Paternal Occupational Exposure Around Conception and Spina Bifida in Offspring

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A.L.M. Verbeek, MD, PhD, and G.A. Zielhuis, PhD, MSc

A multi-center case-referent study was conducted on the relation between paternal occupational exposure and spina bifida in offspring. Cases were born between 1980 and 1992 in The Netherlands. Referents were recruited from hospitals and from the general population. Postal questionnaires were used to gather information on occupation and potential confounders. Through job-specific telephone interviews with 122 case fathers and 411 referent fathers, detailed exposure information was collected on specific tasks, the use of chemical or physical agents, frequency of exposure, and use of protective equipment. The study yielded statistically significant associations between spina bifida and low exposure to welding fumes (OR = 1.6, 95% CI: 1.0–2.6) and low exposure to UV radiation during welding (OR = 2.6, 95% CI: 1.2–5.6), and suggestive findings of an association between spina bifida and moderate or high exposure to cleaning agents, moderate or high pesticide exposure (OR = 1.7, 95% CI: 0.7–4.0), and stainless steel dust (OR = 2.0, 95% CI: 0.8–5.2). No associations were identified for other paternal occupational exposures, such as organic solvents.

KEY WORDS: spina bifida; neural tube defects; birth defects; male-mediated teratogenesis; occupational exposure; pregnancy; epidemiology; case-referent study

INTRODUCTION

Most teratogenic substances are thought to affect the child through the mother. Therefore, the majority of studies assessing the role of occupational exposure as a cause of congenital malformations have focused on maternal exposures [Sever, 1994]. However, a potential for reproductive toxicity in men as a result of occupational exposure was also established, leading to increased concern about the role of male reproductive toxicants in adverse pregnancy outcomes [Sever, 1995]. Some mechanisms concerning male-mediated teratogenesis have been proposed [Colie, 1993; Olshan and Faustman, 1993]. Paternal occupational exposure to chemicals or radiation could theoretically result in genetic damage to germ cells or in concentrations of teratogenic substances in the seminal fluid. These substances might affect the child at conception or later, during embryonic development [Hales et al., 1986]. Also, indirect exposure of the mother could be caused by carry-home exposure of the father.

As a number of studies have reported a relation between neural tube defects and socioeconomic status [Leck, 1974; Nevin et al., 1981; Elwood and Elwood, 1980; Little and Elwood, 1992], studies on the association between these defects and parental occupation were indicated and were indeed suggested in several epidemiologic studies. Some case-referent studies evaluated associations between a large set of paternal occupations and spina bifida. Schnitzer et al. [1995] recently conducted a case-referent study with 176 cases of spina bifida and 2,279 referents using self-reported information on paternal occupation from telephone interviews. They found moderately increased risks for vehicle manufacturers, electronic equipment operators, welders, and carpenters and woodworkers, although the latter three effect...
estimates were imprecise. Olshan et al. [1991] compared paternal occupations of 534 cases of spina bifida with 1,033 referents. Information on the occupation of the father was collected from birth certificates. Increased risks were observed for forestry and logging workers, paper workers, printers, service-station attendants, and personal service workers. In an earlier phase of our case-referent study, we did an analysis on occupational titles, in which we compared 347 spina bifida cases with 1,566 referents [Blatter et al., 1996]. Postal questionnaires were used to assess the occupation of the father. We saw increased risks for welders and transport workers, although these were not statistically significant.

Several studies have investigated only some specific occupations or were small-scale studies. Occupations that were identified as a risk factor in two or more of these studies are painters [Olsen, 1983; Brender and Suarez, 1990; Fedrick, 1976], transport and communication workers [Fedrick, 1976; Polendnak and Janerich, 1983], and farmers [Polendnak and Janerich, 1983; Balarajan and McDowall, 1983; Hammond and Canache, 1991].

Although few of the above findings are consistent, these studies provide some evidence for associations between spina bifida and paternal occupation. However, an important limitation of the studies mentioned is that occupational titles are used as a surrogate for occupational exposure. As Sever [1995] and Olshan et al. [1991] point out, there is a need for large-scale case-referent studies that include improved assessment of paternal exposure and allow for potentially confounding factors. To our knowledge, no studies have been performed that investigate the effect of occupational exposure of the father on the risk of spina bifida in offspring. We evaluated this relation in a multi-center case-referent study including a relatively large number of spina bifida cases. To get detailed exposure information about the period around conception, job- and task-specific telephone interviews were performed.

**Data Collection**

Data collection was carried out in two steps. First, postal questionnaires were sent to the parents of the total study population to collect information on the occupation of the father and potentially confounding factors around conception. This part of the study has been previously described in more detail elsewhere [Blatter et al., 1996]. Second, detailed information on paternal occupational exposure was collected from a subset of the fathers by means of telephone interviews. Only fathers who gave consent for participation and who had an occupation with potential for chemical or physical exposure according to the postal questionnaire were interviewed. Detailed interviews with fathers who did not have a job or who worked in jobs without hazardous exposure were deemed irrelevant. The interviewed group included primarily painters, printers and paper workers, metal workers and mechanics, construction workers, transport workers, agricultural workers, health care workers, and laboratory workers. Because exposure in certain occupations, such as general practitioners, physiotherapists, and higher-level technical occupations, was uncertain, fathers with these occupations were not interviewed and not included in the analyses. Exposure of the remaining fathers (teachers, social workers, and clerical and managerial staff) was assumed to be negligible. These men were included in the analyses as non-exposed.

The period of interest ranged from three months before conception until one month after conception, calculated from the duration of pregnancy reported in the questionnaire by the mother. In order to pose job-specific questions to the participants, 17 different questionnaires were specifically designed for printers, painters, plastic or rubber workers, paper workers, metal workers, mechanics, welders, plumbers, bricklayers or joiners, tilers, roadworkers, roofers, carpenters, agricultural workers, transport workers, health care workers, and laboratory workers. Men who could not be classified into one of these groups were interviewed using a general open-ended questionnaire or parts or combinations of the existing questionnaires.

In each interview, traditional work history questions on job title, type of industry, company name, and number of hours worked, were asked first. Subsequently, questions were posed to inquire about every occupational task that had possibly been performed and the associated use of chemicals and radiation, the frequency of the activity or exposure, the use of protective devices, and exposure through proximity of colleagues. Tilers, for instance, were asked whether they
used mortar or glue; agricultural workers were asked whether they sprayed pesticides using a tractor or backpack sprayer; and printers were asked whether they had to refill the ink supply and wash the ink rollers. The questionnaires were designed by the investigators on the basis of occupational hygiene information, comparable to the job-specific modules used by Stewart and Stewart [1994] in the USA. At the end of each interview, a checklist with 17 categories of exposure was used to get information on any agents that might have been missed. Again, detailed questions were asked for the agents that were reported using the checklist.

Estimation of the level of exposure for each exposure category was based on the self-reported interview information (exposure, yes or no; frequency of exposure in hours per week; kind of protective equipment used) and on the professional judgment of the investigators. A 4-point scale was used to indicate the level of exposure (not exposed, lightly exposed, moderately exposed, or heavily exposed).

### Analysis

The prevalence of exposure was evaluated among fathers in certain occupational groups and in the total group of possibly exposed (interviewed) and nonexposed workers. Within each of the well-defined occupational groups with potential for exposure (see Tables II through IV), descriptive analyses were performed in order to identify differences between cases and referents. For each occupational group, only agents specific for that group were included in these analyses. The chi-square test was used to calculate P-values for the categories for which prevalences differed between cases and referents.

After combining all occupational groups, frequency distributions and odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated. To be parsimonious, 39 of the 72 exposure categories that we coded are not presented. Criteria for exclusion of exposure categories from Table V were: fewer than ten exposed subjects (cases and referents) and a probable local working mechanism, in which case the exposure categories were considered irrelevant with respect to a possible teratogenic effect. For instance, various types of dust and asbestos were not presented. For exposure categories with ten or fewer exposed cases, the level of exposure was dichotomized into no exposure vs. any level of exposure. ORs were separated for exposure vs. any level of exposure. ORs were separated for exposure catego­

### RESULTS

Three hundred forty-seven case fathers (77%) and 1,566 referent fathers (68%) returned the questionnaire in the first phase of the study. From these fathers, 277 (80%) and 1,063 (68%), respectively, were available for participation in a personal interview. Of the 277 case fathers, 122 had an occupation with potential for chemical or physical exposure and were interviewed; 100 had a nonexposed occupation. Of the 1,063 referents, 411 were potentially exposed and interviewed; 353 had a nonexposed occupation. The remaining fathers had occupations in which exposure was uncertain and were excluded from this phase of the study.

Table I presents the distribution of potentially confounding factors for cases and referents. Both paternal and maternal education of the cases was slightly lower than that of the referents. Furthermore, small differences were seen in alcohol use. The largest differences were found in the

### Table I. Distribution of Potentially Confounding Factors for Cases of Spina Bifida and Referents in a Study on Paternal Occupational Exposure, The Netherlands, 1980–1992

<table>
<thead>
<tr>
<th>Potential confounders</th>
<th>Cases (n = 222)</th>
<th>Referents (n = 764)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal education*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>69 (31.7)</td>
<td>202 (26.5)</td>
</tr>
<tr>
<td>Middle</td>
<td>90 (41.3)</td>
<td>277 (36.4)</td>
</tr>
<tr>
<td>High</td>
<td>59 (27.1)</td>
<td>283 (37.1)</td>
</tr>
<tr>
<td>Maternal education*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>70 (32.3)</td>
<td>199 (26.2)</td>
</tr>
<tr>
<td>Middle</td>
<td>103 (47.5)</td>
<td>362 (47.7)</td>
</tr>
<tr>
<td>High</td>
<td>44 (20.3)</td>
<td>198 (26.1)</td>
</tr>
<tr>
<td>Paternal alcohol use</td>
<td>185 (83.3)</td>
<td>659 (86.5)</td>
</tr>
<tr>
<td>Maternal alcohol use</td>
<td>114 (52.1)</td>
<td>446 (58.5)</td>
</tr>
<tr>
<td>Paternal smoking</td>
<td>107 (48.4)</td>
<td>354 (46.4)</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>88 (40.5)</td>
<td>303 (39.8)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>99 (45.2)</td>
<td>311 (40.8)</td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td>84 (38.5)</td>
<td>242 (32.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (0.5)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Maternal use of antiepileptics</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Homocysteinaemia</td>
<td>2 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ovulation stimulating agents</td>
<td>9 (4.1)</td>
<td>26 (3.4)</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>1 (0.5)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Paternal family history of NTDs</td>
<td>16 (7.2)</td>
<td>11 (1.4)</td>
</tr>
<tr>
<td>Maternal family history of NTDs</td>
<td>10 (4.5)</td>
<td>8 (1.1)</td>
</tr>
</tbody>
</table>

*Low: comparable with up to grade 9; middle: comparable with grades 10–14; high: comparable with grade 15 and higher.
### Table II. Occupational Exposure of Fathers of Spina Bifida Cases and Referents Among Industrial Workers by Occupational Group, The Netherlands, 1980-1992

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th>Total (%)</th>
<th>Referents</th>
<th></th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Light</td>
<td>Moderate or heavy</td>
<td></td>
<td></td>
<td>Light</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Printers, painters, plastic and paper workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>4</td>
<td>3</td>
<td>70.0</td>
<td>14</td>
<td>12</td>
<td>68.4</td>
</tr>
<tr>
<td>Lute or glue</td>
<td>1</td>
<td>2</td>
<td>30.0</td>
<td>3</td>
<td>6</td>
<td>23.7</td>
</tr>
<tr>
<td>Ink or pigment</td>
<td>0</td>
<td>3</td>
<td>30.0</td>
<td>7</td>
<td>9</td>
<td>44.7</td>
</tr>
<tr>
<td>Paint (with turpentine base)</td>
<td>0</td>
<td>5</td>
<td>50.0</td>
<td>2</td>
<td>10</td>
<td>31.5</td>
</tr>
<tr>
<td>Paint removers</td>
<td>2</td>
<td>0</td>
<td>20.0</td>
<td>2</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>3</td>
<td>0</td>
<td>30.0</td>
<td>4</td>
<td>1</td>
<td>13.2</td>
</tr>
<tr>
<td>Metal workers and mechanics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>7</td>
<td>2</td>
<td>32.0</td>
<td>34</td>
<td>11</td>
<td>27.4</td>
</tr>
<tr>
<td>Metal dust</td>
<td>7</td>
<td>12</td>
<td>67.9</td>
<td>23</td>
<td>33</td>
<td>58.9</td>
</tr>
<tr>
<td>Metal working fluids</td>
<td>3</td>
<td>4</td>
<td>25.0</td>
<td>15</td>
<td>14</td>
<td>30.5</td>
</tr>
<tr>
<td>Paint (with turpentine base)</td>
<td>5</td>
<td>0</td>
<td>17.9</td>
<td>20</td>
<td>2</td>
<td>23.3</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>10</td>
<td>3</td>
<td>46.4</td>
<td>26</td>
<td>24</td>
<td>52.6</td>
</tr>
<tr>
<td>Soldering fumes</td>
<td>3</td>
<td>2</td>
<td>17.8</td>
<td>15</td>
<td>12</td>
<td>28.4</td>
</tr>
<tr>
<td>Construction workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>0</td>
<td>1</td>
<td>7.1</td>
<td>4</td>
<td>0</td>
<td>10.0</td>
</tr>
<tr>
<td>Wood dust</td>
<td>5</td>
<td>6</td>
<td>78.6</td>
<td>12</td>
<td>12</td>
<td>60.0</td>
</tr>
<tr>
<td>Lute</td>
<td>4</td>
<td>1</td>
<td>35.7</td>
<td>10</td>
<td>5</td>
<td>37.5</td>
</tr>
<tr>
<td>Glue</td>
<td>3</td>
<td>0</td>
<td>21.4</td>
<td>14</td>
<td>3</td>
<td>42.5</td>
</tr>
<tr>
<td>Paint (with turpentine base)</td>
<td>7</td>
<td>0</td>
<td>50.0</td>
<td>22</td>
<td>1</td>
<td>57.5</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>4</td>
<td>0</td>
<td>28.6</td>
<td>4</td>
<td>0</td>
<td>10.0</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>1</td>
<td>0</td>
<td>7.1</td>
<td>3</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Primer</td>
<td>2</td>
<td>0</td>
<td>14.3</td>
<td>2</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Mortar and cement</td>
<td>1</td>
<td>0</td>
<td>50.0</td>
<td>2</td>
<td>8</td>
<td>25.0</td>
</tr>
<tr>
<td>Transport workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>3</td>
<td>0</td>
<td>11.1</td>
<td>12</td>
<td>1</td>
<td>18.8</td>
</tr>
<tr>
<td>Cleaning agents</td>
<td>4</td>
<td>0</td>
<td>14.8</td>
<td>11</td>
<td>0</td>
<td>15.9</td>
</tr>
<tr>
<td>Fuels</td>
<td>12</td>
<td>0</td>
<td>44.4</td>
<td>29</td>
<td>1</td>
<td>43.5</td>
</tr>
<tr>
<td>Exhaust fumes</td>
<td>14</td>
<td>10</td>
<td>88.9</td>
<td>34</td>
<td>18</td>
<td>76.8</td>
</tr>
<tr>
<td>Lubricating oil</td>
<td>0</td>
<td>0</td>
<td>0.0</td>
<td>9</td>
<td>5</td>
<td>20.3</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>3</td>
<td>1</td>
<td>14.8</td>
<td>8</td>
<td>0</td>
<td>11.6</td>
</tr>
<tr>
<td>Seated for long periods of time</td>
<td>5</td>
<td>8</td>
<td>18.5</td>
<td>11</td>
<td>15.9</td>
<td></td>
</tr>
</tbody>
</table>

The prevalence of paternal and maternal positive family histories of NTDs: 7.2% and 4.5%, respectively, among the cases, and 1.4% and 1.1% among the referents.

In Table II, the number and the total proportion of exposed industrial workers is presented, itemized by four rather homogeneous occupational groups: painters, printers, plastic and paper workers; metal workers and mechanics; construction workers; and transport workers. Only those agents that were specifically used in these occupations are shown. Moderately and heavily exposed workers were combined into one category, due to small numbers. In general, differences between exposure prevalences were small and based on very small numbers. Exposure to welding fumes seemed to be more frequent among case fathers in printers, painters, plastic and paper workers (30% vs. 13%, $P = 0.20$), just as for construction workers (29% vs. 10%, $P = 0.11$). In addition, exposure to primers (14% vs. 5%, $P = 0.27$) and mortar and cement (50% vs. 25%, $P = 0.08$) was more frequent among case fathers with construction work; exposure to glue occurred less often in fathers of cases (21% vs. 43%, $P = 0.16$). Except for wood dust and mortar and cement, moderate or high exposure occurred infrequently in construction workers. For the groups of metal workers and transport workers, no differences in exposure frequencies were observed. Except for exhaust fumes, moderate or high exposure rarely occurred in
transport workers. “Being seated for long periods of time” was included because of the hypothesis of an adverse effect of increased sperm temperature. No difference was found between cases and referents.

Table III presents the distribution of occupational exposure in agricultural workers. No differences were seen in the total number of pesticide users between fathers of cases and referents. However, moderate or high exposure to pesticides was more frequent in cases than in referents (73% vs. 35%, \( P = 0.05 \)). Moreover, 45% of the case fathers worked with a backpack sprayer, compared to 29% of the referent fathers (\( P = 0.24 \)). Exposure to welding fumes was also more frequent in case fathers than referent fathers (45% vs. 21%, \( P = 0.10 \)), but all but one of the men were lightly exposed. In Table IV, exposure of health care workers and laboratory workers is shown. The exposure levels were combined due to small numbers of exposed. No differences were observed between exposure of cases and referents.

Table V presents the results of the adjusted ORs with 95% confidence intervals for all fathers in the possibly exposed occupations (n = 533) and nonexposed occupations (n = 433) combined. Most adjusted ORs did not differ from the crude ORs, except for moderate or high exposure to cleaning agents, low exposure to UV radiation during welding, and exposure to stainless steel dust. Except for low exposure to welding fumes and low exposure to UV radiation during welding, all of the 95% CIs included unity. An increased risk was found for moderate or high exposure to cleaning agents (OR = 2.1, 95% CI: 0.7–6.6), which was not statistically significant, and for low exposure to welding fumes (OR = 1.8, 95% CI: 1.0–3.6). A statistically significantly increased OR was also found for low exposure to UV radiation during welding (OR = 2.6, 95% CI: 1.2–5.6). Stainless steel dust (OR = 2.0, 95% CI: 0.8–5.2), ammonia (OR = 1.8, 95% CI: 0.8–5.0), and moderate or high exposure to pesticides were associated with spina bifida (OR = 1.7, 95% CI: 0.7–4.0). As exposure to the latter agents might be associated with an agricultural occupation of the mother, which appeared to be a risk factor for spina bifida [Blatter et al., 1996], we performed an analysis in which we adjusted for agricultural occupation of the mother. The ORs did not change substantially after correction (OR\(_{\text{total welding fumes}} = 1.2, \text{OR}_{\text{low}} = 1.5, \text{OR}_{\text{moderate pesticides}} = 1.6 \)). Finally, it has to be noticed that among the multitude of comparisons, a number of decreased risks of spina bifida were found as well.

**DISCUSSION**

This study did not identify any strong associations between paternal occupational exposure to chemicals or radiation shortly before pregnancy and the risk of spina bifida in offspring. Associations that were not always
An increased risk of spina bifida for welders has been found before in a study in Atlanta [Schnitzer et al., 1995]. We also found an association with welders in an analysis on occupational titles in the Dutch case-referent study [Blatter et al., 1996], of which a large part of the population was used in the present study to thoroughly investigate the influence of occupational exposure. In both studies, however, confidence intervals were wide. Scandinavian investigators reported that sperm quality and fertility seem to be reduced among welders [Mortensen, 1988; Bonde et al., 1990].

In accordance with the increased risk that we found for moderate or high pesticide exposure, Brender and Suarez [1990] also found a slightly increased risk for pesticide exposure (OR = 1.3, 95% CI: 0.8–2.1). However, exposure was inferred from occupational title and not assessed by means of detailed exposure information. We are unaware of any studies that have investigated paternal occupational


<table>
<thead>
<tr>
<th>Chemical or physical agent</th>
<th>Cases (n = 7)</th>
<th>Referents (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Solvents</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>Chloroform-containing solvents</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>Cleaning agents</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Disinfectants</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Biological material</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>Anineplastic drugs</td>
<td>1</td>
<td>14.3</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>1</td>
<td>14.3</td>
</tr>
</tbody>
</table>

statistically significant were found between low exposure to welding fumes and UV radiation during welding, high or moderate exposure to pesticides, stainless steel dust, and high or moderate exposure to cleaning agents and spina bifida. The slightly increased risk for exposure to welding fumes was primarily caused by an increase among painters, printers, plastic and paper workers, construction workers, and agricultural workers, but not by an increase among the professional welders or metal workers. The level of exposure to welding fumes in these workers was low, but less protective equipment was used by these workers than by professional welders (46% compared with 86%). The increased risk for UV radiation during welding might be a proxy for the risk of exposure to welding fumes. Because UV radiation is visible to the worker, it might be less prone to subjective interpretation of the participant.

We also found an association with welders in an analysis on occupational titles in the Dutch case-referent study [Blatter et al., 1996], of which a large part of the population was used in the present study to thoroughly investigate the influence of occupational exposure. In both studies, however, confidence intervals were wide. Scandinavian investigators reported that sperm quality and fertility seem to be reduced among welders [Mortensen, 1988; Bonde et al., 1990].

In accordance with the increased risk that we found for moderate or high pesticide exposure, Brender and Suarez [1990] also found a slightly increased risk for pesticide exposure (OR = 1.3, 95% CI: 0.8–2.1). However, exposure was inferred from occupational title and not assessed by means of detailed exposure information. We are unaware of any studies that have investigated paternal occupational


<table>
<thead>
<tr>
<th>Chemical or physical agent</th>
<th>Cases (n = 222)</th>
<th>Referents (n = 764)</th>
<th>OR adj</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleaning agents</td>
<td>13</td>
<td>47</td>
<td>0.8</td>
<td>0.4–1.7</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>39</td>
<td>0.6</td>
<td>0.2–1.3</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>6</td>
<td>8</td>
<td>2.1</td>
<td>0.7–6.5</td>
</tr>
<tr>
<td>Disinfectants</td>
<td>6</td>
<td>22</td>
<td>0.8</td>
<td>0.3–2.2</td>
</tr>
<tr>
<td>Solvents</td>
<td>29</td>
<td>132</td>
<td>0.7</td>
<td>0.4–1.1</td>
</tr>
<tr>
<td>Low</td>
<td>19</td>
<td>100</td>
<td>0.6</td>
<td>0.4–1.1</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>10</td>
<td>32</td>
<td>0.9</td>
<td>0.4–2.0</td>
</tr>
<tr>
<td>Ink</td>
<td>5</td>
<td>23</td>
<td>0.8</td>
<td>0.3–2.2</td>
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<tr>
<td>Pigment</td>
<td>2</td>
<td>12</td>
<td>0.5</td>
<td>0.1–2.9</td>
</tr>
<tr>
<td>Paint (with turpentine base)</td>
<td>24</td>
<td>89</td>
<td>1.0</td>
<td>0.6–1.6</td>
</tr>
<tr>
<td>Low</td>
<td>18</td>
<td>70</td>
<td>1.0</td>
<td>0.6–1.7</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>6</td>
<td>19</td>
<td>1.0</td>
<td>0.4–2.7</td>
</tr>
<tr>
<td>Glue or lute</td>
<td>14</td>
<td>52</td>
<td>0.8</td>
<td>0.4–1.6</td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>29</td>
<td>1.0</td>
<td>0.5–2.3</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>4</td>
<td>23</td>
<td>0.6</td>
<td>0.2–1.7</td>
</tr>
<tr>
<td>Welding heat</td>
<td>22</td>
<td>69</td>
<td>1.0</td>
<td>0.6–1.7</td>
</tr>
<tr>
<td>Low</td>
<td>13</td>
<td>40</td>
<td>1.1</td>
<td>0.5–2.1</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>9</td>
<td>29</td>
<td>0.9</td>
<td>0.4–2.1</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>35</td>
<td>95</td>
<td>1.3</td>
<td>0.8–2.0</td>
</tr>
<tr>
<td>Low</td>
<td>30</td>
<td>65</td>
<td>1.6</td>
<td>1.0–2.6</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>5</td>
<td>30</td>
<td>0.6</td>
<td>0.2–1.5</td>
</tr>
<tr>
<td>Welding UV</td>
<td>17</td>
<td>35</td>
<td>1.6</td>
<td>0.8–3.1</td>
</tr>
<tr>
<td>Low</td>
<td>15</td>
<td>18</td>
<td>2.6</td>
<td>1.2–5.6</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>2</td>
<td>17</td>
<td>0.5</td>
<td>0.1–2.0</td>
</tr>
<tr>
<td>Soldering fumes</td>
<td>6</td>
<td>38</td>
<td>0.6</td>
<td>0.2–1.4</td>
</tr>
<tr>
<td>Metal dust</td>
<td>29</td>
<td>92</td>
<td>1.1</td>
<td>0.7–1.8</td>
</tr>
<tr>
<td>Low</td>
<td>12</td>
<td>46</td>
<td>1.0</td>
<td>0.5–1.9</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>16</td>
<td>43</td>
<td>1.3</td>
<td>0.7–2.4</td>
</tr>
<tr>
<td>Iron dust</td>
<td>7</td>
<td>22</td>
<td>1.0</td>
<td>0.4–2.5</td>
</tr>
<tr>
<td>Aluminum dust</td>
<td>5</td>
<td>14</td>
<td>1.3</td>
<td>0.5–3.6</td>
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<tr>
<td>Steel dust</td>
<td>9</td>
<td>29</td>
<td>1.1</td>
<td>0.5–2.4</td>
</tr>
<tr>
<td>Stainless steel dust</td>
<td>7</td>
<td>14</td>
<td>2.0</td>
<td>0.8–5.2</td>
</tr>
<tr>
<td>Metal working fluids</td>
<td>8</td>
<td>30</td>
<td>0.9</td>
<td>0.4–2.0</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>3</td>
<td>13</td>
<td>0.6</td>
<td>0.1–2.5</td>
</tr>
<tr>
<td>Artificial fertilizer</td>
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<td>21</td>
<td>0.7</td>
<td>0.2–2.0</td>
</tr>
<tr>
<td>Pesticides</td>
<td>11</td>
<td>35</td>
<td>0.9</td>
<td>0.4–1.9</td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>18</td>
<td>0.2</td>
<td>0.0–1.4</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>9</td>
<td>17</td>
<td>1.7</td>
<td>0.7–4.0</td>
</tr>
<tr>
<td>Fuels (all low exposure)</td>
<td>19</td>
<td>71</td>
<td>0.8</td>
<td>0.5–1.4</td>
</tr>
<tr>
<td>Exhaust fumes</td>
<td>51</td>
<td>137</td>
<td>1.2</td>
<td>0.8–1.8</td>
</tr>
<tr>
<td>Low</td>
<td>35</td>
<td>92</td>
<td>1.2</td>
<td>0.8–1.7</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>16</td>
<td>45</td>
<td>1.3</td>
<td>0.7–2.5</td>
</tr>
<tr>
<td>Lubricating oil</td>
<td>13</td>
<td>73</td>
<td>0.6</td>
<td>0.3–1.1</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>34</td>
<td>0.7</td>
<td>0.3–1.6</td>
</tr>
<tr>
<td>Moderate or high</td>
<td>6</td>
<td>39</td>
<td>0.5</td>
<td>0.2–1.3</td>
</tr>
<tr>
<td>Photochemicals</td>
<td>2</td>
<td>11</td>
<td>0.7</td>
<td>0.2–3.3</td>
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<tr>
<td>Ammonia</td>
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<td>12</td>
<td>1.8</td>
<td>0.7–5.0</td>
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<tr>
<td>Plastic</td>
<td>4</td>
<td>23</td>
<td>0.5</td>
<td>0.2–1.7</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>5</td>
<td>16</td>
<td>0.9</td>
<td>0.3–2.7</td>
</tr>
<tr>
<td>Electromagnetic fields</td>
<td>4</td>
<td>22</td>
<td>0.7</td>
<td>0.2–2.1</td>
</tr>
<tr>
<td>Biological materials</td>
<td>7</td>
<td>32</td>
<td>0.6</td>
<td>0.2–1.4</td>
</tr>
</tbody>
</table>

*Adjusted by means of restriction for maternal use of antiepileptics, maternal homocysteinaemia or diabetes, and consanguinity, and by means of logistic regression analysis for evolution-stimulating agents, oral contraceptives, parity, maternal and paternal family history of neural tube defects (NTD), and maternal and paternal alcohol use and smoking.
exposures to pesticides and the risk of spina bifida, but farmers have been associated with spina bifida by Polednak and Janerich [1983], Balarajan and McDowall [1983], and Hammond and Canache [1991].

We found an increased risk for moderate or high exposure to cleaning agents, which often include solvents, but no differences in (other) solvent exposure were observed in this study. Taskinen et al. [1989] performed a small-scale nested case-referent study on solvents and congenital malformations in general, using questionnaires and biological monitoring to assess the exposure to six organic solvents. Slightly increased risks were found for toluene, xylene, and miscellaneous organic solvents, but numbers were small and no firm conclusions could be drawn. Brender and Suarez [1990] found an increased risk of anencephaly for fathers with occupations associated with solvent exposure (OR = 2.5, 95% CI: 1.6–4.1). We found no difference in exposure between case and referent fathers who worked in health care. This is consistent with the findings of Matte et al. [1993], who conducted a case-referent study with 211 cases of spina bifida focusing on the potential associations with employment in health care. They did not find an association between spina bifida and paternal health care employment or any specific exposure.

The present study has some potential limitations that deserve consideration. Exposures occurred between 2 and 15 years before the interview. Therefore, recall of early exposures might be limited, probably causing bias toward the null value. Differential recall between case and referent fathers may also have occurred, as the time lag between exposure and interview was unequally distributed in cases and referents. Thirty-six percent of the case fathers reported exposures for the most recent period (one to five years ago) compared to 22% of the referent fathers. Therefore, recall might have been better for cases. Whether inaccurate recall of earlier periods causes a bias by under- or overreporting cannot be inferred. Also, another form of information bias may have occurred. Although generally there is concern that parents of cases recall exposures better, and overreport exposures compared to referent parents, our experience is that case fathers sometimes tend to ascribe their child’s birth defect to other factors, such as the nuclear accident in Chernobyl, genetic factors, recreational drug use, or poor living conditions. We tried to enhance recall and reduce information bias by asking about exposure indirectly with questions about concrete tasks and by asking direct questions about chemicals used in these tasks. In addition, the self-reported information was reviewed and adjusted by the professional judgment of the investigators with respect to frequency and other details of exposure. Shaw and Gold [1988] mention a number of studies specifically evaluating information bias on exposures during pregnancy; the presence of information bias was not demonstrated. However, information bias can never be ruled out in a study using self-reported data.

A limitation of two-step data collection is that nonresponse accumulates. The response rates for the postal questionnaires were 77% for case fathers and 68% for referent fathers. In the postal questionnaire, the fathers were asked whether they were willing to participate in a personal interview at a later time. Eighty-one percent of the case fathers and 69% of the referent fathers answered positively. Differences in nonresponse between fathers with different occupations could have resulted in selection bias. Comparison of the initial total population (n_cases = 347, n.refs = 1,566) with the population used in this study (n_cases = 222, n.refs = 764) yielded only small differences between the occupational distributions.

As a selection of only live-born spina bifida cases was studied, the small effects that were found in this study might be a result of the so-called "inverse dose-response relationship": a very high exposure could result in infertility or early fetal loss, whereas a lower exposure might result in a congenital malformation recognized at birth [Selevan and Lemasters, 1987]. Furthermore, misclassification on the outcome variable may have occurred. As open spina bifida probably differs from closed spina bifida with respect to pathogenesis and etiology [Lemire, 1988], and these different forms cannot always be clinically distinguished, the case group may have been diluted with a few closed lesions. This may have led to a bias toward the null value.

The present study has several strengths which probably reduce misclassification relative to other studies on paternal occupation and spina bifida [Shaw and Gold, 1988]. We did not use job titles in this study as a surrogate for occupational exposure, nor did we infer exposure by means of job exposure matrices, which are often unspecific. Postal questionnaires were first used to collect information on the fathers’ occupation shortly before pregnancy. We then interviewed the potentially exposed participants with job-specific questionnaires, in which questions were asked about all the tasks that possibly were performed, the frequency and duration of the tasks, and the associated chemical or physical exposure, use of protective devices, and use of chemicals by colleagues. In this way, we were able to form relatively homogeneous exposure groups.

Information on potentially confounding factors was gathered by means of postal questionnaires. This might have minimized misclassification on the confounders as questionnaire information or lifestyle factors may be less influenced by the tendency to give socially desirable answers than information gathered in a face-to-face situation or during telephone interviews [Armstrong et al., 1992]. In addition, data on potentially confounding factors related to the father were available from the paternal questionnaire, but data on factors related to the mother were reported by the mother herself in the maternal questionnaire. Therefore, the ORs
could be adjusted for all potential confounders. Periconceptional folic acid use was not taken into account as a confounder, as this vitamin was not added to multivitamin supplements nor separately available in the Netherlands during the study period. Education was not adjusted for, because of the risk of over-adjustment. We were not able to adjust for maternal occupational exposure, as we only had information on maternal exposures for a part of the fathers.

We did perform an additional analysis adjusting for maternal agricultural occupation, which appeared to be a risk factor for spina bifida [Blatter et al., 1996]. No differences were observed.

Finally, a relatively large number of spina bifida cases was included in this study. The study had a power of 96% to detect a twofold statistically significantly increased risk of solvent exposure, a power of 90% to detect a twofold increased risk of welding fumes and paint, and a power of 75% to detect a twofold increased risk of glue and lute. However, for exposure to stainless steel dust, the power was only 29% to detect an OR of 2, and for moderate or high pesticide exposure, the power was 42%.

Our research findings may also be viewed in terms of the population attributable proportion, which is the proportion of cases in the target population that is attributable to the exposure under study. As the risks of spina bifida from welding fumes or high or moderate pesticide exposure are only slightly elevated, and the exposure prevalences in the population are low, the population attributable proportions are small also. For exposure to welding fumes it is 3%, for high or moderate pesticide exposure it is 1.5%. Attributable proportions computed with ORs of exposure to high or moderate pesticide exposure equal to 2, 4, or 6, are 2%, 6%, and 10%, respectively. This enables us to draw the conclusion that paternal occupational exposure does not seem to play a major role in the causation of spina bifida. Still, the associations between spina bifida and welding UV, welding fumes, stainless steel dust, and pesticides deserve further in-depth study, which may elucidate more of the multifactorial etiologic mechanisms of spina bifida.

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REFERENCES


