

A review of studies on maternal occupational exposures and birth defects, and the limitations associated with these studies

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The proportion of pregnant women who work during pregnancy is increasing as more women move into previously male-dominated occupations. With this move, occupational exposure to chemical or physical factors during pregnancy could be further increased. In the last decade, there have been many reports on the causes of birth defects. Unfortunately, most reported associations between occupational exposures and adverse reproductive outcomes in epidemiological studies are equivocal and often controversial. Many reported associations are only suggestive. More information is needed before firm conclusions can be drawn. The major reasons for ambiguous findings are due to limitations of study methodology, e.g. inappropriate endpoints, multiple confounders, low study power and inadequate analysis methods. It must also be noted that maternal work, and therefore exposure, may also differ greatly from country to country.

Key words: Birth defects; industry; limitations; maternal occupation.

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Introduction

Birth defects are an important contributor to infant mortality among all racial/ethnic groups [1]. However, the concept of congenital malformation is not strictly defined [2]. A broader definition might also include functional and metabolic disorders that, although present, may not necessarily be recognizable at birth, but are apparent only later [3].

Worldwide surveys show that the frequency of birth defects varies greatly from country to country. The frequency depends on the duration of observation after birth, the types of malformation included, and the differences in reporting and statistical procedures of collection [4].

Today, women constitute nearly 50% of the workforce in many countries, and most are in their reproductive years. Women are employed in occupations with expos-

ures to strenuous physical exertion, chemicals, ionizing radiation, heat, noise, vibration, infectious agents and stress. These factors may, in some instances, pose risks to pregnant workers and their developing fetuses [5].

The existence of hazardous substances in the workplace has raised concerns about their potential for adverse reproductive effects. Identification of associations between maternal occupational exposures and congenital malformations in their offspring may provide the opportunity for preventing such exposures and thus reduce the risk of malformation [6].

Postulated pathogenic pathway and relevant periods for reproductive hazards used in consideration of epidemiological studies

Table 1 summarizes the relevant periods of occupational exposure and postulated action of possible reproductive hazards in causing birth defects. The aetiology of congenital anomalies in humans is not well understood [7].

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Table 1. Relevant period of occupational exposures for birth defects

Relevant period		Postulated action
Acute	First month before conception First trimester of pregnancy: organogenesis period	Generation of a new mutation during the formation of an ovum cell Maximum risk to the developing fetus, and causing a variety of localized birth defects
	Second trimester of pregnancy	Slight risk for some defects
Non-acute	Lifetime of 1 month before conception and 6 months after conception	Potential storage of chemicals, germ cell damage, stem cell damage

Although DNA replication is a very accurate process, a small number of new mutations are generated at every cell division [8]. The generation of a new mutation during the formation of an ovum or sperm cell can cause an early miscarriage or birth defect. The generation of new mutations during embryogenesis can cause a variety of localized birth defects. The molecular delineation of these errors in somatic and gonadal cells has clarified the basis of some birth defects, and has both refined and complicated genetic counselling for a number of paediatric conditions. The processes responsible for these new mutations occur in all cells.

Human reproduction is a complex process and can be affected in many phases by both host and environmental factors. Many studies have found it difficult to distinguish the occupational causes of congenital malformations from other factors related to parents' characteristics and their living environment. Extrapolation of results of animal studies to humans is complicated because there are structural and functional differences between species, and the mechanisms of harmful effects are seldom known. There is also a paucity of conclusive epidemiological studies on this topic. Thus, at present, knowledge on the potential reproductive toxicity of even rather common occupational exposures is limited and in many cases only suggestive [4].

Most congenital malformations are believed to be due to the interaction of both environmental and genetic influences. According to Taskinen [4], malformations are divided into: those of simple genetic origin caused by single major mutant genes (~7.5% of all congenital malformations in the live born); those due to interactions between hereditary tendencies and usually undefined non-genetic factors (~20% of malformations); those associated with chromosome aberrations (~6% of malformations); those attributed to discrete environmental factors (~6.5% of malformations); and those with no identified cause (~60% of malformations). Occupational and environmental agents are the suspected cause of at least some of the ~60% of birth defects whose aetiology is unknown [9].

The pathogenesis of malformation has been described as occurring in successive stages. It can be a consequence

of genetic damage before conception and/or of the direct action of an agent on the embryo or fetus. Both processes can operate as a result of male and/or female exposure at different moments during conception and pregnancy [10]. For example, gene mutations, chromosome aberrations, mitotic interference, lack of metabolic precursors or energy, enzyme inhibition or osmolar imbalance may be the initial changes after teratogenic insult. These changes may lead to abnormal cell death, failed cell interactions, reduced biosynthesis, abnormal morphogenetic movement or mechanical disruption of tissues. Abnormal embryogenesis may also be the result of damage in one or more phases of development [4].

Maternal exposure to teratogens during organogenesis is the best-known causative pathway for producing birth defects. However, some defects could arise after the critical organogenesis period [11]. Within parents, later effects (i.e. birth defects due to past exposures) could be related to stem cell damage and to the storage of chemicals in the body [10,11].

In addition to those abnormalities conventionally considered birth defects, in recent years, a number of ecologists, epidemiologists, endocrinologists and toxicologists have called attention to the potential hazardous effects of endocrine disrupters. A hypothesis has been proposed that certain chemicals may disrupt the endocrine systems (endocrine-disrupting mechanism) [12]. These chemicals are particularly damaging during the embryonic, fetal and early postnatal periods because they resemble or interfere with the hormones, neurotransmitters, growth factors and other signalling substances that normally control development. The effects are in many cases irreversible, and are often expressed as changes in function rather than as obvious birth defects or clinical disease [13].

Epidemiological studies on maternal occupational exposure and birth defects

Table 2 gives a summary of the occupational groups reported to be significantly associated with birth defects.

Health care workers and related occupational exposures

The reproductive health of workers in the health care services has received considerable attention. Health care workers may be occupationally exposed to a number of chemical and physical hazards, including known and suspected teratogens, such as viruses, anaesthetic gases, sterilants, mercury, cytotoxic drugs and ionizing radiation [14,15].

A recent population-based case-control study assessed the risk of congenital defects among offspring of health care workers [14]. The study analysed parental occupational histories for 4915 case babies with serious birth defects (live-born or stillborn infants), registered during the years 1968–1980 by the Metropolitan Atlanta Congenital Defects Program registry, and 3027 control live-born babies without defects during the same period, matched to cases by year and quarter of birth, race and hospital of birth. Occupational information was obtained by telephone interview. After adjusting for maternal age, education and alcohol consumption, they found that offspring of mothers employed in a nursing occupation during the peri-conceptional period had a modest excess risk of having at least one congenital defect [relative risk (RR) 1.42, 95% CI 1.06–1.88]; the offspring were at increased risk of having anencephaly or spina bifida (RR 2.00, 95% CI 1.01–4.30), coarctation of the aorta (RR 2.06, 95% CI 1.10–3.82), genital system defects (RR 1.61, 95% CI 1.03–2.53) and urinary system defects (RR 3.43, 95% CI 1.41–8.34). Offspring of mothers employed in administrative or clerical jobs in the health care industry also had a modest excess risk of defects (RR 1.35, 95% CI 0.96–1.90), including a statistically significant excess risk of limb defects. They also found associations between neural tube defects and potential exposure to anaesthetic gases and to ionizing radiation, but each association was based on only three cases.

Ionizing radiation is historically known to be teratogenic to the human embryo and fetus. Harmful effects have been suggested [4].

The results of a study on medical radiographers showed a borderline excess of chromosomal anomalies other than Down's syndrome in the children of female radiographers (RR 3.9, 95% CI 1.3–9.0; based on five observations) [16]. The overall risks of major congenital malformation (RR 1.0, 95% CI 0.9–1.2) or chromosomal anomaly (RR 1.4, 95% CI 0.8–2.3) were comparable with the general population rates. However, the numbers of these cases were small and the findings, thus, should be interpreted cautiously.

Neural tube defects showed a significant association with parental preconception exposure to low-level ionizing radiation, but again the numbers of cases were small [17]. In contrast, some studies have not revealed any

association between exposure to ionizing radiation or short waves or microwaves and malformations [18–22].

A study of occupational exposure to ionizing radiation among orthopaedic surgeons and among obstetricians and gynaecologists revealed a higher rate of congenital abnormalities as compared with the normal population in both groups ($P < 0.01$) [23]. However, there was no statistically significant difference in the rate of congenital abnormalities between the offspring of orthopaedic surgeons and the rate for obstetricians and gynaecologists. The findings suggested that the increased rate of abnormalities observed in these two groups is more likely to be associated with factors other than exposure to X-rays.

Another paper has also reported an increased, albeit not statistically significant, risk of congenital malformation for infants whose mothers were exposed to radiation before [odds ratio (OR) 1.9, 95% CI 0.7–5.3] and during early (OR 1.9, 95% CI 0.7–4.9) pregnancy [24].

Studies on exposure to metals among female dental workers during pregnancy have shown contradictory results. A study on the effect of occupational exposure to metallic mercury on the pregnancy of female dental workers in Sweden showed that there was no increase in congenital malformations in the offspring of female dentists, dental assistants or dental technicians [25]. However, in a study from Poland, five cases of spina bifida were reported in the children of 57 dental workers [26].

For exposure to anaesthetic gases, evidence of an increased risk of congenital malformation had generally been considered inconclusive in earlier studies [27]. A case-control study showed that maternal exposure to anaesthetic gases during the first trimester of pregnancy did not increase the risk for congenital heart disease in the offspring [20,28].

In another study, the risk of congenital defect was examined in 47 913 pregnancies of women employed for 15 h a week or more at the time of conception in 60 occupations [29]. Probability estimates were used to calculate the expected numbers of the adverse outcomes by occupational category. The expected numbers (E) were then compared with the observed numbers (O) as ratios (O/E). Within this study, 152 pregnancies of doctors and nurses who had administered antineoplastic drugs in the first month were examined. Eight defects, miscellaneous in type, were observed, compared with 4.05 expected (O/E 1.98, $P = 0.05$).

Two case-control studies reported that maternal exposure to disinfectants during the first trimester of pregnancy was not a factor associated with the risk of conal malformations and ventricular septal defect [28,30].

Laboratory personnel related and solvent-exposed occupations

No specific types of malformation have been found to be

Table 2. Maternal occupational groups reported to be significantly associated with birth defects

<i>Maternal occupations/suspected reproductive hazards</i>	<i>Birth defects</i>	<i>Statistical results</i>	<i>Refs</i>
Health care workers and related exposures			
Nurses (preconceptional exposure)	Anencephaly/spina bifida	RR 2.00 (95% CI 1.01–4.3)	[14]
	Coarctation of aorta	RR 2.06 (95% CI 1.10–3.82)	
	Genital system defects	RR 1.61 (95% CI 1.03–2.53)	
	Urinary system defects	RR 3.43 (95% CI 1.41–8.34)	
Administrative/clerical jobs	Limb defects		
Medical radiographers	Chromosomal anomalies other than Down's syndrome	RR 3.9 (95% CI 1.3–9.0)	[16]
Orthopaedic surgeons, obstetricians and gynaecologists	^a	$P < 0.01$	[23]
Dental workers (during pregnancy)	^a		[25]
Doctors and nurses	^a	O/E 1.78 ($P = 0.05$)	[22]
Laboratory personnel related and solvent-exposed occupations			
Organic solvents (first trimester)	^a	RR 13.0 (95% CI 1.8–99.5)	[38]
Organic solvents	^a	OR 1.64 (95% CI 1.16–2.3)	[39]
Lacquers or paints	Congenital heart defect	$P < 0.05$	[20,30]
	Conal malformation of heart	OR 2.9 (95% CI 1.2–7.5)	
Organic solvents	Ventricular septal defects	RR 1.8 (95% CI 1.0–3.4)	[28]
Organic solvents (during pregnancy)	Oral clefts	OR 7.9 (90% CI 1.8–44.9)	[41]
	Digestive anomalies	OR 11.9 (90% CI 2.0–149)	
Organic solvents (first 2 months after conception)	Multiple anomalies	OR 4.5 (90% CI 1.4–16.9)	
	Cleft lip and/or cleft palate	OR 1.62 (95% CI 1.04–2.52)	[42]
Aromatic solvents	^a	Ratio of 18:8 ($P = 0.04$)	[43]
Glycol ethers (first trimester)	Overall	OR 1.44 (95% CI 1.10–1.90)	[44]
	Neural tube defects	OR 1.94 (95% CI 1.16–3.24)	
	Multiple anomalies	OR 2.00 (95% CI 1.24–3.23)	
	Cleft lip	OR 2.03 (95% CI 1.11–3.73)	
Electromagnetic-exposed occupations			
Visual display units	Renal urinary group of defects	OR 1.84 (90% CI 1.07–3.15)	[46]
Certain service occupations			
Clerical sector	^a	O/E 1.21 ($P = 0.02$)	[29]
Telephone and postal clerks	Developmental defects	O/E 1.14 ($P = 0.02$)	
Receptionists and information clerks	^a	O/E 1.74 ($P < 0.05$)	
	^a	O/E 1.68 ($P < 0.05$)	
Social scientist group	Developmental defects	O/E 1.77 ($P < 0.05$)	
Office machine operators	Chromosomal defects	O/E 3.05 ($P < 0.05$)	
Food and beverage service	Developmental defects	O/E 1.46 ($P < 0.05$)	
	Musculoskeletal defects	O/E 1.46 ($P < 0.05$)	
Leather and textile dye workers			
Leather industry	Oral cleft	OR 6.18 (95% CI 1.48–25.69)	[48]
Leather and shoe manufacturing	Oral cleft	OR 3.9 (99% CI 1.5–9.8)	[49]
	Isolated cleft palate	OR 5.4 (95% CI 1.8–13.4)	
Textile dye workers	Multiple anomalies	OR 1.9 (99% CI 1.0–3.8)	
Leather workers	Musculoskeletal defects	O/E 2.13 ($P < 0.05$)	[29]
Dye workers	Conal septal defects	OR 2.9 (95% CI 1.2–7.5)	[50]
Laundry workers and dry cleaners			
Cleaners and janitor	Oral cleft	OR 8 (90% CI 1.5–8)	[41]
Agriculture-related and pesticide-exposed occupations			
Agricultural workers	^a	Crude OR 1.34 (95% CI 1.07–1.68) Adjusted OR 1.8 ($P < 0.01$)	[54,55]
Agricultural workers	Orofacial clefts	OR 1.9 (95% CI 1.1–3.5)	[56]
Agricultural occupations/lived on farm	Spina bifida	OR 2.2 (95% CI 1.3–3.8)	[52]
Agriculture occupations	Spina bifida	OR 5.6 (95% CI 1.8–17.8)	[57]
Farmers	Spina bifida	OR 2.76 (95% CI 1.07–7.13)	[58]
	Hydrocephaly	OR 3.49 (95% CI 1.34–9.09)	
Pesticide-exposed	Limb reduction defects	OR 2.50 (95% CI 1.06–5.90)	

Table 2. Continued

Pesticide applicers	Neural tube defect	OR 1.6 (95% CI 1.1–2.5)	[59]
	Limb anomalies	OR 1.6 (95% CI 1.0–2.7)	
Agricultural workers	Limb defects	OR 3.9 (95% CI 1.6–9.8)	[60]
Agricultural work (during acute risk period)	Nervous system defects/oral clefts/multiple anomalies	OR 3.16 (95% CI 1.11–9.01)	[61]
Agriculture and horticulture	a	O/E 2.61 ($P < 0.05$)	[29]
	Developmental defects	O/E 4.54 ($P < 0.01$)	
Manufacture and related chemical-exposed occupations			
Lead exposure	Neural tube defects	OR 2.87 (95% CI 1.05–6.38)	[64]
Chemical exposure before conception	a	OR 1.7 (95% CI 1.2–2.5)	[24]
Chemical exposure during first trimester	a	OR 3.5 (95% CI 2.1–5.9)	[24]
	Cardiovascular malformations	RR 1.37 ($P < 0.01$)	[20]

^aOverall major birth defects/general malformations without specific findings.

consistently associated with laboratory work, although there is a perception of an increased risk of malformations among the offspring of laboratory workers [4]. An increased risk of malformation in the offspring has been found in some early studies [31–34], but negative findings have also been reported [35].

Available epidemiological data indicate that the fetuses of laboratory technicians who routinely handle organic solvents might be at increased risk for malformations, particularly when exposure occurs during the first trimester of pregnancy [36].

Solvents, in general, are suspected of injurious effects on reproductive processes [37], with occupational exposure to organic solvents during pregnancy being associated with an increased risk of major fetal malformations. Symptomatic exposure appears to predict a higher fetal risk for malformations, the increased risk of major fetal malformation among women who reported symptoms associated with organic solvent exposure being increased (RR 13.0, 95% CI 1.8–99.5) [38].

The risks for major malformations and spontaneous abortion from maternal exposure to organic solvent during the first trimester of pregnancy or up to 20 weeks of gestation were summarized in a recent meta-analysis [39]. In total, reports of 559 studies were obtained from the literature search. The OR for major malformations ($n = 7036$ patients) with organic solvent exposure was 1.64 (95% CI 1.16–2.30). The available epidemiological data indicate that the children of laboratory technicians who routinely handle organic solvents may be at increased risk for malformations. This is most important during the first trimester of pregnancy. This statistically significant association warrants further investigation [39,40].

Two papers have reported possible associations between cardiovascular malformations and maternal occupational exposure to various factors during the first trimester of pregnancy. In these papers, 406 cases and

756 controls were studied retrospectively [20,30]. The cases were taken from all infants diagnosed with cardiovascular malformations born in Finland during 1982 and 1983. The controls were randomly selected from all normal births in the country during the same period. All mothers were interviewed ~3 months after delivery by a midwife, using a structured questionnaire. Overall maternal exposure to chemicals at work was more prevalent among the case group (35.8%) than the control group (26.2%, $P < 0.01$). Among specific chemical exposure groups, maternal exposure to lacquers or paints was significantly associated with the risk of congenital heart disease. Exposure to organic solvents during the first trimester seemed to increase the risk of ventricular septal defect ($P < 0.05$), and the adjusted relative OR for conal malformations of the heart was 2.9 (95% CI 1.2–7.5). However, the limited power of this investigation needs to be borne in mind.

A further paper has reported that exposure to organic solvents at work was associated with an increased adjusted OR of 1.8 (95% CI 1.0–3.4) for ventricular septal defects [28]. The risk of ventricular septal defects was not associated with any of the maternal habits monitored, e.g. smoking, or coffee, tea, cola, acetylsalicylic acid or diazepam consumption.

Additional information is available from a hospital-based case-referent study conducted in France to assess the risk of major congenital defects in relation to maternal occupational exposure before and during pregnancy [41]. The cases were live-born babies, stillbirths or fetuses of any gestational age resulting from therapeutic abortion. Only major defects detected prenatally or during the perinatal period (from birth to 7 days after birth) were included. Malformations of known environmental or family origin were excluded. The results suggested that mothers of the 'case' children with oral clefts were more often exposed to solvents during pregnancy (crude OR 7.9, 90% CI 1.8–44.9). Digestive anomalies (adjusted OR

11.9, 90% CI 2.0–149) and multiple anomalies (adjusted OR 4.5, 90% CI 1.4–16.9) were also associated with occupational exposure to solvents at work. These results are not entirely independent of each other, since 15 oral clefts out of 29 also had multiple anomalies, as did 15 digestive anomalies out of 22. It was not possible to assess the duration of exposure during pregnancy with precision. The cases and referents differed with respect to several suggested risk characteristics, including delivery age, geographical origin of mother, employment status of mother at the time of pregnancy, parity and socio-economic status of the family. Owing to the small sample size, the estimates of effects were not very precise and results were at the limit of statistical significance ($P < 0.1$).

A case-control study in France, concerning the relationship between maternal organic solvent exposure and oral clefts, showed that maternal occupational exposure during the first 2 months after conception had slightly but significantly increased risk of offspring with cleft lip and/or cleft palate (OR 1.62, 95% CI 1.04–2.52), mainly due to exposure to halogenated aliphatic solvents (OR 4.40, 95% CI 1.41–16.15) [42].

Maternal exposure to aromatic solvents, including toluene, has been associated with a significant excess of malformations in general, and urinary tract malformations in particular. In analyses by nine chemical categories, only exposure to aromatic solvents showed a clear excess frequency of exposure in cases compared with referents (ratio 18:8; $P < 0.05$), most evident in the urinary tract group (9:0) [43]. A comparison of cases and referents exposed to aromatic solvents showed that most of the excess appeared to be associated with toluene and the defects were varied but predominantly renal-urinary or gastrointestinal.

Glycol ethers are found in a wide range of domestic and industrial products, many of which are present in women's working environment. The risk of congenital malformations related to glycol ether exposure during pregnancy was evaluated as part of a multi-centre case-control study, conducted in six regions in Europe [44]. The study comprised 984 cases of major congenital malformations and 1134 controls matched for place and date of birth. Cases were defined as live births, stillbirths and induced abortions with a confirmed major congenital morphological defect that was discovered prenatally, at birth or within the first week of life, and the cause of which was unknown. Interviews of the mothers provided information about occupation during pregnancy, socio-demographic variables and other potential risk factors (medical history, tobacco, alcohol, drugs). A chemist specializing in glycol ethers evaluated exposure during pregnancy, using the job description given by the mother, without knowledge of case or control status. The malformations were classified into 22 subgroups. The overall

OR of congenital malformation associated with glycol ether exposure during the first trimester of pregnancy was 1.44 (95% CI 1.10–1.90), after adjustment for several potential confounders. The association with exposure to glycol ethers appeared particularly strong in three subgroups: neural tube defects (OR 1.94, 95% CI 1.16–3.24), multiple anomalies (OR 2.00, 95% CI 1.24–3.23) and cleft lip (OR 2.03, 95% CI 1.11–3.73). In this last subgroup, risk, especially of an isolated defect, tended to increase with level of exposure.

Electromagnetic field-exposed occupations

Concerns have been raised regarding a possible relationship between occupational electromagnetic (EM) field exposures and adverse reproductive effects. The epidemiological evidence for this possible relationship is inconclusive. Evidence is lacking for a strong association between a woman's use of a video display terminal (VDT) during pregnancy and adverse reproductive outcomes. There were some suggestive findings for congenital malformations, but there were too few data to reach a conclusion [45].

Data from the Montreal survey on occupational factors in pregnancy were used to test the hypothesis that visual display units (VDUs) constitute a hazard to reproduction [46]. Use of a VDU was recorded in 4712 current and 2164 previous pregnancies of women in full-time employment at the time of conception. After allowance for seven confounding variables, the number of pregnancies was increased to include women who worked 15 h or more a week. In all but one of nine groups of congenital defect examined, confidence limits for the RR included unity in both current and previous pregnancies. The RRs for the renal-urinary group of defects were raised in both current (RR 1.84, 90% CI 1.07–3.15) and previous pregnancies (RR 1.66, 90% CI 0.82–3.25). There was no prior reason to suspect a causal link with this type of defect, and interpretation remains open to question.

In a meta-analysis of VDT use during pregnancy and congenital malformations, the pooled OR was 1.0 (95% CI 0.9–1.2) [47]. Maternal exposure to VDTs during the first trimester of pregnancy was not reported to be associated with the risk of an atrial septal defect [19].

With respect to low-level EM field exposures other than VDTs, the paucity of data prevents one from determining whether there are reproductive health risks associated with such exposures. Therefore, this is an area that needs further investigation. Given that altered growth may be an underlying biological effect of EM field exposures, endpoints that might be pursued in future studies include congenital malformations not associated with chromosomal anomalies [45].

Maternal exposure to microwave ovens or VDTs at

work was not associated with the risk of conal malformations/ventricular septal defect [28,30].

Service occupations

Within the six main occupational sectors, significantly increased *O/E* ratios in overall congenital malformations were found among certain service occupations (*O/E* 1.21, $P = 0.02$), and in developmental defects for clerical sector workers (*O/E* 1.14, $P = 0.02$) [29]. In a further detailed analysis in 60 occupational groups, the *O/E* ratio for total defects of telephone and postal clerks (1.74), a miscellaneous group of service occupations (1.68), and receptionists and information clerks (1.47) was increased ($P < 0.05$) [29]. An excess *O/E* ratio of 2.19 ($P < 0.01$) was found in child care workers [22]. Findings for one of the three defect groups but not all defects combined showed: for chromosomal defects, an *O/E* of 3.05 in the social scientists group ($P < 0.05$); an excess risk for developmental defects among receptionists and information clerks (*O/E* 1.77, $P < 0.05$), and office machine operators (*O/E* 1.52, $P < 0.05$); and for musculoskeletal defects, food and beverage service workers (*O/E* 1.46, $P < 0.05$) had a significantly elevated risk [29]. The survey failed to identify any other appreciable risk of congenital defect related to occupation.

Leather and textile dye workers and hairdressers

A hospital-based case-control study in Spain assessing the relationship between maternal occupation in the leather industry in the 3 months preceding conception and several groups of congenital defects indicated that there was a significantly elevated risk of oral cleft (OR 6.18, 95% CI 1.48–25.69) [48].

In a registry-based case-control study, a notable and significant association between oral clefts and mothers involved in leather and shoe manufacturing was found (adjusted OR 3.9, 99% CI 1.5–9.8) [49]. The risk was consistently increased when considering cases with isolated cleft palate separately (OR 5.4, 95% CI 1.8–13.4). Moreover, a significant risk was identified for the association between multiple anomalies and textile dye workers (adjusted OR 1.9, 99% CI 1.0–3.8). Although the dilution effect due to studying large and heterogeneous groups of workers and occupations limits the value of this type of study, it provides a good example of the use of a large database to search for teratogenic risk with the aid of malformation registries.

Maternal exposure to dyes has been reported to be a significant risk factor for conal septal defects (OR 2.9, 95% CI 1.2–7.5) [50].

The risk of congenital defect was examined in 47 913 pregnancies of women employed for 15 h a week or more at the time of conception. For musculoskeletal defects,

there was significant elevated risk for leather workers in the manufacturing sector (*O/E* 2.13, $P < 0.05$) [29].

The results of a historical cohort study indicated an increased risk of adverse reproductive outcomes for hairdressers in the early years that is reduced in later cohorts [51].

Laundry workers and dry cleaners

The results of a hospital-based case-referent study, which assessed the risk of major congenital defects in relation to maternal occupational exposure before and during pregnancy, suggested that mothers of the case children with oral clefts were more often exposed to solvents during pregnancy (crude OR 7.9, 90% CI 1.8–44.9) and worked more often as cleaners (OR 8, 90% CI 1.5–8) [41].

A suspected increased risk of spina bifida was found for cleaning women in a case-control study based on information collected on specific tasks undertaken in the period just after conception (OR 1.7, 95% CI 0.9–3.4) [52]. A matched case-control study involving dry cleaner and laundry workers throughout Finland who had become pregnant during the study period showed that three women out of four had worked in early pregnancy. The OR (5.9, 95% CI 1.0–35.7) for congenital malformation was significantly increased for exposure to solvents other than tetrachloroethylene among laundry workers and dry cleaners during the first trimester of pregnancy [53].

Agriculture-related and pesticide-exposed occupations

Previous epidemiological research has yielded inconsistent results on the association of birth defects with maternal involvement in agricultural activities and/or occupational exposure to pesticides. Significant associations have been observed with all congenital malformations (crude OR 1.34, 95% CI 1.07–1.68; and adjusted OR 1.8, $P < 0.01$) [54,55].

A nationwide time- and area-matched case-referent study showed an adjusted OR of 1.4 (95% CI 0.9–2.0), when all birth defects were pooled and maternal agricultural work was compared with non-agricultural work in the first trimester of pregnancy [56]. For orofacial clefts, the corresponding OR was 1.9 (95% CI 1.1–3.5), indicating that the occurrence of orofacial cleft was associated with agricultural work in the first trimester of pregnancy. However, a number of potential biases arose in this study. Often, the interviewer could not be truly blinded to the case/control status of the interviewee. Mothers of malformed infants could have recalled their exposure more thoroughly than the mothers of healthy infants (recall bias). Although the original size of the study seemed large, the numbers in the final comparisons

concerning pesticide exposure in the agricultural work were so small that the observed elevated point estimate of the OR for orofacial clefts could have been affected if even one reference mother had forgotten her exposure. Therefore, the data did not allow a proper study of pesticide exposure, but only of the broad category of agricultural work in general.

The results of a register-based linkage study in Sweden suggested an increased risk of spina bifida for the infants of women in agricultural occupations or those who lived on a farm (OR 2.2, 95% CI 1.3–3.8), but they did not provide insight into any specific occupational risk factors [52].

Another multi-centre case-control study in The Netherlands also found an increased risk of spina bifida for maternal agricultural occupations (OR 5.6, 95% CI 1.8–17.8) [57].

A registry-based investigation in Norwegian farmers found moderate increases in risk for spina bifida and hydrocephaly, the association being strongest for exposure to pesticides in orchards or greenhouses (spina bifida: five exposed cases; OR 2.76, 95% CI 1.07–7.13; hydrocephaly: five exposed cases; OR 3.49, 95% CI 1.34–9.09) [58]. Exposure to pesticides, in particular in grain farming, was also associated with limb reduction defects (OR 2.50, 95% CI 1.06–5.9) [58].

A case-control study of maternal pesticide exposure and selected congenital anomalies showed that women who reported that a professional applied pesticides to their homes had increased risks for neural tube defect-affected pregnancies (OR 1.6, 95% CI 1.1–2.5) and limb anomalies (OR 1.6, 95% CI 1.0–2.7) [59]. In addition, women who reported living within 0.25 miles of an agricultural crop had an increased risk of having offspring with neural tube defects (OR 1.5, 95% CI 1.1–2.1). In this study, data were sparse for many of the comparisons, possibly resulting in imprecise effect estimates. For many subjects in this study, there were multiple sources of potential pesticide exposures, and there was no more specific information on the chemical and level of exposure. Consequently, we could not discriminate adequately whether the observed effects were valid, whether biased exposure reporting contributed to the observed elevated risks, or whether non-specific measurement of exposure was responsible for many of the observed estimated risks not being elevated.

Limb defects were found to be associated with maternal agricultural work in a cross-sectional study (crude OR 3.9, 95% CI 1.6–9.8) [60].

A hospital-based case-control study in Spain investigated 261 live cases with selected defects (nervous system, cardiovascular, oral clefts, hypospadias/epispadias, musculoskeletal and unspecified anomalies) during the first years of life and 261 controls [61]. Exposure was estimated during the acute risk period (the month before

conception and the first trimester of pregnancy) and the non-acute risk period (before the acute period and/or during the second trimester of pregnancy) using interviews. A statistically significant association for maternal involvement in agricultural work during the acute risk period was found (adjusted OR 3.16, 95% CI 1.11–9.01), primarily due to an increased risk for nervous system defects, oral clefts and multiple anomalies. The power of this study to detect a significant OR of ≥ 3.00 for maternal involvement in agricultural work during the acute risk period and all selected congenital malformations was relatively low. The analysis of maternal handling of pesticides and groups of congenital malformations was limited by small numbers.

In a detailed analysis involving 60 occupational groups, the *O/E* ratio for overall defects was increased among agricultural and horticultural workers (*O/E* 2.61, $P < 0.05$) [29]. The findings for one of the three defect groups but not for all defects combined showed that the occupational group agriculture and horticulture had an excess risk for developmental defects (*O/E* 4.54, $P < 0.01$). There were two cases of tracheo-oesophageal fistula, a rare defect, among eight defects (1.32 expected) in agriculture and horticulture. With these few exceptions, the survey failed to identify other appreciable risks of congenital defect related to occupation. Although there were >100 000 pregnancies in this study, the power to detect risks in some occupational groups is limited, as the positive results were based on small numbers. The negative findings could also be due to a lack of sensitivity and discriminant ability in the method of exposure estimation.

A register-based study to evaluate the possible increased risk for offspring of pesticide applicators indicated that the birth defect rate for all birth anomalies was significantly increased in children born to private applicators [62]. Specific birth defect categories, circulatory/respiratory, urogenital and musculoskeletal/integumental, showed significant increases.

Manufacture and related chemical-exposed occupations

Metal-exposed occupations

The reported potential reproductive toxicities of metals are largely based on animal data, whilst the data on the effects of metal exposure on pregnancy outcome in humans are scanty and somewhat contradictory [4]. A significantly increased frequency of malformations, and some specific multiple malformations, among the offspring of women who had worked at a copper smelter during pregnancy were reported in one epidemiological study [63].

Prenatal lead exposure seems to affect offspring, although the present findings are inconsistent [4]. In

Norway, all births from 1970–1993 with possible maternal or paternal occupational lead exposure were studied [64]. Offspring of lead-exposed mothers had an increased risk of neural tube defects (OR 2.87, 95% CI 1.05–6.38), but no increased risk was identified for the offspring of exposed fathers.

Significantly increased *O/E* ratios for congenital malformations were found among children of women in the manufacturing occupations (*O/E* 1.14, $P < 0.05$), attributable to the manufacture of metal and electrical goods (*O/E* 1.36, $P < 0.05$), when 60 occupational categories were analysed [22].

Chemical-exposed occupations

A hospital-based case–control study in China indicated that birth defects were significantly associated with maternal exposure to chemicals before and during the first trimester of pregnancy (adjusted OR 1.7, 95% CI 1.2–2.5; and OR 3.5, 95% CI 2.1–5.9, respectively) [24].

In the Montreal survey from May 1982 to May 1984, 301 women who had an infant with an important congenital defect (for the most recent birth) were individually matched with 301 women whose infants were normal [43]. Both cases and referents were drawn from a comprehensive survey of pregnancies in Montreal, 1982–1984, and limited to women employed ≥ 30 h a week until at least the 13th week of gestation. Occupational exposure to chemicals was investigated and the results classified without knowledge of case–referent status. In matched-pair analysis, the overall frequency of chemical exposure was higher in cases than referents (63:47). Excesses were found in the cardiac and miscellaneous defect groups (ratios of 10:5 and 15:7, respectively).

In a Finnish study to investigate possible associations between cardiovascular malformations and maternal occupational exposure to various factors during the first trimester of pregnancy, 406 cases and 756 controls were studied retrospectively [20]. Infants with cardiovascular malformation were identified independently from the Finnish Register of Congenital Malformations or the Children's Cardiac Register. All the mothers were interviewed ~3 months after delivery using a structured questionnaire. Overall maternal exposure to chemicals at work during the first trimester was more prevalent among the case group (35.8%) than the control group (26.2%, $P < 0.01$, χ^2 test). This was also true in most of the ontogenetic groups including ventricular septal defect (VSD, $P < 0.05$), conus arteriosus syndrome (CAS, $P < 0.01$), hypoplastic left ventricle (HLV, $P < 0.05$) and other defects (O, $P < 0.05$) of congenital heart disease. However, the power of this study was relatively weak when testing the teratogenicity of specific chemicals. This study might also have been subject to a variety of

sources of error: incomplete reporting of cases, difficulty in recalling events in early pregnancy, as well as selective recall were all potential sources of bias. There were also difficulties in controlling for confounding factors and problems of chance association [20].

Excesses of congenital defects with *O/E* of 2.02, which reached a 10% significance level, were reported for those engaged in plastics and rubber manufacture [29]. Further analyses of chemical exposure profiles for each occupational group showed no evidence of any increased risk, perhaps due to lack of sensitivity and discrimination in this method of exposure estimation.

Discussion

Many of the associations described between occupational exposures and adverse reproductive outcomes in epidemiological studies are equivocal and often controversial. Some of the reasons why weaker teratogens have not been identified may be methodological. Besides the usual bias and confounding that tend to reduce the scope of studies in environmental epidemiology, investigations of reproductive outcomes raise specific difficulties as to what constitutes a final reproductive outcome [44]. Moreover, maternal work and therefore exposure may differ greatly from country to country.

Considering the main limitations in research carried out to date, future research will benefit from taking the following basic issues into account.

Validity of birth defect ascertainment

Since the concept of congenital malformation is not strictly defined, inclusion criteria vary from study to study. The ascertainment of the congenital malformations can be influenced by differences in the source of malformation information, the period between birth and detection of the malformations, and diagnostic definition of a specific malformation.

Ascertainment of birth defects has been accomplished from a variety of sources. For example, vital statistics records (birth certificate, death and fetal death certificate), interviews with parents or postal questionnaires, medical records, and active or passive reporting as part of a surveillance system. The use of different information sources may result in variation in the inclusion and exclusion of a given malformation, and the completeness and accuracy of malformation information in some sources may be doubtful.

Birth certificates are frequently used to ascertain congenital malformation because of their relative ease and low cost, but the drawback is that the malformation information on birth certificates is notoriously incomplete and of low accuracy. This may cause underestimation of the actual problem of birth defects.

Birth defect information obtained from interviews of parents or postal questionnaires may have poor reliability due to low response rate and uncertainty in the recognition and recall of malformation. It may introduce misclassification of malformation cases. Socio-economic status and educational level may influence a person's ability and willingness to participate in interview and questionnaire studies, potentially confounding results. Furthermore, selection by exposure or pregnancy outcome between the respondents and non-respondents may introduce bias [6].

Medical records/hospital data are more reliable than questionnaire data, since the information is based on medical diagnoses and is recorded at the time of the event. Frequently, however, the record data are not sensitive, and variations in health care-seeking behaviour may weaken the validity of the data. This may be influenced by parents' socio-economic status, educational level and area of residence.

Surveillance systems, such as population-based birth defect registries and health surveillance programmes from hospitals where there is active monitoring for birth defects, would be a more reliable system. With these types of surveillance system, the amount of information may be large and relatively complete, and have relatively accurate ascertainment. Several studies have shown some under-reporting in registry data [6,20].

Detecting periods and the complex relationship between reproductive endpoints

The length of the prenatal and postnatal period in detecting birth defects varies considerably among studies. According to postulates on the pathogenesis of malformation, an effect of a reproductive hazard can occur during several stages of conception and pregnancy [10]. The processes can operate as a result of parents' exposure at different times related to pregnancy. In addition, depending on the level and timing of exposure, any single given compound may lead to different outcomes (e.g. different patterns of malformations or fetal loss) [8,10].

While some epidemiological studies have found no increased risk for birth defects from parental occupational exposure, others have reported significant associations with spontaneous abortion/stillbirth [46,53,65–69]. Malformations identified late during gestation or at birth are survivors of a cohort of malformations rather than including all abnormalities, thus perhaps inducing selection bias [44]. Studies that only include congenital malformations present at birth are likely to underestimate true numbers because many birth defects are associated with a high prenatal mortality [70]. Studies that follow up the birth for some time are more likely to detect other

malformations that cannot be diagnosed immediately at birth.

Estimation of occupational exposures

Preconception occupational exposures of either parent could theoretically contribute to the subsequent development of offspring with a malformation. Both dose and duration of exposure are likely to be important [6]. Measurement of exposure during all relevant periods according to postulated mechanisms of toxicity is a key issue.

Defining exposure time relative to embryological development allows for a greater likelihood of identifying a particular agent or agents as possible teratogens, but imprecision in estimation of fetal age makes it difficult to know the actual date of conception, which leads to variation in estimates of the critical period for harm and misclassification of exposure status.

In most studies of occupational exposures related to congenital malformations, it is difficult to assess the extent of exposure accurately. The validity of reported occupational exposures is crucial to risk estimation and entirely dependent on sources of information and inclusion of validity checks.

There are several sources of exposure information used in epidemiological studies. The advantages and disadvantages of the commonly used sources are listed in Table 3. They are best regarded as complementary, as each has its strengths and weakness.

In most studies, exposure status has been estimated by an occupational hygienist or other specialist, in order to get accurate exposure assessment. Potential problems arise when judgements vary among individuals. Blinding the occupational hygienist to the case/control status of an individual is difficult. Inaccurate assessment by the hygienist may also reduce the power to detect associations because of non-differential misclassification [71].

It is worth mentioning that most studies simply used the occupation description or just occupation title as a surrogate of workplace exposure, with some also using working hours and duration of employment. These indices do not quantify dose accurately. There is no information about the exact exposure concentration in the workplace. When the conclusions of the studies are written, a number of crucial problems are raised by this, particularly as the extent of exposures may differ between countries even when the same occupation title is used. It is also important whether or not the workers were using protective devices. Furthermore, different coding systems for occupation and industry used in epidemiological studies in different countries also make the findings of studies incomparable when the exposure estimates are based primarily on the occupation and or industrial classification. Although occupational titles are similar, the

Table 3. Comparison of the sources for occupational exposure estimation

<i>Sources</i>	<i>Advantages</i>	<i>Disadvantages</i>
Birth certificates	<ol style="list-style-type: none"> 1. Ease of access and low cost 2. Less recall bias 	<ol style="list-style-type: none"> 1. Data may be incomplete, and sensitivity is ranged 2. The recorded parental occupation at the time of birth on the birth certificate may not be the parents' usual occupation or occupation at conception or at the critical time during pregnancy, and may be subject to misclassification, which would lead to an attenuation of relative risk estimates 3. Classifying exposed or non-exposed by occupation title on the certificate may cause information bias 4. Confounder information related to congenital malformation is limited
Interview with questionnaire	<ol style="list-style-type: none"> 1. Subjects can be queried directly in a detailed and standard way about occupational exposure (substance, timing, protective gear and work habit) 2. Confounder information may be available 	<ol style="list-style-type: none"> 1. May not know with certainty about exposures as subjects may have changed job from time to time 2. Easy-to-contact effect: the parent who is easily contactable becomes the respondent 3. A specific job title may not provide valid and complete information about specific occupational exposure 4. Information bias is more likely. Parents of a child with malformations may recall exposures better than parents of a non-affected child. This may cause differential misclassification of exposure, and overestimate the association
Company records	They are not subject to recall bias and tend to be more complete in recording occupational exposure	<ol style="list-style-type: none"> 1. Lacking the updating of exposure status change over time 2. A company may not be cooperative in sharing records for studies of potential adverse health effects of occupational exposures, so the completeness and validity of data or even the possibility to obtain data in this way may be not available 3. Exposures from any given job title or position may change over time, but this may not be recorded routinely in the company records 4. Information of potential confounders may be insufficient
Birth defect register	<ol style="list-style-type: none"> 1. Sometimes 'prospective' information is collected in large populations that may contain medical information of interest and can be used for an analysis of this type, therefore, is efficient 2. Less recall bias and selection bias 	<ol style="list-style-type: none"> 1. Information is not collected for specific study. In some registries, information is rather scanty. Usually they lack detailed records of occupational exposures and confounder information 2. Miscoding and wrong data entries exist

nature of the work could differ between countries. In addition, the nature of certain occupational exposures may have changed over time. When this happens, using occupation as a surrogate of workplace exposure can result in inconsistent findings.

Potential bias

There are several types of potential bias that specifically affect the validity of studies of occupational exposure and reproductive health [72].

Infertile worker effects

This is the bias that results from mistaking the direction

of causation: employed status is the result rather than the cause of childlessness.

Desperation and privilege effects

The decision whether or not to work reflects a number of aspects of a woman's life. Women who have young children and a job are mainly either those who have a professional career and can afford private child-care arrangements, or those who may be driven to go out to work by financial pressures and/or because of an unsatisfying home life owing to bad housing, isolation, etc. These problems can cause stress in their own right and additional risks may arise as a consequence of these, e.g. smoking. Moreover, women in a disadvantaged social

position would be most likely to have occupations that are poorly paid and unpleasant to work in. These effects of life-in-general may be attributed solely to the effect of work, resulting in false-positive associations between workplace exposures and reproductive risk. The effect of this bias is probably greatest for those with child-care responsibilities.

Unstable pregnancy and related effects

A woman who has a pregnancy that is precarious, and which is seen as such, is likely to leave employment early during pregnancy. Unlike the first two biases, this bias, if ignored, leads to a false-negative association between having a job and reproductive risk.

Potential confounders

Place of birth, delivery age, residence, education, family income, medical and obstetrical history, pregnancy history (infections and drug treatment), smoking and drinking, hobbies, initiation of prenatal care, weight gain during pregnancy, pregnancies in diabetics, nutrition, etc. can all affect the outcome of pregnancy [4,73]. All these listed factors, if not considered (and sometimes they may be very difficult to ascertain), could confound the results of studies of birth defects. The effect of low socio-economic status can sometimes only be separated from the effect of occupational exposure with great difficulty [74].

Reference group

Matching procedures used in case-control studies for multiple factors diminish the availability of suitable referents and thus decrease the numbers of case-control combinations in the study, which affects the statistical power. Matching has been criticized because it may cause some inefficiency in case-referent studies [75]. There has been extensive ongoing discussion of the question of whether to use births affected by a malformation or a normal group as a reference [76].

Sample size and statistical analysis

Defining groups of malformations for analysis is a trade-off between the loss of statistical power induced by 'splitting' and the possible increase in misclassification resulting from 'lumping' together unrelated malformations [44]. Because specific malformations are rare, the practice of grouping malformations broadly is often undertaken to increase sample size with concomitant increases in study power. However, grouping data may decrease biological validity even if the grouped malformations are suspected to have a similar aetiology. It may be that most epidemiological studies cannot draw consistent conclusions because of their small sample size

for specific malformations, although sometimes the total study sample seems large. Often the data are insufficient to allow classification into specific malformations.

Some studies have aggregated occupations for analysis because of the small number of subjects in each category; this grouping may also have introduced error.

There are ~200 specific congenital malformations at the four-digit level of the International Classification of Diseases (Ninth Version). If analysis is carried out for each one (multiple tests), we could expect to have some statistically significant results simply by chance. Thus, the process of specifying individual malformations increases the number of statistical tests and the potential for false positives.

Non-response

Usually, there is no available parental occupational information for the non-respondents; it may introduce potential selection bias when there is differential non-participation in study groups.

Summary

The associations between occupational exposure and adverse reproductive outcomes in epidemiological studies are equivocal and often controversial. This fact should not reduce the search for risk factors that have a role in causing congenital malformation since more and more interesting findings are emerging. As mentioned in the Discussion, there are many limitations in the currently published literature.

In theory, a teratogenic agent can cause an increase in all types of malformations, but all experience, so far, shows that some sort of specificity usually exists. The teratogenic effect of a specific occupational exposure is unlikely to result in a general increase in all types of malformation, although it may increase the risk of more than one malformation, particularly if the exposure occurs during a specific time of gestation when more than one organ system is developing [6].

Since the total malformation rate (according to a given definition) may not reveal a change in the rate of a specific type of malformation, it is useful to study malformations on a more detailed level [2]. It is unhelpful to group congenital malformations into a single outcome because they are most likely to be heterogeneous outcomes with distinct aetiologies [6].

Because of the variation among different countries with respect to occupational exposures, caution should be taken when making comparisons between studies.

In view of the incompleteness of results and the methodological shortcomings of the epidemiological studies, there is a need for suitably designed epidemi-

ological investigations on the reproductive consequences of occupational exposure. More information is needed before firm conclusions can be drawn. In addition to present knowledge, information regarding other possible occupational effects on reproduction is needed.

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