ORIGINAL ARTICLE

Adverse reproductive outcomes among male painters with occupational exposure to organic solvents

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Objectives: To assess the risks of reproductive disorders and birth defects in offspring of male painters with exposure to organic solvents, and to determine the shape of the dose-response relationship.
Methods: Random samples of painters and carpenters were drawn from workers affiliated with the Dutch Trade Union for Construction Workers, the Netherlands, 2001. Information on reproductive outcomes, occupational exposures, and lifestyle habits was retrospectively obtained through self-administered questionnaires filled in by 398 painters exposed to organic solvents in paints, thinners, and cleansers in the period of three months before the last pregnancy, and 302 carpenters with little or no exposure to solvents. A statistical model was used to estimate quantitative exposure measures.
Results: Workers employed as painters at three months before pregnancy had an increased risk (odds ratio 6.2, 95% CI 1.4 to 27.9) of congenital malformations in offspring compared to carpenters. There was a positive exposure-response trend with increasing exposure to organic solvents based on quantitative model predicted exposure estimates using toluene as a marker. There was some indication of an increased risk of functional developmental disorders in offspring among painters with intermediate and high model predicted exposure. The risk of low birth weight children seemed to be slightly increased among painters as well. Results for other reproductive outcomes (time to pregnancy, spontaneous abortion, and preterm birth) did not show increased risks.
Conclusion: This study showed a positive association between paternal occupational exposure to organic solvents and congenital malformations in offspring. However, the small numbers of cases, especially when examining different exposure levels, as well as the self-reported nature of exposure and outcome variables, may hamper interpretation of the results.

Organic solvents are widely used in various industrial settings, such as electronics, shoemaking, furniture manufacturing, painting, printing, dry cleaning, metal industries, reinforced plastic industries, and the production of paints, glues, and other chemicals. Occupational exposure to solvents has been associated with several adverse health effects, in particular with chronic toxic encephalopathy (CTE) and cancer.[1] Because organic solvents can pass the blood–testis barrier and the placenta,[2] they may also have adverse reproductive or developmental effects. Many studies have been done on occupational exposure to organic solvents and adverse reproductive and developmental outcomes in both humans and experimental animals.[2–4] The majority of human studies have been performed among women and focused on prolonged time to pregnancy, spontaneous abortion or stillbirth, low birth weight, and developmental disorders.

The role of paternal exposure to organic solvents has received less attention, despite increasing concern about male reproductive function. Due to the widespread occupational exposure to organic solvents among men, adverse health effects could have a considerable public health impact. Mechanisms by which male occupational exposure may cause reproductive and developmental defects are still largely unknown, although several potential mechanisms have been proposed.[5–9] Epidemiological studies of organic solvents and male fertility show contradictory results. Weak associations between exposure to some specific types of solvents and semen abnormalities, disturbances in sexual behaviour, and hormonal imbalance have been reported.[10] Studies on time to pregnancy, an indication for fertility, showed no clear results.[11] In a review, Chia and Shi concluded that paternal employment as a painter and in other occupations with exposure to organic solvents was repeatedly, albeit not consistently, associated with birth defects.[12] A recent meta-analysis by Logman *et al* showed an association with major malformations, but not with spontaneous abortion.[13] However, none of the previous studies had good exposure data that allowed quantitative estimates. Painters are an occupational group with potentially high exposure to organic solvents, such as petroleum solvents, toluene, xylene, ketones, alcohols, esters, and glycol ethers,[14] during handling of paints, thinners, and cleansers. Thinners are organic solvent mixtures which may contain xylene and/or toluene and other organic solvents.[15] In the Netherlands, statistical models have recently been developed to describe trends in exposure to organic solvents among painters.[16] The aims of the current study were to assess the risks of reproductive disorders or developmental defects in offspring of male painters with exposure to organic solvents compared to non-exposed workers, and in particular to determine the extent to which these risks relate to estimated quantitative levels of exposure to organic solvents among painters.

METHODS

Study population

The study population consisted of a random sample of 1578 male painters and 1537 male carpenters born between 1950

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; CTE, chronic toxic encephalopathy; MBD, minimal brain dysfunction; OR, odds ratio; SD, standard deviation; TTP, time to pregnancy

and 1975, who were in the membership register of the Trade Union for Construction Workers in the Netherlands in 2001. Painters constitute a large job category in which organic solvent exposure is highly likely, whereas carpenters have little or no exposure to solvents. These two occupational categories were expected to have comparable educational levels, socioeconomic status, and lifestyles. The sample size was based on a statistical power of 80% to find an odds ratio (OR) of 2 for congenital malformations, the least frequently occurring outcome, assuming a 65% response rate. The Regional Committee on Research Involving Human Subjects approved the study protocol.

Data collection

A self-administered questionnaire, including informed consent and a return addressed envelope, was sent to all workers by mail. After two weeks, a first reminder was sent to all non-respondents; a second reminder was sent four weeks later. Subjects who did not want to participate were asked to provide one or more reasons. To avoid selective non-response and information bias, the study was presented as a study on pregnancy, working conditions, and lifestyle habits in general. The questionnaire focused on the most recent pregnancy and related adverse pregnancy outcomes, such as time to pregnancy (TTP), spontaneous abortion, preterm delivery, low birth weight, congenital malformations, functional developmental disorders, and childhood cancer in offspring. The most recent pregnancy was chosen in order to limit recall bias and to avoid dependency issues due to multiple pregnancies. The questions addressed paternal and maternal job title, occupational exposures, and lifestyle habits (e.g. smoking, alcohol consumption), and the use of prescribed medication before and during pregnancy.

Exposure assessment

Information on chemical and physical occupational exposure was derived from the questionnaire. Job titles at three months before and during pregnancy were combined with self-reported exposure to paints, thinners, or cleansers during these time periods. Painters with exposure were compared to carpenters without reported exposure to these substances.

For a quantitative exposure assessment, we used the model described by Burstyn and Kromhout.[16] This statistical model was developed in order to characterise historical exposure to solvents of commercial painters in the Netherlands on the basis of measurement data collected between 1980 and 1999 (304 measurements from 137 workers). Toluene was selected as a marker for solvent exposure, since measured hydrocarbon exposures (toluene, xylene, ethyl-benzene, n-decane, and n-hexane) appeared to be strongly correlated. The model of exposure to toluene explained 86% of between-worker and 11% of day-to-day variability. Determinants (of ln(mg/m^3 toluene)) included in the model were: year of using solvent based paint (slope (β) = −0.12 for number of years since 1980), use of solvent based paint versus no paint ($\beta = 2.82$), use of water based paint versus no paint ($\beta = 0.74$), working in small rooms (<50 m^3) versus large rooms or outdoors ($\beta = 0.45$), shipyard painting versus house painting ($\beta = -2.25$), spray painting versus manual painting ($\beta = 1.68$), and an intercept ($\beta = -2.84$). For prediction of mean individual exposures, one half of the estimate of residual logarithmic within-worker variance (½ × 2.22) was added to the model prediction before exponentiation. If painters reported using both solvent and water based paints concurrently in the same time period, the overall exposure estimate was calculated as the weighted mean of these scenarios under the assumption that they were equally likely. Because the model was based on measurements for the period 1980–99, we assumed that there was no time trend for workers who fathered a pregnancy beyond these years. For painters who worked indoors, we could not differentiate between small and large rooms. Therefore, we classified subjects usually working indoors as working in ''small rooms'', whereas subjects usually working outdoors or both indoors and outdoors were classified as working in ''large rooms or outdoors''. As we had no information on work location and application method used, we assumed determinants associated with the lowest exposures, i.e. house painting and manual painting.

Outcome measures

Time to pregnancy was defined as the period of unprotected intercourse leading to a clinically detected pregnancy. Workers who reported a TTP of zero or one month, while they had not stopped using contraceptives, or reported that the pregnancy was not planned, were excluded from the analyses for TTP (n = 38). The cut point for prolonged TTP was 12 months. A spontaneous abortion was defined as a pregnancy that ended before 20 weeks of gestation. A delivery at less than 37 weeks of gestation was classified as preterm. The cut point for low birth weight was 2 500 g. The analyses for birth weight were always adjusted for preterm birth. Birth defects in offspring were obtained from an open ended question on physical or mental disability diagnosed in the child, in which the parent was asked to describe the disability. We categorised these birth defects into structural congenital malformations and functional developmental disorders. In addition, one question specifically addressed the diagnosis of attention deficit hyperactivity disorder (ADHD), minimal brain dysfunction (MBD), or hyperactivity. Children with these disorders were included in the category of functional developmental disorders. The following five reported birth defects, with the father's current occupation between brackets, were not considered as congenital malformations: not hearing high tones (painter), chronic obstructive pulmonary disease (carpenter), lungs not developed (carpenter), ptosis left eyelid (carpenter), and little pigmented nevus with hair on the temple (carpenter). Two cases with a heritable congenital malformation (muscular disease and tuberous sclerosis) were excluded from the analyses. In both cases, the anomalies were also present in first degree relatives.

Potential confounding factors

Potential confounding factors considered were maternal age, parental smoking and alcohol use, maternal use of prescribed medication, and maternal occupational exposures. Year of pregnancy was considered as well as an indicator for level of exposure. Categories of maternal occupations with potential chemical exposure were: nurses or other medical jobs, hairdressers, agricultural work, cleaning work, working with paint, ink, glue, or other solvents, industrial or transport work, dry cleaning, and artists working with ceramics or paints. Potential physical exposure was assumed for women in medical jobs or childcare, hairdressing, agriculture, cleaning, and several other physically demanding jobs.

Statistical analysis

A non-response analysis was performed by means of descriptive statistics. The analyses among participants were restricted to workers who had children or whose wives or partners (further referred to as ''wives'') had ever been pregnant. Odds ratios with 95% confidence intervals (CI) were calculated by univariate and multiple logistic regression analysis using the SAS system.[17] Confidence intervals for crude odds ratios based on small numbers (less than 10) were evaluated by the mid-*p* exact method.[18] Linear trends in odds ratios were estimated assuming constant differences

between exposure categories. Potential confounding factors were evaluated by their distribution among the exposure groups and their association with the outcome variable in the reference group, before inclusion in multiple logistic regression models. To assess effects of potential under-reporting of congenital malformations in the non-exposed referent group, sensitivity analyses were performed by adding cases to this group in order to obtain a prevalence of 1.5%, which has been reported for other non-exposed study groups.[19–21] Finally, the analyses for TTP, censored at 12 months, were evaluated by a Cox's proportional hazards model as well, and crude and adjusted fecundability ratios (FR) with 95% confidence intervals were calculated.

RESULTS

Study population

Of 3115 workers invited to participate in the study, eight workers did not meet the sample criteria and 30 questionnaires were undeliverable, leaving 3077 workers eligible. In total, 1340 workers responded (44%; 41% for painters and 46% for carpenters), while 415 (13%) subjects actively refused to participate by returning the questionnaire. Reasons for non-participation (multiple answers could be provided) were primarily: they never participate in research (n = 153, 37%), or they did not feel like completing the questionnaire (n = 140, 34%). Other reasons for non-participation included "useless" (17%), "no time" (12%), and "too personal or too emotional questions" (6%). The mean age of the respondents was 37.9 years (standard deviation (SD) 7.7), which was comparable to the mean age of the sampled population (37.5 years, SD 7.7). The mean age of the actively refusing subjects was slightly older (39.0 years, SD 7.9). There were no differences in current employment status between respondents and non-respondents: 98% were employed, 2% were occupationally disabled, and 0.2% were unemployed.

The analyses were restricted to 934 subjects who ever fathered a pregnancy, excluding 376 subjects who did not have children and had never tried to conceive, as well as 30 subjects who tried to conceive without successes. Table 1 shows descriptive statistics of the study population by job held at data collection. Painters were somewhat older than carpenters. Likewise, the wives of painters had their last pregnancies longer ago than carpenters' wives. In both groups, more than 80% of the workers were employed in the same job at the time of data collection as at three months before pregnancy. Changing jobs or exposure to paints, thinners, or cleansers after the date of conception was negligible: only one carpenter reported exposure in the first month of his wife's pregnancy, but there were no observed adverse health outcomes in the child. Therefore, we do not report results of the analyses by job title or exposure during pregnancy separately.

Job title at three months before pregnancy

Combining information on job title with self-reported use of paints, thinners, or cleansers at three months before pregnancy resulted in 398 painters with exposure to these substances and 302 carpenters without exposure. Painters who reported no exposure (n = 13), carpenters who did report exposure (n = 84), painters and carpenters with unknown exposure (n = 4), and 133 workers with other or unknown job descriptions at three months before pregnancy were not taken into account in the further analyses.

Painters fathered their most recent pregnancy on average 10.6 years ago (SD 7.0); this time was 9.0 (7.5) years among carpenters. Some differences between painters and carpenters were also observed for parental smoking before and during pregnancy, and for parental alcohol use before pregnancy. There was no increased risk of prolonged TTP (OR = 1.1, 95% CI 0.7 to 1.9) among painters compared to carpenters (table 2). Using information on TTP on a continuous scale in a Cox's proportional hazards model showed no differences in fecundability (FR = 0.9, 95% CI 0.8 to 1.1). There were no increased risks of spontaneous abortion (OR = 1.1, 95% CI 0.4 to 2.7) or preterm birth (OR = 1.2, 95% CI 0.7 to 2.2), whereas some indication was found for a higher risk of low birth weight (OR = 1.7, 95% CI 0.9 to 3.2). The results show an increased risk of birth defects in offspring (OR = 2.4, 95% CI 1.2 to 4.9), mainly due to a higher risk of congenital malformations (OR = 6.2, 95% CI 1.4 to 27.9). Malformations reported by painters were: cardiovascular (n = 4), gastrointestinal (n = 2), central nervous system (n = 1), eye (n = 1), and urogenital malformations (n = 1), oro-facial clefts (n = 3), Down's syndrome (n = 1), and other syndromes (n = 3). Non-exposed workers reported one urogenital defect and one hip dysplasia. In both occupational groups, about 50% of the reported cases of functional developmental disorders had a diagnosis of ADHD, MBD, or hyperactivity.

Calculation of exact confidence intervals by the mid-*p* exact method resulted in similar lower confidence limits, although upper confidence limits were higher compared to the approximated limits. However, this did not change the interpretation of the results. Evaluating potential under-reporting of congenital malformations in the reference group and increasing the number of cases in this group to four in order to obtain a prevalence comparable to that reported in other non-exposed groups of 1.5% resulted in a lower, but still increased, crude odds ratio of 2.9 (95% CI 1.0 to 8.9).

Quantitative exposure estimates at three months before pregnancy

For the quantitative exposure estimation, an additional 17 painters were excluded because of missing information on model determinants (5 for unknown year of conception, and 12 for unknown working indoors, outdoors, or both), leaving 381 painters in the analyses. Two carpenters with missing year of pregnancy were excluded as well, leaving 300 non-exposed carpenters in the reference group. Among painters, model predicted toluene exposure at three months before pregnancy ranged from 0.17 to 4.66 mg/m^3 (geometric mean 0.62 mg/m^3, geometric standard deviation 2.40). These values were all well below the Dutch occupational exposure limit for toluene of 150 mg/m^3.

Exposed workers were categorised, using the tertiles of the estimated exposures (0.17 to 0.38, 0.38 to 1.02, and 1.03 to 4.66 mg/m^3), in order to determine dose-response associations (table 3). The mean number of years since the most recent pregnancy increased with exposure level from 3.2 (SD 2.6) years to 9.8 (SD 3.8) years and 18.0 (SD 4.4) years among low, intermediate, and high exposed workers, respectively. Non-exposed workers had fathered their most recent pregnancy on average 9.0 (SD 7.5) years ago. Some differences were also observed between the three exposure groups and the referent group for maternal age, parental smoking, and alcohol use before and during pregnancy, maternal chemical or physical occupational exposure, and maternal medication use before and during pregnancy. Therefore, these variables were included in the analyses as potential confounders.

The odds ratios for prolonged TTP were similar in all exposed categories and not increased compared to non-exposed workers. The analyses for TTP with Cox's proportional hazards models showed similar results. Ten of the 11 reported cases of spontaneous abortion in wives of exposed workers occurred in the low exposure group, giving an increased crude odds ratio of 2.5 (95% CI 1.0 to 6.2). These

Table 1 Descriptive statistics for 472 male painters and 462 male carpenters, Trade Union for Construction Workers, Netherlands, 2001

	Job title at data collection					
	Painter		Carpenter		Total	
Characteristic	n	(%)	n	(%)	n	(%)
Number of subjects	472	(100)	462	(100)	934	(100)
Year of birth						
Before 1955	136	(28.8)	103	(22.3)	239	(25.6)
1955–64	220	(46.6)	192	(41.6)	412	(44.1)
1965 or later	116	(24.6)	167	(36.1)	283	(30.3)
Pregnancy history						
Children	452	(95.8)	440	(95.2)	892	(95.5)
No children, wife currently pregnant	10	(2.1)	12	(2.6)	22	(2.4)
No children, wife ever pregnant	10	(2.1)	10	(2.2)	20	(2.1)
Year of last pregnancy						
Before 1985	114	(24.2)	88	(19.0)	202	(21.6)
1985–94	185	(39.2)	149	(32.3)	334	(35.8)
1995 or later	164	(34.7)	216	(46.8)	380	(40.7)
Unknown	9	(1.9)	9	(1.9)	18	(1.9)
Job title and exposure status* three months before pregnancy						
Painter, exposed	397	(84.1)	1	(0.2)	398	(42.6)
Painter, not exposed	13	(2.8)	–	–	13	(1.4)
Painter, exposure unknown	3	(0.6)	–	–	3	(0.3)
Carpenter, exposed	2	(0.4)	82	(17.7)	84	(9.0)
Carpenter, not exposed	8	(1.7)	294	(63.6)	302	(32.3)
Carpenter, exposure unknown	–	–	1	(0.2)	1	(0.1)
Other	35	(7.4)	64	(13.9)	99	(10.6)
Unknown	14	(3.0)	20	(4.3)	34	(3.6)

*Exposure to paints, thinners, or cleansers.

cases were all reported for pregnancies that occurred after 1995. On adjusting for year of miscarriage and other potential confounders, the odds ratio for the lowest exposed group decreased to 1.3 (95% CI 0.5 to 3.4).

There were no clear differences in preterm birth among the exposure groups, whereas the risk of low birth weight seemed to increase slightly with increasing exposure from 1.5 (95% CI 0.5 to 4.3) in the low exposed group to 1.9 (95% CI 0.8 to 4.7) in the high exposed group (p value of test for trend 0.05).

A dose-response relationship (p value of test for trend 0.03) was observed for all birth defects with odds ratios increasing from 2.1 (95% CI 0.7 to 5.9) in the low exposed group to 3.0 (95% CI 1.3 to 7.0) and 2.2 (95% CI 0.8 to 6.0) in the intermediate and high exposed groups, respectively. Looking more specifically at congenital malformations, we initially saw a 9-fold increased risk in the low exposed group (95% CI 1.8 to 44.0) and 4-fold increased risks in the intermediate and high exposed groups with confidence intervals ranging from approximately 0.8 to 24. After adjustment for confounding factors, the risk of congenital malformations increased with exposure level from 6.8 (95% CI 1.3 to 35.9) in the low exposure group to 8.9 (95% CI 0.8 to 95.9) in the high exposure group (p value of test for trend 0.04). However, these results were based on small numbers of reported cases. On increasing the number of reported cases of congenital malformations among the referent group from two to four (1.5%) to evaluate potential underreporting, the crude odds ratios decreased to 4.5 (95% CI 1.3 to 15.6) for low exposed workers, 2.2 (95% CI 0.5 to 8.9) for intermediate exposed, and 2.1 (95% CI 0.5 to 8.4) for high exposed workers. However, this could not explain the positive trend we observed with the adjusted odds ratios. For functional developmental disorders, the initial trend of increasing odds

Table 2 Odds ratios for reproductive outcomes by job held at three months before pregnancy among 398 male painters exposed to paints, thinners, or cleansers and 302 male carpenters without exposure

	Reported cases		OR, crude		OR, adjusted*	
Outcome variable	Painters	Carpenters	OR	95% CI	OR	95% CI
Prolonged time to pregnancy†	47	33	1.1	0.7–1.8	1.1	0.7–1.9
Spontaneous abortion‡	13	10	0.9	0.4–2.2	1.1	0.4–2.7
Preterm birth§	37	21	1.3	0.7–2.2	1.2	0.7–2.2
Low birth weight¶	41	21	1.4	0.8–2.6	1.7	0.9–3.2
Birth defects, all	37	11	2.5	1.3–5.1	2.4	1.2–4.9
Congenital malformations	16	2	5.9	1.3–25.9	6.2	1.4–27.9
Functional developmental disorders	21	9	1.7	0.8–3.8	1.6	0.7–3.6

OR, odds ratio; CI, confidence interval.
*Adjusted for year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, and maternal smoking, alcohol use, chemical occupational exposure, physical occupational exposure, and medication use during pregnancy.
†Longer than 12 months.
‡Less than 20 weeks of gestation.
§Less than 37 weeks of gestation.
¶Less than or equal to 2500 g, adjusted for gestational age.

Table 3 Crude and adjusted* odds ratios for reproductive outcomes by tertiles of model predicted exposure to toluene (mg/m^3) at three months before pregnancy among 381 male painters exposed to organic solvents and 300 non-exposed male carpenters

		Painters, exposure tertile†		
Outcome variable	**Carpenters**	**Low (0.17 to 0.38)**	**Intermediate (0.38 to 1.02)**	**High (1.03 to 4.66)**
Number of subjects	300	127	126	128
Prolonged TTP				
Obs	33	18	15	13
OR–crude (95% CI)	1.0	1.3 (0.7–2.4)	1.1 (0.6–2.1)	0.9 (0.5–1.9)
OR–adjusted (95% CI)	1.0	1.2 (0.5–2.5)	1.1 (0.5–2.2)	1.1 (0.5–2.7)
Spontaneous abortion				
Obs	10	10	1	0
OR–crude (95% CI)	1.0	2.5 (1.0–6.2)	0.2 (0.0–1.7)	–
OR–adjusted‡ (95% CI)	1.0	1.3 (0.5–3.4)	0.4 (0.0–3.2)	
Preterm birth				
Obs	21	11	14	12
OR–crude (95% CI)	1.0	1.3 (0.6–2.8)	1.5 (0.7–3.0)	1.2 (0.6–2.5)
OR–adjusted (95% CI)	1.0	1.6 (0.7–3.9)	1.5 (0.7–3.2)	0.8 (0.3–2.0)
Low birth weight¶				
Obs	21	9	14	18
OR–crude (95% CI)	1.0	0.9 (0.4–2.3)	1.3 (0.6–2.9)	2.2 (1.0–4.6)
OR–adjusted (95% CI)	1.0	1.5 (0.5–4.3)	1.6 (0.7–3.8)	1.9 (0.8–4.7)
Birth defects—all				
Obs	11	9	14	13
OR–crude (95% CI)	1.0	2.1 (0.8–5.1)	3.0 (1.3–6.8)	2.6 (1.1–5.9)
OR–adjusted (95% CI)	1.0	2.1 (0.7–5.9)	3.0 (1.3–7.0)	2.2 (0.8–6.0)
Congenital malformations				
Obs	2	7	4	4
OR–crude (95% CI)	1.0	9.0 (1.8–44.0)	4.4 (0.8–24.4)	4.2 (0.8–23.2)
OR–adjusted (95% CI)	1.0	6.8 (1.3–35.9)	3.9 (0.6–24.5)	8.9 (0.8–95.9)
Functional developmental disorders				
Obs	9	2	10	9
OR–crude (95% CI)	1.0	0.5 (0.1–2.5)	2.5 (1.0–6.4)	2.1 (0.8–5.5)
OR–adjusted (95% CI)	1.0	0.4 (0.0–3.2)	2.9 (1.1–7.7)	1.5 (0.5–4.6)

Obs, reported number of cases; OR, odds ratio; CI, confidence interval.
*Adjusted for year of pregnancy, maternal age at conception, paternal smoking and alcohol use before pregnancy, and maternal alcohol use, smoking, chemical occupational exposure, physical occupational exposure, and medication use during pregnancy.
†Estimated long term average exposure to toluene (mg/m^3), used as a marker for exposure to organic solvents.
‡For the adjusted odds ratios, the intermediate and high exposed workers were combined in order to provide a valid model fit.
¶Adjusted for gestational age.

ratios with increasing exposure ($p = 0.04$) seemed to disappear after correction for confounding ($p = 0.19$).

Again, no significantly different results were obtained after calculation of exact confidence intervals by the mid-p exact method. It was not possible to assess the influence of take-home exposure, because 95% of the painters took their working clothes home for washing, while none of the carpenters reported the use of specific clothing.

DISCUSSION

The response rate for this study was moderate (44%). Painters are a frequently studied working population and may no longer be motivated to engage in research due to ''participation fatigue''. The non-response among painters (46%) was slightly higher than among carpenters (40%). In addition, studies on reproductive health performed among men often have much lower response rates than those among women.[4] Since the study was presented as general research on pregnancy, work, and lifestyle habits, not putting any emphasis on organic solvent exposure, painters with adverse pregnancy outcomes had no other reasons to participate than carpenters with similar problems. Still, some selection bias cannot be ruled out, because of the study focus on pregnancy outcomes in combination with a higher awareness among painters of recognised negative health effects of organic solvents in general.

We cannot be certain that the observed excess risks are entirely attributable to exposure to organic solvents. Although solvents are important substances of paints, thinners, and cleansers, there are other chemicals in these products, which could have been responsible for our findings. For example, lead, a substance of paint in the past, has been associated with adverse pregnancy outcomes,[22 23] and it is possible that workers were exposed to lead during painting or during sanding of old lead containing layers of paint. In this study, we cannot investigate the combined exposure to lead and organic solvents. We were also not able to identify any specific types of solvents responsible for the elevated risks, since paints, thinners, and cleansers usually contain mixtures of solvents.

The regression model used to predict individual quantitative exposure levels to toluene as proxy for organic solvents exposure could have introduced exposure misclassification. Exposure misclassification depends on the validity of the measurements the model was based on, the validity of the model, and the validity of information from the questionnaires. The first two issues were addressed in the original paper.[16] Missing or false information on determinants of exposure or model parameters is of more importance. We did not have information on whether the workers were involved in painting of houses or ships, while this was an important model determinant. This could have introduced misclassification within the categories of exposed workers. However, since the total number of painters in shipyards is relatively small, shipyard painters are usually affiliated with another trade union, and shipyard painting was never abstracted from the job titles, we suppose that misclassification by this exposure determinant is unlikely. Misclassification in the dichotomous exposure variable (exposed painter versus non-exposed carpenter) could be present as well. Recall bias could have been introduced due to a higher awareness of

Main messages

- Previous research has suggested an adverse effect of occupational organic solvent exposure on male reproductive health, although results have been inconclusive.
- This study shows that male painters with exposure to organic solvents in the period of three months before pregnancy have an increased risk of congenital malformations in offspring compared to non-exposed workers. A positive exposure-response trend was observed with increasing model based quantitative exposure estimates using toluene as a marker of mixed solvents.
- Interpretation of the results may be hampered by small numbers of reported cases and the self-reported nature of exposure and outcome measures.

Policy implications

- New studies should be conducted to evaluate the reproductive health of current workers with lower levels of occupational solvent exposure due to replacement of solvent based products by water based products.

occupational exposures among painters, as well as a more thorough recall of exposures among couples that experienced reproductive problems. This form of differential misclassification may have led to some overestimation of risk estimates, but it is an unlikely cause of the monotonic exposure-response trend that was observed for congenital malformations.

Birth defects in this study were based on self-reported information. A study on the reliability of self-reported major congenital malformations found that maternal reports were in close agreement with physicians' reports.[24] However, to our knowledge, studies on paternal reporting are not available from the literature. The prevalence of children with congenital malformations among carpenters was 0.7%. Other studies reported percentages among non-exposed workers between 1% and 2%,[19–21] while estimations within the general population vary from 2%[25] to 2.4%.[26] A reason for the lower prevalence of congenital malformations could be underreporting in questionnaire studies, because less severe malformations were involved or limited recall of malformations after successful surgery. Sensitivity analyses for the crude odds ratios by adding cases to the non-exposed group and increasing the prevalence of children with congenital malformations to 1.5% showed that underreporting by carpenters would cause a decrease of the observed risks, but could not entirely explain the observed results. However, although potential underreporting of outcome is unlikely to be differential, with a small number of cases the effect estimates are not very precise or stable. Even a slight differential tendency to over- or underreport could have substantial impact.

On adjusting for potential confounding factors, the odds ratio for congenital malformations among painters with high exposure increased from 4.2 to 8.9, whereas the confidence interval became very wide. This large increase is likely to result from statistical bias due to sparse data.[27] The risk estimates for congenital malformations are based on small numbers and risk estimates for other outcomes do not show similar increases after adjustment for confounders. Therefore, without questioning the observed positive association for congenital malformations, we cannot be certain about the exact magnitude of the risk gradient.

The suggestion of increased risks of a child with functional developmental disorders among painters was mainly due to workers within the intermediate category. The mean age of these workers' children was higher than that of non-exposed workers, while low-exposed workers had younger children compared to the reference group. Functional developmental disorders are often recognised years after the child was born, but the odds ratios were adjusted for these age differences. Another explanation for the results could be information bias on the outcome variable. Painters may be more aware of the fact that they are working with hazardous chemicals and may therefore be more concerned about possible health related effects, leading to overreporting of functional developmental disorders.

The initial increased risk of spontaneous abortion among workers in the lowest exposure group was biased by year of pregnancy, since 97% of these workers experienced their wives' pregnancies recently (1990 or later) compared to 37% among non-exposed workers. Recent abortions are more often recalled than those that have occurred earlier.[28] In addition, pregnancy losses during more recent years were more likely to be recognised, because of the increasing use of sensitive home pregnancy tests. But more importantly, when studying the outcome of the most recent pregnancy in a retrospective design, the time interval between conception and data collection could act as a confounder when the exposure studied has changed over time.[29] A wanted pregnancy ending in fetal loss is likely to be replaced by other pregnancies until a viable one is conceived. Even with perfect recall, this replacement phenomenon produces a lowered overall rate of spontaneous abortion among most recent pregnancies.[29] This was indicated by the low overall rate of spontaneous abortions in this study of 3%. The rate increased to 5% for pregnancies conceived after 1990, but this is still below rates of 10–15% found in the general population.[29] After adjustment for year of pregnancy, the risk for spontaneous abortion among workers in the lowest exposed group was no longer elevated. In addition, recall differences might be a possible cause for the low reporting of spontaneous abortion. Male partners may not know or remember miscarriages as well as females.

Since the questionnaire addressed the fathers, data on maternal occupational exposure, lifestyle habits, and medication use were obtained using the fathers as surrogate respondents. Although we cannot exclude the possibility that spouses were consulted while completing the questionnaire, this might have introduced non-response and misclassification. However, the period around birth of children is usually well recalled, even several years afterwards.[30] In addition, the use of a structured questionnaire with not too much detail with regard to the wives' exposures might have minimised the chances of bias.[31]

When comparing our results with those of other studies, we have to take into account that in several studies job title was used as a proxy for exposure.[12] We showed that using only job title could lead to considerable misclassification. Among workers employed as a carpenter at three months before pregnancy, 22% were exposed to paints, thinners, or cleansers, while 3% of the painters reported no exposure. Using a combination of job title and exposure, we were able to confirm associations between male painters or male exposure to organic solvents and congenital malformations that were reported in the literature.[12 13]

Conclusion

This study among painters with potentially high occupational exposure to organic solvents in the preconceptional period showed that they have an increased risk of congenital malformations in offspring compared to carpenters with no or negligible exposure to these agents. An exposure-response relationship was demonstrated with quantitative exposure estimates to toluene, used as a marker for organic solvents. There was also some indication for increased risks of low birth weight and of functional developmental disorders in offspring, in particular among painters with intermediate exposure levels. However, the strength of the results may be hampered by small numbers of reported cases and the self-reported nature of exposure and outcome measures.

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