Chemical exposures at work in early pregnancy and congenital defect: a case-referent study

J C McDONALD, J LAVOIE, R CÔTÉ, A D McDONALD

From the Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec H3A 3C2, Canada

ABSTRACT Three hundred and one women who in their most recent pregnancy had given birth to an infant with an important congenital defect were individually matched with 301 women whose children were normal. Both cases and referents were drawn from a comprehensive survey of pregnancies in Montreal, 1982–4, and limited to women employed 30 or more hours 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), due to excesses in the cardiac and miscellaneous defect groups (ratios of 10:5 and 15:7 respectively). In analyses by nine chemical categories only exposure to aromatic solvents showed a clear excess (18:8; $p \simeq 0.04$), most evident in the urinary tract group (9:0). A comparison of cases and referents exposed to aromatic solvents showed that most of the excess was associated with toluene; the defects were varied but predominantly renal-urinary or gastrointestinal.

Case control studies in Finland have shown associations of organic solvent exposure with defects of the central nervous system[1][2] and of oral clefts.[3] Although efforts were made to avoid response bias, it could not be eliminated; these studies therefore require confirmation. In a comparison of 67 female lamination workers exposed to styrene and 67 employees in textile and food production there was no difference in the proportions of malformed children.[4] A cohort of women who used styrene was linked to the Finnish Register of Congenital Malformations. The malformations observed ·were fewer than expected but the numbers were small.[5]

Laboratory workers who are exposed to solvents and other chemicals were found in Sweden to have an increased risk of gastrointestinal atresia, although this appeared to be lower than at first thought.[6][8] In a series of university laboratory employees no excess risk of congenital malformations was found in those exposed to solvents (492) compared with those not so exposed (496)[9] nor was an increased risk found for children of Danish laboratory workers in a case-referent study of malformations of the gastrointestinal tract, extremities, or oral clefts.[10] In the latter study there was also no increase in defects of the central nervous system in occupations where solvents were used.

An excess of macerated stillbirths and congenital defect was observed in leatherworkers who were mainly employed in the British shoe industry.[11] Among the malformations were three cases of trisomy 18 in an estimated 1200 births—a ratio of 1:400; the expected ratio was about 1:5000 births. An increased risk of stillbirth in leatherworkers, but not of fetal malformation, was later reported by our group in Canada.[12] Cleft lip and palate were studied in Iowa and Michigan, two states where pesticides are widely used,[13] with some evidence of an association. Potential exposure of agricultural workers and their wives to 2-4-5-T was examined in New Zealand with essentially negative results.[14][16] A study of children of Australian VietNam veterans exposed to herbicides was also negative.[17] After the Seveso disaster in northern Italy dioxin, which occasionally contaminates 2-4-5-T, was not incriminated as a teratogen.[18]

Metals generally pass the placenta[19] and so are potentially hazardous to the fetus. In female employees of a smelter in Northern Sweden exposed to lead, arsenic, and sulphur dioxide some increase in the rate of congenital malformations was reported[20]; it was thought unlikely that lead could have been responsible.[21] Several studies have shown a correlation between lead concentrations in children and

mental development. In most of these the lead was probably absorbed after birth[22]; however, the confounding effect of socioeconomic status could not be eliminated. There is no evidence that metallic mercury is a fetal hazard but, when converted in the environment to organic forms, serious damage resulted in two major epidemics. The disease was first recognised in Japan in 1953 in an infant in Minamata City; subsequent cases in the area were traced to the consumption of fish contaminated by mercury from industrial effluent. Children and adults were affected and, in congenital cases, there was gross cerebral damage and growth retardation.[23] The Japanese epidemic lasted for a long time and the situation is still under observation. In Iraq, where a large epidemic was caused by contaminated grain, the disease was similar but fewer infants were affected.[24]

Two chemicals—vinyl chloride monomer (VCM) in the plastics industry and hexachlorophene used by nurses for hand washing—have come under suspicion. Although some excess of congenital malformations was observed in cities with VCM plants,[25] in case-control studies in West Virginia[26] and Quebec[27] no evidence of a hazard to the fetus was found. A report was published of malformations in children of nurses exposed to hexachlorophene[28]; the methodology was criticised[29] and the findings not confirmed in a later study.[30]

Montreal survey

This scanty and largely inconclusive information on the effects of chemical exposure on fetal development, paralleled by similar ignorance regarding spontaneous abortion, stillbirth, and prematurity, led us to conduct a large survey of pregnancies in Montreal.[31] During a two year period, 11 May 1982 to 10 May 1984, 56 067 women were interviewed immediately after delivery or spontaneous abortion in 11 hospitals covering some 90% of births in Montreal. Questions were asked systematically in English or French on employment and personal factors by bilingual nurse interviewers using an eight page questionnaire. Information was thus obtained for the 56 067 current and 48 582 past pregnancies of these women —104 649 pregnancies in all. This was supplemented by detailed questions on various types of occupational exposure and on demands and conditions of work undertaken by the women during their pregnancies.

In the ascertainment of pregnancy outcome special attention was given to spontaneous abortion, stillbirth, birth weight, gestation period, and congenital defect. In current pregnancies the information was obtained from medical records and in previous pregnancies by questioning the mothers; in both the

data were supplemented by further inquiries addressed to physicians and hospitals.

Results of a first analysis dealt with broad categories of adverse pregnancy outcome— spontaneous abortion, stillbirth, prematurity, and congenital defect—as related to full time employment in the first trimester.[31] Sixty specific types of employment were considered, as defined by standard classifications of Statistics Canada. The purpose of this analysis was to put the main risks in general perspective in preparation for detailed examination of each type of adverse outcome. The volume of data from questionnaires and additional field inquiries on both work demands and various types of occupational exposure, together with the complex variety of hours and patterns of work, necessitated this phased approach.

So far as congenital defects were concerned, the preliminary report showed that of 23 007 women employed at the time of their current conception and still pregnant at the 20th week, 822 (3·6%) gave birth to a child with defect. The comparable figures in the previous pregnancies of 17 886 women were similar, 605 (3·4%). After allowance by logistic regression for seven confounding factors, the ratio of observed (0) to expected (E) numbers of defects was increased significantly ($p < 0.05$) in service ($O/E = 1.17$) and manufacturing ($O/E = 1.14$) sectors. Analysis of the data in 60 occupational categories showed significantly increased ratios in women employed in child care ($O/E = 2.19$; $p < 0.01$), in certain service occupations ($O/E = 1.54$; $p < 0.05$), and in the manufacture of metal and electrical goods ($O/E = 1.36$; $p < 0.05$).

In the present paper we report on the findings from a case-referent study that compared chemical exposures in the first trimester for a selected sample of women who in their current pregnancy gave birth to a malformed infant with those of similar women whose children were normal.

Selection of subjects

The *case series* comprised 301 women who, in their current pregnancy (that just completed at time of interview) had given birth to a live or stillborn infant considered to have an important congenital defect. Only women employed for 30 or more hours a week from time of conception until the end of the 12th week of pregnancy were included. In the series were 51 women whose pregnancy had been terminated because a fetal defect had been detected by ultrasound or amniotic fluid cytology. Spontaneous abortions of a defective fetus before the 20th week of pregnancy were not included. Among the 301 pregnancies were six in which the defect was present in one of twins and

one in which both twins were affected. Infants with defects considered minor, of genetic aetiology, or unlikely to be caused by chemical exposure in early pregnancy disqualified the mothers from case or referent series. On this basis minor defects such as birth marks and skin tags, together with congenital dislocations, club foot, hernias, and undescended testes were excluded. All serious cases of hypospadias were included but only a 50% systematic sample of the more numerous cases of minor degree. Cases excluded as of genetic origin were mainly of polydactyly or syndactyly. The distribution of the 301 cases finally selected is shown in table 1 by diagnostic category.

The *referent (control) series* was also drawn from women employed for 30 or more hours a week for the first 12 weeks of pregnancy from women whose infants were considered normal. For each case, a referent was selected from the same hospital matched so far as possible for gravidity, educational level, (primary, secondary, college, or university), maternal age (plus or minus 1 year), and date of delivery. An exact match was not always achieved but the distributions of these variables in cases and referents were closely similar (see table 1).

Table 1 *Analysis of case-referent pairs by matching variables and estimated severity of chemical exposure*

Type of defect and No of cases	Mean value of matching variables*			Chemical exposure grade					
				All grades			Moderate or severe		
	Age (y)	Gravidity	Education†	Case only	Referent only	Both	Case only	Referent only	Both
Central nervous system:									
Anencephaly (27)	27·11 (+0·15)	1·52	2·26 (+0·04)	3	5	—	1	2	—
Spina bifida (28)	27·75 (+0·07)	1·82	2·29 (+0·21)	6	5	4	2	3	—
Hydrocephaly (4)	28·25	1·25	2·50 (−0·25)	1	—	1	1	1	—
Microcephaly (2)	27·00	1·50	2·00	1	—	1	1	—	—
				11	10		5	6	
Cleft lip or palate (20)	25·85	1·55	2·25 (−0·05)	4	3	3	2	1	—
Cardiac group:									
Transposed great vessels (6)	25·17	2·00 (−0·17)	2·67 (−0·17)	—	1	—	—	—	—
Left heart hypoplasia (4)	27·50	2·00	2·50	2	1	—	1	—	—
Pulmonary atresia/stenosis (4)	28·00 (+0·75)	1·75	2·25 (−0·25)	—	—	—	—	—	—
Coarctation of aorta (6)	29·67	2·00	2·33 (−0·16)	1	1	2	1	1	—
Fallot's tetralogy (7)	27·71	1·14	2·29 (+0·14)	4	—	—	3	—	—
Other single defect (14)	28·07 (−0·5)	1·86 (−0·07)	2·29 (+0·14)	1	1	2	1	2	—
Multiple defects (8)	28·63	1·38	2·50	2	1	1	—	1	—
				10	5		6	4	
Gastrointestinal group:									
Tracheo-oesophageal fistula (4)	27·75	2·50 (−0·25)	2·50	2	—	1	1	—	—
Intestinal atresia (4)	28·50	2·00	2·00 (+0·25)	—	—	1	—	—	1
Anal atresia/stenosis (8)	27·38	1·50	2·38	1	2	—	—	2	—
Omphalocele/gastroschisis (11)	22·45 (+0·01)	1·09	2·18 (+0·09)	1	2	4	3	2	—
Diaphragmatic hernia (5)	25·20·(+0·2)	1·40	2·60 (−0·20)	2	2	—	—	1	—
				6	6		4	5	
Renal-urinary group:									
Hypospadias (51)	25·96	1·26	2·51 (−0·02)	11	12	5	4	4	1
Hydronephrosis (15)	27·20	1·47	2·53 (−0·06)	3	2	1	—	1	—
Polycystic kidney (5)	26·40	1·20	2·60	—	2	—	—	1	—
Renal agenesis/dysplasia (8)	27·75 (−0·12)	1·63	2·50 (−0·25)	3	—	2	—	1	—
				17	16		4	7	
Miscellaneous:									
Cataract (1)	25·00	1·00	2·00	1	—	—	1	—	—
Limb deformities (9)	26·00	1·11	2·56 (−0·12)	4	1	—	1	—	—
Multiple defects (41)	28·29 (+0·29)	1·83	2·42 (−0·03)	9	5	3	2	2	—
Trisomy (excl Down's) (9)	31·33 (−0·44)	2·11	2·44	1	1	1	1	—	—
				15	7		5	2	
Total (301)				63	47	32	25	25	2

*Where these are not identical, the deviation of referents from cases is shown in parentheses.
†Educational level reached: primary = 1; secondary = 2; college/university = 3.

Field inquiry

The histories of employment in the current pregnancy of the 602 women selected for study were photocopied from the questionnaires and passed to two of us (JL and RC—occupational hygienists), unidentified as to case or referent status. The records were then divided into two groups according to the Standard Industrial Classification (SIC),[32] as used in the Canadian census. In the first group were included jobs in which we thought chemical exposure could have occurred. These included work in manufacturing (SIC 01–39), wholesale and retail trades (SIC 51–2, 55–60, 63), hospitals and services (SIC 86, 91–9), and certain types of teaching and research in the arts and sciences (SIC 85). In the second group were all other occupations— that is, those in which chemical exposure seemed improbable. These included clerical, administrative work in communications and public services (SIC 48–9), construction and transport (SIC 40–7), commerce (SIC 53–4, 61–2, 64–5), finances, insurance, real estate and business (SIC 70–7), government services (SIC 81–4), and other types of work in teaching and research (SIC 85).

In the first group information about possible exposures was usually obtained by visits from JL or RC to the workplace. In the second group information was obtained by telephone from the employer or other appropriate person. Each case-referent pair was numbered in sequence and code letters A or B assigned to case or referent in random order. The pairs were then divided between the two hygienists, kept blind as to code, odd numbered pairs to JL and even to RC. Field inquiries were made by visit or telephone according to plan or, if outside greater Montreal, in whatever way seemed most efficient. JL and RC systematically discussed their findings in various employment situations to improve and standardise the quality of the information obtained.

After recording the products to which the women were exposed at work, chemical compositions were determined where necessary by correspondence with the manufacturers. Two parameters of severity were estimated for each exposure (a) average intensity during the period of use and (b) maximal intensity reached. Both parameters were separately graded as light, moderate, or heavy. This was a subjective judgment using agreed guidelines: "slight" implied that the exposure though known to be present was not readily detectable, "moderate" that it was readily detectable but at levels below any control limit, and "strong" present at levels that caused discomfort. In addition, the estimated duration of maximal exposure per week was recorded. These quantitative assessments of exposure proved difficult to make and have limited validity.

For the purpose of analysis all chemical exposures recorded for any case or referent were listed alphabetically and classified in consultation with an experienced toxicologist into nine categories: aliphatic solvents, aromatic solvents, plasticisers and plastics, metals (including fume), oils, detergents, gases, a combined group of bactericides, fungicides and pesticides, and a miscellaneous remainder. Inevitable problems in classification were resolved without knowledge of pregnancy outcome. The miscellaneous group largely comprised acids, bases, surface irritants, and substances that, in the opinion of our toxicological adviser, were unlikely to be absorbed or to have fetotoxic potential.

Of the 602 women investigated, 428 (71%) had no chemical exposure of any sort; the remaining 174 women were exposed to one or more of 260 identifiable chemicals or compounds, 256 of which were allocated to one of the nine categories and four to two categories. Three quarters (74%) of the 174 women were exposed to more than one chemical, 63 (37%) from two to five, 36 (21%) from six to ten, and 28 (16%) 11 or more. The proportion of cases exposed (32%) was slightly higher than of referents (26%), mainly due to an excess of single exposures (30 compared with 15). The proportion of women with multiple exposures was similar in the two groups (cases 22%; referents 18%).

Results

The data were analysed in case-referent pairs by type of malformation and type of exposure in terms of intensity and nature. Each pair was first examined for any recorded chemical exposure and classified as concordant or discordant in three grades of severity. This analysis, shown in table 1, indicates that there were few differences in the distribution of moderate or severe exposures for specific defects and their referents but rather more differences when exposures of all grades were considered. Two groups of defects had an excess of cases only exposed compared with referents only: cardiac (10:5) and miscellaneous (15:7). Within the cardiac group some evidence of inequality (4:0) is seen with the seven cases of Fallot's tetralogy. The four exposures in question had little in common: three of moderate severity included chemicals used in printing (acetic acid, hydroquinone, ammonium thiocyanate), soldering (toluene, turpentine, pine resin fume), and nursing (isopropanol, chlorhexidine, gluconate); the light exposure was to detergents used in a snack bar. In the miscellaneous group were four limb deformities in which the mother was exposed compared with one referent (4:1). In all four exposed cases cleansing agents were used—three containing sodium hypochlorite; in only one was the exposure of

moderate degree. Among the cases of multiple defect no particular chemical agent appeared to be responsible for the excess (9:5).

An analysis is presented in table 2 by the nine chemical categories without regard for severity of exposure. The pairs in which both case and referent were exposed are shown separately to indicate the overall frequency of contact with the various materials. Except for the aromatic solvents (case-referent ratio 18:8), the differences appear small and unimportant; most of the difference is concentrated within renal-urinary defects (ratio 9:0). In this group six of the nine exposures were to toluene, together with xylene in one and isophorone and an aromatic solvent (type unspecified) in another; two of the three other exposures were to benzyl alcohol and B phenoxy ethanol and one to styrene and aromatic solvent (type unspecified).

Details of the 19 cases and nine referents exposed to aromatic solvents (including the one concordant pair) are set out in table 3. The difference between the two series is almost wholly in respect of toluene (11:3) with perhaps some excess of aromatic solvent (type unspecified) (7:4). The defects associated with the latter two solvents were varied: renal-urinary (7), gastrointestinal (4), cardiac (2), spina bifida (2), and cataract (1). Most of the exposures were in manufacturing jobs.

Discussion

Of the nine groups into which individual chemical exposures were classfied, only aromatic solvents showed a suspicious excess of cases. As this was not examined as a prior hypothesis (although it might have been because of previous reports, see above), its statistical significance ($Z = 1\cdot77$; one sided $p \simeq 0\cdot04$) in the McNemar test[33] may be an overestimate. In previous reports[2,3,34,35] solvent exposure of various types has been associated with increased risk of de-

Table 2 *Analysis of case-referent pairs by type of chemical exposure: all grades of severity. (Group subtotals in parentheses)*

Type of defect / Case/referent	Aliphatic solvents +/−	−/+	Aromatic solvents +/−	−/+	Plasticisers etc. +/−	−/+	Metals (incl fume) +/−	−/+	Oils +/−	−/+	Bactericides/pesticides etc. +/−	−/+	Detergents +/−	−/+	Gases +/−	−/+	Miscellaneous +/−	−/+
Central nervous system:																		
Anencephaly	1	4		1	1		1	2	1	2	1	3		4	2	1	2	1
Spina bifida	5	4	2	2	3	1	1	1		1	3	3	1	3	2	1	1	4
Hydrocephaly	1						1	1					1		1			1
Microcephaly		1						1									1	
	(7)	(9)	(2)	(3)	(4)	(1)	(3)	(5)	(1)	(3)	(4)	(6)	(2)	(7)	(5)	(1)	(4)	(6)
Cleft lip/palate	(3)	(3)	(0)	(0)	(2)	(3)	(2)	(1)	(2)	(2)	(2)	(2)	(2)	(2)	(0)	(1)	(3)	(4)
Cardiac group:																		
Transposed great vessels									1									
Left heart hypoplasia	1				1		1						1				1	1
Pulmonary atresia/stenosis																		
Coarctation of aorta	2	1		1	1			1		1	1		1	1			1	1
Fallots tetralogy	2		1			1			1		1			2			3	
Other single defects	1	1	1			1	1	1	1	2				2	1	1	1	1
Multiple defects	1	2	1	1	1						1	1	1	1	1	1	1	
	(7)	(4)	(3)	(2)	(3)	(2)	(3)	(2)	(2)	(4)	(2)	(2)	(5)	(4)	(2)	(2)	(7)	(3)
Gastrointestinal group:																		
Tracheo-oesophageal fistula	1								2		2				1		2	
Intestinal atresia										1				1				2
Anal atresia	1	1						1		1			1	2				
Omphalocele		3	2	2		1	1			3		3	1	3			2	2
Diaphragmatic hernia	2	2	1			1				1		1						1
	(4)	(6)	(3)	(2)	(0)	(2)	(1)	(1)	(2)	(6)	(2)	(4)	(2)	(6)	(1)	(0)	(4)	(5)
Renal-urinary group:																		
Hypospadias	6	12	6		5	3	3	1	3	3	4	3	7	7	1	2	7	9
Hydronephrosis	1	2	1		1	2	2			2		1		2		1	1	1
Polycystic kidney		2				1		1		1		2		1		1		2
Renal agenesis	3	1	2			2			2	1	1		2			1	2	
	(10)	(17)	(9)	(0)	(6)	(8)	(5)	(2)	(5)	(7)	(5)	(6)	(9)	(10)	(1)	(5)	(10)	(12)
Miscellaneous:																		
Cataract	1		1														1	
Limb deformities	1				1					1	4	1	1				2	
Multiple defects	8	5		1	1	1	2	2	3	1	3	1	5	2	2	1	4	3
Trisomy (excl 21)	1				1				1					2				
	(11)	(5)	(1)	(1)	(3)	(1)	(2)	(2)	(4)	(2)	(7)	(2)	(6)	(4)	(2)	(1)	(7)	(3)
Total discordant	42	44	18	8	18	17	16	13	16	24	22	22	26	33	11	10	35	33
Total concordant +/−	17	198	1	274	5	259	2	270	2	269	6	251	3	239	0	280	8	225

Table 3 *Occupation and aromatic solvent exposure in 19 cases and nine referents from one concordant and 26 discordant pairs*

Exposure* (grade in parentheses) Cases (19)	Job		Defect	Exposure* Referents (9)	Job	
Toluene (2)	Assembler	Aircraft manufacture	Cataract	Toluene (2)	Technician	Hospital
Toluene (2)	Assembler	Blind manufacture	Hypospadias gr 2	Toluene (2)	Assembler	Belt manufacture
Toluene (2)	Assembler	Belt manufacture	Hypospadias gr 1			
Toluene (2)	Assembler	Shoe manufacture	Omphalocele			
Toluene (2)	Assembler	Belt manufacture	Omphalocele			
Toluene (2)	Assembler	Electrical products	Fallot's tetralogy			
Toluene (1)	Technician	Hospital	Renal agenesis			
Toluene (1)	Beautician	Self employed	Hypospadias gr 1			
Toluene (2), AS (2)	Technician	Biology laboratory	Cardiac	Toluene (2), AS (2)	Assembler	Goggles
Toluene (1), xylene (1)	Packer	Plastics manufacture	Renal agenesis			
Toluene (1). AS (1), isophorone (1)	Packer	Plastics manufacture	Hydronephrosis			
AS (2)	Clerk†	Medical clinic	Intestinal atresia			
AS (1)	Assembler	Metal products	Diaphragmatic hernia	AS (2)	Assembler	Shoe manufacture
AS (1)	Clerk	Car sales	Spina bifida	AS (1)	Saleswoman	Paints
AS (1)	Supervisor	Door manufacture	Spina bifida	AS (1)	Cleaner	Office building
AS (2), styrene (1)	Painter	Plastics manufacture	Hypospadias gr 1			
Benzyl alcohol (1)	Laundry	Hospital	Cardiac (multiple)	Benzyl alcohol (1)	Nurse	Hospital
Benzyl alcohol (1), B phenoxy ethanol (1)	Nurse	Hospital	Hypospadias gr 1	Benzyl alcohol (1)	Nurse	Hospital
Benzyl alcohol (1), B phenoxy ethanol (1)	Nurse	Hospital	Hypospadias gr 2	Phenols (1)	Nurse†	Hospital

*Aromatic solvent (AS)—type unspecified.
†Concordant pair.

fects of the central nervous system, oral clefts, gastrointestinal atresia, and sacral agenesis. In some of these studies there was the possibility of response bias whereas our data on exposure were collected and coded without knowledge of outcome.

Our results throw most suspicion on toluene and to a lesser extent on aromatic solvent, type unspecified, which commonly contains toluene. The associated anomalies, although predominantly renal-urinary and gastrointestinal, were quite heterogeneous and the reported exposures were not impressive. Organic solvents cross the placenta,[36] however, and concern has been expressed that toluene, increasingly used as a substitute for benzene, is embryotoxic.[37] The exposures were probably low but there is evidence that toluene may be taken up and accumulated in fatty tissue better than most other solvents.[38] Three cases reported by Hersh et al describe a variety of central nervous system, craniofacial, and limb anomalies in children born to women who inhaled (sniffed) large quantities of pure toluene in pregnancy.[39] Two of these three children had also urinary tract abnormalities similar to those observed in our study.

Overall, our data suggest that in Montreal—perhaps in North America generally—some 30% of pregnant women have some occupational exposure to chemical substances, usually at a low level. In this study only women without a major change in occupation before the 13th week of pregnancy were included; others may have left work earlier or been reassigned to a job without chemical exposure. Paternal exposure will be examined later.

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