely exposures	Likelihood of conception inversely associated with maternal occupational solvent exposure at beginning of unprotected intercourse (fecundability ratios, low and high vs no exposure)	low 0.7 (0.5-1.1) high 0.4 (0.3-0.7)		Maternal age, previous induced abortion or ectopic pregnancy, recent IUD use, alcohol, age at menarche, unplanned pregnancy, intercourse frequency
			Likelihood of conception inversely associated with maternal occupational exposure to aliphatic and halogenated hydrocarbons but not other solvents	trichloroethylene 0.6 (0.3-1.3) styrene 1.0 (0.5-1.9)		Other solvents, recent contraceptive use, age at menarche

¹¹ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

¹² 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			(fecundability ratios, high vs no exposure)	toluene 0.7 (0.4-1.3)	
				xylene 0.9 (0.5-1.8)	
				aliphatic hydrocarbons 0.6 (0.4-1.1)	
				halogenated hydrocarbons 0.5 (0.3-1.0)	
(Correa et al. 1996), Baltimore	Retrospective cohort study, semiconductor workers (females and married males), 1980-1989; self-reported reproductive history, 1150 pregnancies among 3007 female employees and wives of male employees; assessed subfertility (required at least 12 mos of unprotected intercourse to conceive)	Estimated exposure to ethylene glycol ethers and self-reported occupational histories and job-exposure matrix based on plant records; main exposure occurred during chemical mixing and photolithography processes	Female employee subfertility associated with occupational exposure to ethylene glycol ethers during year before conception (relative risks, low, medium and high vs no exposure)	1.5 (0.7-3.1) 1.8 (0.8-4.3) 4.6 (1.6-13)	Maternal age, education, previous fetal loss, parity, year of conception, study plant
			Male employee subfertility not associated with occupational exposure to ethylene glycol ethers during year before conception (relative risks, low, medium and high vs no exposure)	1.2 (0.6-2.7) 1.6 (0.8-3.5) 1.7 (0.7-4.3)	As above
(Paul 1997), USA	Review of literature on developmental and reproductive outcomes and occupational exposures		Limited evidence of associations between reduced semen quality and men with likely occupational exposure to solvents including ethylene glycol ethers, chloropropene, carbon disulphide		
			Limited evidence of		

			reduced fertility among women with likely solvent exposure in the semiconductor industry		
(Spinelli et al. 1997), Italy	Retrospective cohort study, 622 women who delivered live born infants in 4 hospitals during early 1993; self-reported time to pregnancy	Mother-reported parental occupational exposures	Likelihood of conception not associated with maternal or paternal preconceptional occupational solvent exposure (fecundability ratios, exposed vs unexposed)	maternal solvent exposure 1.1 (0.8-1.6) paternal solvent exposure 1.0 (0.8-1.3)	Maternal age, parity, intercourse frequency, smoking, alcohol, coffee, tea
(Smith et al. 1997), USA	Case-control study, 281 infertile women (male partners had normal semen quality), 216 fertile women	Self-reported occupational and other exposures	Infertility associated with occupational solvent exposure	1.7 (CI 1.1-2.7)	Date of onset of infertility or first pregnancy
(Sallmen et al. 1998), Finland	Retrospective cohort study, 282 couples involving men monitored for occupational organic solvent exposure (trichloroethylene, tetrachloroethylene, 1,1,1-trichloroethane, styrene, xylene, toluene); assessed time to conception	Self-reported paternal occupational exposure when unprotected intercourse initiated, biological exposure indices; exposure intensity estimated from frequency of solvent use and biological monitoring data	Borderline inverse association between likelihood of conception and paternal occupational organic solvent exposure (fecundability ratios, low/intermediate and high vs unexposed men)	low/intermediate 0.7 (0.5-1.1) high 0.8 (0.6-1.1)	Paternal smoking, maternal age, age at menarche, menstrual cycle length, intercourse frequency, smoking, organic solvent exposure, year of pregnancy
			Among subgroup of couples attempting their first pregnancy, inverse association between likelihood of conception and paternal occupational organic solvent exposure (fecundability ratios, low/intermediate and high vs unexposed men)	low/intermediate 0.5 (0.3-1.0) high 0.4 (0.2-0.7)	As above
(Bull et al. 1999), Norway	Cohort study, 741 married men employed on offshore oil rigs, car mechanics or carpenters; 301 pregnancies analyzed for time to conceive and 580 for early fetal death	Maternal and paternal self-reported information on occupation	Likelihood of pregnancy not associated with exposure to oil and oil products (fecundability ratio)	1.0 (0.7-1.3)	Maternal age, parity, previous reproductive tract infections, prenatal coffee consumption

(Plenge-Bonig and Karmaus 1999), Germany	Retrospective cohort study, 150 men and 90 women employed in printing industry; self-reported reproductive experience, estimated time to conception	Self-reported occupational exposures, expert assessment of exposure levels by job activity; toluene used as exclusive solvent since 1960 in colour printing for catalogues and magazines in Germany	Likelihood of conception not associated with paternal occupational toluene exposure during period of attempting conception; also, no association with exposure intensity (fecundability ratios)	any exposure 1.1 (0.9-1.2) low exposure 0.8 (0.5-1.3) medium 0.8 (0.5-1.5) high 1.1 (0.8-1.6)	Maternal age, smoking
			Likelihood of conception inversely associated with maternal occupational toluene exposure during period of attempting conception (fecundability ratio, exposed vs unexposed)	0.5 (0.3-0.8)	Maternal smoking, parity, nationality
(Taskinen et al. 1999), Finland	Retrospective cohort study, 602 women in wood fabrication industry; assessed self-reported time to conception	Exposure intensity estimated from self-reported work history plus air measurements and proportion of workday exposed; assessed exposure to formaldehyde, organic solvents, wood preservatives, glues	Likelihood of conception inversely associated with high maternal occupational formaldehyde exposure (fecundability ratios by exposure intensity)	low 1.1 (0.9-1.4) medium 1.0 (0.7-1.3) high 0.6 (0.4-0.9)	Maternal employment, smoking, alcohol, menstrual cycle irregularity, parity
			Likelihood of conception not associated with high maternal occupational organic solvent exposure (fecundability ratios by exposure intensity)	low 0.9 (0.7-1.2) medium 0.9 (0.7-1.2) high 1.0 (0.6-1.5)	As above plus formaldehyde
(Tielemans et al. 1999), The Netherlands	Cross-sectional study (letter to editor), 836 couples seeking <i>in vitro</i> fertilization treatment; assessed <i>in vitro</i> fertilization success (number of	Self-reported exposures to pesticides, organic solvents, metal dust or fumes, welding fumes	<i>In vitro</i> fertilization rate not associated with male partner exposure to organic solvents		Female age, indication for <i>in vitro</i> fertilization, previous birth, female

	oocytes fertilized)				education
(Tielemans et al. 1999), The Netherlands	Case-control study, based on infertility clinics; assessed 692 men with sperm concentration < 20x10 ⁶ /ml or < 50% motile or < 14% normal morphology (case group A), 267 men with sperm concentration < 5x10 ⁶ /ml or < 10% motile or < 5% normal morphology (case group B) and 61 men with azoospermia (no sperm)(case group C), 207 controls with sperm concentration ≥ 20x10 ⁶ , ≥50% motile sperm and ≥14% normal morphology; assessed total case groups and subgroups with primary infertility defined as never having fathered a child	Self-reported occupational history, job-exposure matrix; urine from 69 cases and 20 controls tested for nickel, chromium, cadmium and manganese	Poor semen quality (case group A) not associated with solvent exposure (82 exposed cases)	1.0 (CI 0.6-1.6)	Female partner's age, education, clinic
			Borderline association between poor semen quality (case group A) in subgroup with primary infertility and exposure to aromatic solvents (49 exposed cases)	1.9 (CI 0.9-4.2)	As above
			Azoospermia (case group C) associated with exposure to aromatic solvents in subgroup with primary infertility	3.4 (CI 1.5-7.7)	As above
		18/99 cases and 1/18 controls had detectable levels of solvent metabolites in urine	Borderline and imprecise association between poor semen quality (case group A) and urinary solvent metabolite levels (odds ratio)	7.0 (CI 0.8-60)	As above
(Tielemans et al. 2000), The Netherlands	Cohort study, 726 couples seeking <i>in vitro</i> fertilization; assessed implantation rate, i.e., the number of gestational sacs seen with ultrasound at 6-7 wk of pregnancy divided by the	Self-reported parental occupational exposures (both parents) including specific questions on organic solvents, metal dust/fumes,	Implantation success not associated with maternal or paternal occupational exposure to organic solvents, metal dust/fumes,	maternal exposure 1.3 (0.6-3.0) paternal	Indication for IVF, maternal age, number of oocytes fertilized, date of oocyte retrieval

	number of implanted embryos	welding fumes, pesticides	welding fumes or pesticides (odds ratios, exposed vs unexposed)	exposure 1.1 (0.7-1.7)	
			Implantation success inversely associated with high paternal occupational exposure to organic solvents (odds ratios, highly exposed vs unexposed)	0.2 (0.06-0.9)	As above
(Xiao et al. 1999), China	Cohort study, 24 married workers exposed to organic solvents, 40 non-exposed workers, 1994-1996; assessed semen quality and acrosin levels reflect (indicator of sperm ability to penetrate the zona pellucida and achieve fertilization)	Exposed to benzene, toluene and xylene in shoemaking, spray painting or paint manufacturing; measured blood and semen solvent levels	Exposed workers had significantly lower sperm vitality and activity and semen acrosin levels (avg differences, exposed minus unexposed, p<0.05 for each)	sperm vitality (%) -14 sperm activity grade -0.65 acrosin -13 U/L	
			Prevalence of low semen volume and sperm vitality higher among men with occupational organic solvent exposure (% of men, exposed vs unexposed, p<0.05 for each)	semen vol < 2ml 9 vs 2% sperm vitality ≤ 75% 8 vs 32%	
			Semen liquefaction time (min) and sperm concentration (X10 ⁶ /ml) associated with blood benzene levels (mult regression coefficients±SE)	semen liquefaction time 4.7±2.3 sperm conc 0.005±0.001	
(Oliva et al. 2001), Argentina	Cross-sectional study, 177 male partners from couples at infertility clinics, 1995-1998; assessed semen quality and serum FSH, LH,	Self-reported occupational exposures during previous 10 yr	Semen quality inversely associated with occupational solvent exposure (odds ratios)	concentration <10 ⁶ /ml 2.6 (0.9-8.3)	Age, abstinence duration, income, clinic, BMI, smoking

	testosterone and estradiol-17 β levels			total count <3x10 ⁶ 2.5 (0.8-7.9)	
				<50% motile 3.1 (1.0-9.5)	
				< 30% normal morphology 3.0 (1.0-9.0)	
(Wennborg et al. 2001), Sweden	Retrospective cohort study, women in biomedical research laboratories, 735 pregnancies among 560 exposed employees, 68 pregnancies among 27 unexposed employees, 1990-1994; assessed time to conception	Self-reported information on occupational exposures including solvents (acetone, benzene, chloroform, diethylether, phenol, styrene, toluene, trichloroethylene, xylene, other) during time to conception	Likelihood of conception inversely associated with maternal preconceptual occupational exposure to organic solvents in general and acetone in particular (fecundability ratio)	any organic solvent 0.8 (0.7-0.9) acetone 0.7 (0.5-1.0)	Cycle order, maternal age, paternal age, paternal laboratory work and fertility problems
(Xiao et al. 2001), China	Cohort study, 24 married workers exposed to organic solvents, 40 non-exposed workers, 1994-1996 (see Xiao et al 1999 above); assessed semen quality and enzyme levels: acrosin, LDH-C4, γ -GT – note: acrosin levels reflect ability of sperm to penetrate the zona pellucida and achieve fertilization, LDH-C4 levels reflect ability of sperm to generate energy and γ -GT levels reflect prostate function	Exposed to benzene, toluene and xylene in shoemaking, spray painting or paint manufacturing; measured blood and semen solvent levels	Exposed workers had lower sperm activity and lower semen enzyme levels (avg differences, exposed minus unexposed)	sperm activity grade -0.65 acrosin -13 U/L LDH-C4 -705 U/L γ -GT -5.7 U/L	
			Sperm vitality (%) and activity (grade) and semen acrosin levels were inversely associated with duration of exposure (mult regression coeff \pm SE)	sperm vitality -0.96 \pm 0.19 sperm activity -0.046 \pm 0.015 acrosin -0.77 \pm 0.18	
			Sperm concentration was	sperm conc	

			associated with blood benzene levels and semen γ -GT level was inversely associated with blood benzene levels	0.005±0.001 γ -GT -5.6±0.4		
(Cherry et al. 2001), Montreal, Canada	Fertility clinic-based case-control study, 1972-1991; used clinic and hospital records to assess semen quality; Montreal: 208 cases with <12 million active sperm/ml, 446 controls with active sperm counts of 12+ million/ml; 10 other Canadian cities: 172 cases, 396 controls	Solvent exposure level assessed using clinic record information on occupation and a job-exposure matrix	Low active sperm counts associated with solvent exposure in Montreal and other cities (odds ratios for low, moderate and high vs no exposure)	Montreal 1.2 (0.8-1.9) 2.1 (1.2-3.4) 3.8 (1.4-11) other cities 1.0 (0.6-1.6) 1.0 (0.5-1.9) 2.9 (1.0-8.3)	+	Possible lead exposure, age, date of clinic visit
(Chen et al. 2002), Taiwan	Retrospective cohort study, 292 pregnancies among 173 non-smoking, non-alcohol-using female workers in semiconductor manufacturing; self-reported time to pregnancy, 1990-1997	Exposure assessed through company officials, personnel record and self-reported job histories	Non-significantly reduced likelihood of conception among women working in photolithography (fecundability ratio, exposed vs unexposed women)	0.8 (0.5-1.3)		Maternal age, work pattern, contraception before attempting conception, gravidity, psychiatric score, sexual intercourse frequency before pregnancy, duration of employment
			Reduced likelihood of conception among women exposed to ethylene glycol ethers (fecundability ratio, exposed vs unexposed women)	0.6 (0.4-0.9)		As above
(Sheiner et al. 2003), Israel	Review of epidemiologic studies of male fertility and occupational exposures		Reduced male fertility is associated with occupational exposures to solvents			
			There is a clear association between reduced semen quality and occupational solvent exposure			

(Kumar 2004), India	Review of epidemiologic studies of developmental and reproductive health outcomes and occupational exposures	Limited evidence of associations between reduced male and female fertility and occupational organic solvent exposure
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Reproductive effects: summary

Female fertility

A cohort study of women employed in the California semiconductor industry found the likelihood of conception during a 5-month period of attempting to conceive was inversely associated with work in the fabrication room and with exposure to ethylene glycol ethers (Eskenazi et al 1995). In a retrospective cohort study of Finnish women monitored for occupational organic solvent exposure, likelihood of conception was inversely associated with maternal occupational exposure at the beginning of unprotected intercourse to halogenated hydrocarbons but not with exposure to other solvents (Sallmen et al 1995). A retrospective cohort study of semiconductor workers in the eastern USA found a dose-response relationship between female but not male subfertility (required at least 12 months of unprotected intercourse to conceive) and estimated intensity of occupational exposure to ethylene glycol ethers during the year before conception (Correa et al 1996). A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced female fertility and occupational exposure to solvents in the semiconductor industry (Paul 1997). An Italian retrospective cohort study found no association between likelihood of conception and maternal preconceptional occupational solvent exposure (Spinelli et al 1997). A US case-control study found an association between female infertility and occupations likely exposed to solvents (Smith et al 1997). A retrospective cohort study of persons employed in printing found an inverse association between likelihood of conception and maternal occupational toluene exposure during the period of attempting conception (Plenge-Bonig and Karmaus 1999). A retrospective cohort study of Finnish women employed in wood fabrication found an inverse association between likelihood of conception and high maternal occupational formaldehyde exposure but not with high organic solvent exposure (Taskinen et al 1999). In a cohort study of couples seeking *in vitro* fertilization in the Netherlands, the embryo implantation success rate was not associated with maternal occupational exposure to organic solvents, metal dust/fumes, welding fumes or pesticides (Tielemans et al 2000). A retrospective cohort study of women in Swedish biomedical research laboratories found inverse associations between likelihood of conception and maternal preconceptional occupational exposure to organic solvents in general and acetone in particular (Wennborg et al 2001). A retrospective cohort study of non-smoking, non-alcohol-using female workers in semiconductor manufacturing in Taiwan found that likelihood of conception was inversely associated with work in photolithography and with exposure to ethylene glycol ethers (Chen et al 2002). A review of epidemiologic studies of developmental and reproductive health outcomes and occupational exposures concluded that there is limited evidence of an association between reduced female fertility and occupational organic solvent exposure (Kumar 2004).

Male fertility

A cohort study of men employed as car mechanics, on offshore oil rigs or as carpenters found no association between likelihood of conception and likely exposure to solvents or other oil products (Bull et al 1999). An Italian retrospective cohort study found no association between likelihood of conception and paternal preconceptional occupational solvent exposure (Spinelli et al 1997). A retrospective cohort study of Finnish men monitored for occupational organic solvent exposure found a borderline inverse association between likelihood of conception and paternal occupational organic solvent exposure; the association was stronger among couples attempting their first pregnancy (Sallmen et al 1998). A cohort of married men employed on offshore oil rigs or as car mechanics or carpenters found no association between likelihood of conception and occupational exposure to oil or oil products (Bull et al 1999). A retrospective cohort study of German males employed in printing found no association between likelihood of conception and intensity of paternal occupational toluene exposure during the period of attempting conception (Plenge-Bonig and Karmaus 1999). In a cross-sectional study of couples seeking *in vitro* fertilization treatment in the Netherlands, reported in a letter to the editor, the *in vitro* fertilization success rate was not associated with male partner exposure to organic solvents (Tielemans et al 1999). In a cohort study of couples seeking *in vitro* fertilization in the Netherlands, the embryo implantation success rate was inversely associated with high paternal occupational exposure to organic solvents (Tielemans et al 2000). A review of epidemiologic studies of male fertility and occupational exposures concluded that reduced male fertility is associated with occupational exposures to solvents, heavy metals, pesticides and other agricultural materials, radiation, heat and welding (Sheiner et al 2003). A review of epidemiologic studies of developmental and reproductive health outcomes and occupational exposures concluded that there is limited evidence of an association between reduced male fertility and occupational organic solvent exposure (Kumar 2004).

Semen quality

A review of literature on developmental and reproductive outcomes and occupation found limited evidence for an association between reduced semen quality and occupational exposure to solvents including ethylene glycol ethers, chloropropene and carbon disulphide (Paul 1997). A case-control study in the Netherlands found no overall association between low semen quality and occupational solvent exposure; among the subgroup of men with primary infertility, however, there were borderline associations between low semen quality and occupational exposure to aromatic solvents and urinary solvent metabolite levels (Tielemans et al 1999). The latter study also found a significant association between azoospermia and occupational organic solvent exposure. A cohort study of married workers found inverse associations between sperm vitality, sperm activity and semen acrosin levels (an indicator of sperm ability to penetrate the zona pellucida and achieve fertilization) and occupation in jobs exposed to organic solvents; there was also an association between semen liquefaction time and blood benzene levels (Xiao et al 1999). Further investigation of this cohort showed that workers exposed to organic solvents had lower sperm activity and lower levels of semen enzymes including acrosin (reflects ability of sperm to penetrate the zona pellucida and achieve fertilization), LDH-C4 (reflects ability of sperm to generate energy) and γ -GT levels (reflects prostate function) (Xiao et al 2001). The latter study also showed that sperm vitality and activity and semen acrosin levels were inversely associated with duration of organic solvent exposure while semen γ -GT levels were inversely associated with blood benzene levels. A cross-sectional study of couples at fertility clinics in Argentina found associations between low sperm concentration, low total sperm count, low percent of motile sperm and high percent of morphologically abnormal sperm and occupational solvent exposure (Oliva et al 2001). A fertility clinic-based case-control study in Canada found a dose-response relationship between low sperm counts and intensity of occupational solvent exposure (Cherry et al 2001). A review of epidemiologic studies of male fertility and occupational exposures concluded that there is a clear association between reduced semen quality and occupational solvent exposure (Sheiner et al 2003).

8. Other health effects

Reference, location	Design	Exposure	Results	Association ¹³	DR ¹⁴	Covariates
(Shepherd and Klein-Schwartz 1998), USA	Descriptive study, poisoning deaths of adolescents age 10-19 yr, USA, 1979-1994, based on national mortality data		There were 4129 suicidal and 3807 accidental poisoning deaths; volatile solvents and gases played important roles in accidental deaths among adolescents age 10-14 yr and in suicidal deaths among youth age 15-19 yr			
(Garrett et al. 1999), Australia	Cross-sectional study, 53 asthmatic, 95 non-asthmatic children, age 7-14 yr; parent-reported respiratory symptoms, pets, family history of allergies; conducted skin prick allergen tests	Measured home indoor air formaldehyde levels on 4 occasions over 1 yr (1994-1995); median level was 16 µg/m ³ (highest value was 139 µg/m ³)	One or more positive skin prick allergen tests was associated with formaldehyde levels (odds ratios, medium and high vs low formaldehyde level; calculated from data in paper)	<20 µg/m ³ 1.0 (referent)		
				20-50 µg/m ³ 3.6 (1.3-9.6)		
				>50 µg/m ³ 6.0 (1.9-20)		
					p-trend=0.02	
			Asthma was associated with formaldehyde levels (odds ratios, medium and high vs low formaldehyde level; calculated from data in paper)	<20 µg/m ³ 1.0 (referent)		
				20-50 µg/m ³ 3.4 (1.1-11)		
				>50 µg/m ³ 4.1 (1.2-15)		
					p-trend=0.02	

Other health effects: summary*Poisonings*

¹³ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

¹⁴ 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

A study of US national mortality data found that there were 4129 suicidal and 3807 accidental poisoning deaths among children and youth age 10-19 years; volatile solvents and gases played important roles in accidental deaths among those age 10-14 years and in suicidal deaths among those age 15-19 years (Shepherd and Klein-Schwartz 1998).

Asthma

A cross-sectional study in Australia found a dose-response relationship between positive reactions to one or more skin prick allergen tests and home indoor air formaldehyde levels (Garrett et al 1999).

Allergies

A cross-sectional study in Australia found a dose-response relationship between childhood asthma and home indoor air formaldehyde levels (Garrett et al 1999).

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