ORIGINAL ARTICLE

# The CHARGE study: an assessment of parental occupational exposures and autism spectrum disorder

Erin C McCanlies,[1] Claudia C Ma,[1] Ja Kook Gu,[1] Desta Fekedulegn,[1] Wayne T Sanderson,[2] Yunin J Ludeña-Rodriguez,[3] Irva Hertz-Picciotto[3]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2018-105395).

[1]Health Effects Laboratory, National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA
[2]University of Kentucky Chandler Medical Center, Lexington, Kentucky, USA
[3]Division of Environmental and Occupational Health, Public Health Sciences, University of California, Davis, California, USA

**Correspondence to**
Dr. Erin C McCanlies, Health Effects Laboratory, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA; eim4@cdc.gov

Received 31 July 2018
Revised 9 April 2019
Accepted 16 April 2019
Published Online First 27 June 2019

Check for updates

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

**To cite:** McCanlies EC, Ma CC, Gu JK, *et al*. *Occup Environ Med* 2019;**76**:644–651.

## ABSTRACT

**Objectives** The aim of this study is to determine if parental occupational exposure to 16 agents is associated with autism spectrum disorder (ASD).

**Methods** Demographic, health and parental occupational data were collected as part of the CHildhood Autism Risks from Genetics and Environment study. The workplace exposure assessment was conducted by two experienced industrial hygienists for the parents of 537 children with ASD and 414 typically developing (TD) children. For each job, frequency and intensity of 16 agents were assessed and both binary and semi-quantitative cumulative exposure variables were derived. Logistic regression models were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI) to assess associations between parental occupational exposures 3 months pre-pregnancy until birth.

**Results** The OR of ASD in the children of mothers exposed to any solvents was 1.5 times higher than the mothers of TD children (95% CI=1.01–2.23). Cumulative exposure indicated that the OR associated with a moderate level of solvent exposure in mothers was 1.85 (95% CI=1.09, 3.15) for children with ASD compared with TD children. No other exposures were associated with ASD in mothers, fathers or the parents combined.

**Conclusion** Maternal occupational exposure to solvents may increase the risk for ASD. These results are consistent with a growing body of evidence indicating that environmental and occupational exposures may be associated with ASD. Future research should consider specific types of solvents, larger samples and/or different study designs to evaluate other exposures for potential associations with ASD.

### Key messages

**What is already known about this subject?**

► The speed with which the incidence of autism has increased suggests the importance of risk factors other than genetics in the aetiology of autism spectrum disorder (ASD) and, currently, several dozen epidemiologic studies have observed associations with prenatal exposures to environmental chemicals and pollutants. Since occupational exposures often exceed environmental levels, investigation of their role as risk factors for ASD is warranted in the search for potentially modifiable aetiologic agents.

**What are the new findings?**

► Maternal occupational exposure to solvents occurred more often in the parents of children with ASD compared with TD children.

**How might this impact on policy or clinical practice in the foreseeable future?**

► Future research should consider maternal occupational exposures to solvents as a potential risk factors in the aetiology of ASD and focus on identifying specific solvents rather than broad categories of solvents. Larger studies or different types of study designs may help to identify other risk factors in the aetiology of ASD and further clarify the role solvents may have in the risk of ASD.

## INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is both costly and leads to lifelong disability.[1] It is a range of conditions with characteristics including repetitive behaviours, impairment in reciprocal social interaction and difficulty communicating.[2] Recent prevalence estimates in the United States indicate that about one in 68 children have ASD and numerous studies demonstrate that the incidence has been steadily increasing.[3 4] The speed with which the incidence has increased suggests the importance of environmental exposures in the risk of ASD.

Chlorinated solvents, diesel particulates and air pollution from motor vehicle emissions are environmental pollutants that have been found to be associated with ASD.[5] By linking the hazardous air pollutants database to census tract data, Windham et al,[5] found that chlorinated solvents, cadmium, mercury, and nickel were associated with ASD. In another study, model-based estimates of both traffic-related and regional air pollution were evaluated in relation to ASD.[6] For traffic-related air pollutant exposures, a mix of nitrogen oxides, elemental carbon and carbon monoxide, the adjusted odds for ASD was about doubled comparing the top quartile versus the lowest quartile. Similar results were found for each trimester and also for several regional criteria air pollutants.[6]

Pesticides include insecticides, fungicides, herbicides and rodenticides, and have been shown to cross the placenta and blood-brain barrier. Higher levels of pesticide metabolites in pregnant mothers at 28 weeks of gestation were significantly



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

associated with reduced motor and cognitive composite scores on the Bayley-III when the infant was tested at 5 months of age.[7 8] Pesticide exposure via diet and exposure to tick/flea treatment has also been found to be associated with ASD.[9 10] The California Pesticide Use Report from 1997 to 2008 was used to evaluate drift exposures from commercial pesticide applications in individuals who participated in the CHildhood Autism Risks from Genetics and Environment (CHARGE) study.[11] Exposure to pesticides, including chloropyrifos and pyrethoids was shown to be associated with ASD either during one or more trimesters of the pregnancy or during the preconception period, indicating that risk is not only associated with exposure during pregnancy, but shortly prior to pregnancy as well.[11]

These studies suggest that environmental exposures are associated with ASD. Of direct relevance to the present study, many of these same exposures may also be found at the workplace. Workplace exposures are associated with poor reproductive outcomes including spontaneous abortion, neurologic and physical malformation, and central nervous system disturbances making them good candidates in the aetiology of ASD.[12 13] Research supports this: Windham et al,[14] found that in mothers, occupational exposure to disinfectants and exhaust and combustion products were associated with ASD. In contrast, maternal occupational exposure to asthmagens was found to be inversely associated with ASD.[15] Using both a job exposure matrix and parental self-report, we previously published a pilot study examining parental occupational exposures and ASD. The study population consisted of 93 children with ASD, 81 typically developing (TD) children, and their parents. We found that exposure to lacquers, varnish and xylene occurred more often in parents of children with ASD compared with parents of TD children. Parents of children with ASD were more likely to report occupational exposure to asphalt and solvents compared with parents of TD children. The aim of the current study is to confirm and extend these previous findings. Using a workplace exposure assessment, 16 agents that have been found to be associated with adverse pregnancy outcomes were evaluated to determine if they are associated with ASD in the larger CHARGE population.

## METHODS

### Study population

The CHARGE study is a population-based case-control study that has been previously described.[16] Briefly, the CHARGE study enrolls children with a previous designation of autism as well as children from the general population, selected from state vital statistics files on births. Eligible children must be between the ages of 2 and 5 years, born in California, living with at least one biologic parent who speaks English or Spanish, and residing in the catchment areas of a specified list of California Regional Centers that coordinate services for persons with developmental disabilities. Children with autism are identified through the California Department of Developmental Services, which administers the Regional Center system, and general population controls are identified from state birth files and are frequency matched to the expected sex distribution, as well as the actual age and catchment area of the autism cases. The National Institute for Occupational Safety and Health (NIOSH) received data on 981 children and their parents who were enrolled in the study beginning in 2003. After excluding parents who did not work during the index period (n=26), or had missing occupational data (n=201 mothers; n=60 fathers) or children with missing diagnostic results (n=4), we had complete data on 750 mothers and 891 fathers and their children (n=537 ASD; n=414 TD).

### Ethics

The CHARGE study protocol was approved by institutional review boards at the University of California, Davis, and the University of California, Los Angeles, and by the State of California Committee for the Protection of Human Subjects and the NIOSH human subjects review board. Written informed consent was collected from all participants, prior to data collection.

### Diagnostic criteria

All the children underwent cognitive, social and medical evaluations at either the University of California, Davis, Medical Investigation of Neurodevelopmental Disorders Institute (UC Davis MIND) in Sacramento, CA or the University of California, Los Angeles (UCLA) Neuropsychiatric Institute. The Mullen Scales of Early Learning (MSEL)[17] and the Vineland Adaptive Behaviour Scales (VABS)[18] were used to evaluate cognitive function, motor skills, socialisation, language and daily living skills in all children. Children with a previous diagnosis of ASD were assessed using the Autism Diagnostic Observation Schedule (ADOS)[19] and their parents were interviewed using the Autism Diagnostic Interview-Revised (ADI-R)[20] to confirm their child's ASD diagnosis. Children selected from the general population were assessed using the Social Communication Questionnaire (SCQ),[21] a short screening instrument for ASD symptoms. If they received scores of <15 on the SCQ and within the normal range on the MSEL and VABS, they were defined as TD . Children who scored≥15 were evaluated for ASD on the ADOS and ADI-R.[19 20 22] The algorithm of Risi et al,[22] was used to assign final diagnosis of ASD or not.

### Demographic and lifestyle characteristics

Demographic, lifestyle and medical data were collected through extensive questionnaires, interviewing the parents on the telephone and birth record review. Information on both parents included their age, level of education, race/ethnicity, birthplace, smoking history, regional centre/geographic location of residence and payment method used for the child's delivery. Level of education was reported as being less than high school, high school/graduate equivalency degree (GED), some college, and graduate or professional degree. A variable 'total years of education' was calculated by summing the two parents' education level. Participants were asked to report their race/ethnicity as white, black, American Indian/Alaska native, Asian, Pacific Islander/Hawaiian native, White Hispanic, non-White Hispanic and multi-racial. Due to small numbers for this study, the participants were collapsed into the following groups: Caucasian; non-Hispanic; African-American; non-Hispanic; Hispanic (any); or Other. The 'other' category consisted of individuals who reported their race/ethnicity as American Indian, Alaska native, Asian, Pacific Islander/Hawaiian native, or multi-racial. Information about the children included the child's age, gender, date of birth, race/ethnicity and duration of breastfeeding.

### Workplace exposure assessment

Information on parental occupational history was collected during the CHARGE study telephone interview. Mothers were interviewed about their job histories and when possible, or if directed by the mother, the father was interviewed about his job history. Approximately, 37% of the fathers responded, otherwise the mothers reported the fathers' job history. Occupational information included, for each job, the place of employment, the months and years of employment, which month(s) of pregnancy (or the postnatal period) the job was held, and the total



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

**Table 1** Means and standard errors or percentages for selected baseline characteristics of the study parents and children stratified by children's autistic status

| | | Autism spectrum disorder (n=537) | | Typically developing (n=414) | |
|---|---|---|---|---|---|
| **Variable** | | **n** | **Mean (SE) or %*** | **n** | **Mean (SE) or %*** |
| Child | Sex | | | | |
| | Male | 456 | 86.1 | 345 | 83.6 |
| | Female | 81 | 13.9 | 69 | 16.4 |
| | Gestational age | 529 | 39.1 (0.1) | 409 | 39.3 (0.1) |
| | Duration of breastfeeding (month) | 532 | 7.5 (0.3) | 406 | 8.7 (0.4) |
| | Race/ethnicity | | | | |
| | Caucasian, non-Hispanic | 270 | 45.8 | 220 | 49.1 |
| | African-American, non-Hispanic | 14 | 2.5 | 12 | 3.6 |
| | Hispanic (any) | 170 | 37.2 | 116 | 32.1 |
| | Other† | 83 | 14.5 | 66 | 15.2 |
| Mothers | Age at delivery | 426 | 30.4 (0.3) | 324 | 29.7 (0.3) |
| | Educational level | | | | |
| | High school/GED‡ or less | 55 | 16.9 | 39 | 17.6 |
| | Some college | 166 | 48.8 | 115 | 46.3 |
| | Bachelor degree | 134 | 23.1 | 116 | 25.4 |
| | Graduate or professional | 71 | 11.2 | 54 | 10.7 |
| | Ethnicity/race | | | | |
| | Caucasian, non-Hispanic | 161 | 57.4 | 213 | 62.7 |
| | African-American, non-Hispanic | 17 | 4.4 | 10 | 3.9 |
| | Hispanic (any) | 100 | 27.7 | 65 | 24.6 |
| | Other† | 48 | 10.5 | 36 | 8.8 |
| | Birthplace | | | | |
| | USA | 338 | 78.3 | 272 | 83.5 |
| | Mexico | 25 | 8.27 | 17 | 7.8 |
| | Outside of USA and Mexico | 63 | 13.5 | 35 | 8.7 |
| | Smoking before or during pregnancy | | | | |
| | Yes | 65 | 20.4 | 31 | 11.2 |
| | No | 351 | 79.6 | 284 | 88.8 |
| | Alcohol consumption during 3 months before pregnancy through delivery | | | | |
| | 0–8 drinks/mth | 214 | 54.1 | 151 | 51.3 |
| | 8+drinks/mth | 199 | 45.9 | 159 | 48.7 |
| Fathers | Age at delivery | 494 | 33.2 (0.3) | 384 | 32.9 (0.4) |
| | Educational level | | | | |
| | High school/GED‡ or less | 103 | 26.1 | 91 | 31.0 |
| | Some college | 158 | 33.7 | 121 | 35.0 |
| | Bachelor degree | 153 | 26.8 | 123 | 24.3 |
| | Graduate or professional | 89 | 13.4 | 53 | 9.7 |
| | Ethnicity/race | | | | |
| | Caucasian, non-Hispanic | 320 | 59.3 | 256 | 60.6 |
| | African-American, non-Hispanic | 22 | 5.2 | 18 | 5.7 |
| | Hispanic (any) | 106 | 26.2 | 81 | 25.2 |
| | Other† | 55 | 9.3 | 33 | 8.5 |
| Mothers+fathers | Total years of parents' years of education | 537 | 28.3 (0.2) | 414 | 28.1 (0.2) |
| | Regional Center | | | | |
| | Alta, far Northern and Redwood Coast | 202 | 36.7 | 189 | 46.9 |
| | North Bay | 73 | 13.2 | 67 | 16.4 |
| | East Bay, San Andreas and Golden Gate | 85 | 14.1 | 71 | 13.7 |
| | Valley Mt, Central Valley and Kern | 93 | 20.2 | 67 | 17.4 |
| | All Los Angeles RCs plus Orange, San Diego, Tricounties and Inland | 84 | 15.8 | 20 | 5.6 |

*Means, standard errors and percentages are weighted, the sample (n) is the exact number and is unweighted
†Other=American Indian, Alaska native, Asian, Pacific Islander/Hawaiian native or multi-racial
‡General Educational Development



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

**Table 2** Frequency distributions of parental occupational exposures by autistic status

| | Autism spectrum disorder (n=537) | | | Typically developing (n=414) | | |
|---|---|---|---|---|---|---|
| Occupational exposure | Mothers (n=426) | Fathers (n=503) | Mothers or fathers (n=537) | Mothers (n=324) | Fathers (n=388) | Mothers or fathers (n=414) |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Anaesthetic gas | 16 (3.8) | 6 (1.2) | 22 (4.1) | 12 (3.7) | 1 (0.3) | 13 (3.1) |
| Asphalt | 1 (0.2) | 2 (0.4) | 3 (0.6) | 0 | 3 (0.7) | 3 (0.7) |
| Automobile/mechanic fluids | 5 (1.2) | 40 (8.0) | 44 (8.2) | 2 (0.5) | 29 (7.5) | 31 (7.5) |
| Cutting/machining fluids | 1 (0.2) | 41 (8.2) | 42 (7.8) | 0 | 37 (9.5) | 37 (8.9) |
| Disinfectants/cleaners | 137 (32.2) | 211 (42.0) | 292 (54.4) | 94 (29.0) | 165 (42.5) | 209 (50.5) |
| Ethylene oxide | 43 (10.1) | 19 (3.8) | 56 (10.4) | 30 (9.3) | 9 (2.3) | 37 (8.9) |
| Metals | 18 (4.2) | 156 (31.0) | 173 (32.2) | 10 (3.1) | 131 (33.8) | 136 (32.9) |
| PCBs* | 1 (0.2) | 0 | 1 (0.2) | 0 | 0 | 0 |
| Perchlorates | 0 | 0 | 0 | 0 | 0 | 0 |
| Pesticides | 6 (1.4) | 15 (3.0) | 20 (3.7) | 5 (1.5) | 16 (4.1) | 19 (4.6) |
| Pharmaceuticals/medicine | 38 (8.9) | 20 (4.0) | 52 (9.7) | 21 (6.5) | 8 (2.1) | 27 (6.5) |
| Phenol | 31 (7.3) | 15 (3.0) | 42 (7.8) | 18 (5.6) | 6 (1.6) | 24 (5.8) |
| Plastics/polymer chemicals | 4 (0.9) | 20 (4.0) | 24 (4.5) | 4 (1.2) | 16 (4.1) | 20 (4.8) |
| Radiation | 30 (7.0) | 7 (1.4) | 35 (6.5) | 18 (5.6) | 4 (1.0) | 20 (4.8) |
| Solvents | 106 (25.9) | 235 (46.7) | 289 (53.8) | 65 (20.1) | 197 (50.8) | 222 (53.6) |

*polychlorinated biphenyls=PCBs

hours worked per week. Information about what the company made or did, the parents' job title and their duties/responsibilities was also collected. Neither task-specific data nor job-specific exposures were collected. All occupational data were sent to NIOSH for exposure assessment and analyses. Each reported job was assigned a 2002 North American Industry Classification System (NAICS; US Census Bureau, 2007) and 2000 Standard Occupational Classification (SOC; Bureau of Labor Statistics, 2000) code. This information was entered into an ACCESS database along with the parents' job history information, duties and responsibilities, which was then used by two experienced industrial hygienists (IHs) to semi-quantitatively estimate occupational exposure levels to 16 agents selected based on evidence in the peer-reviewed scientific literature indicating that they may be associated with adverse pregnancy outcomes, including neurologic, physical malformation or central nervous system disturbances.[12 13] Paint chemicals and solvents/degreasers were combined into one group referred to as solvents in this manuscript. This was done because there was a nearly complete overlap in the exposed parents and because the chemical agents in paint chemicals that are of greatest concern are principally solvents.[23 24] The IHs were blinded to the children's case status (ASD or TD). An ordinal estimate for both the frequency and intensity of exposure for the 16 chemical and physical agents for each job was assigned by the IHs using the following guidelines:

### Frequency

0 unexposed;
1 for infrequent exposure, exposure occurs rarely or a few times per year;
2 for moderate, exposure occurs occasionally, likely weekly or a few times each month;
3 for frequent, exposure occurs frequently, many times per week and likely daily.

### Intensity

0 unexposed, unlikely to be exposed through job activities, not above background;
1 for low intensity of exposure, possibly exposed through job activities, slightly above background levels;
2 for moderate intensity of exposure, probably exposed through job activities, somewhat above background, or;
3 for high intensity of exposure, definitely exposed through job activities, exposures well above background levels.

Overall, the IHs were in good agreement 67% of the time across all agents. Agreement increased to over 80% for jobs with no exposures. Agreement varied when the industrial hygienists were estimating exposures across all agents. For example, the pre-consensus estimates of intensity and frequency of exposure to disinfectants/cleaners, metals, painting chemicals, pesticides and solvents were in good agreement (about 60%). They were in moderate to poor agreement (about 40% to 50%) for agents such as ethylene oxide, pharmaceuticals/medicines, phenol and plastics/polymer chemicals. After each IH independently estimated exposure levels, the estimates were compared and a consensus level reached that was then used to estimate binary and cumulative exposure.

The binary variable classifies parents as exposed if the frequency of exposure was ≥1, or unexposed otherwise. The cumulative exposure was derived by multiplying the [frequency of exposure (0–3)] x [intensity of exposure (0–3)] x [work hours/week] for each job held during the index period and summing across jobs to create a summary score for the index period. For analyses combining mothers' and fathers' exposures, their respective cumulative exposures were summed together. The index period is the period spanning 3 months prior to pregnancy until birth of the study child.

### Statistical analyses

Descriptive statistics were used to characterise the study population. The case-control status of the children (ASD vs TD) served as the binary outcome variable. The occupational exposure data served as the primary predictor variable. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were used to assess associations between parental occupational exposures and ASD using exposure data from mothers only, fathers



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

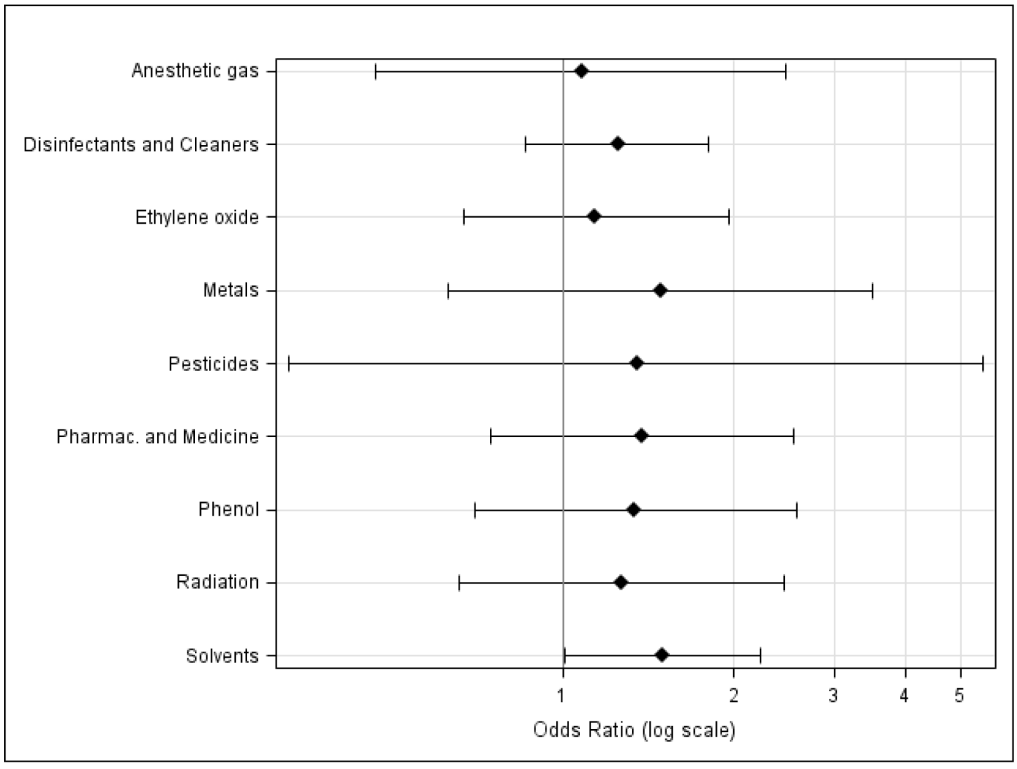


**Figure 1** Adjusted odds ratio and 95% confidence intervals of ASD by mothers' occupational exposures (Yes/No). Odds ratios for asphalt, automobile and mechanic fluids, cutting and machining fluids, polychlorinated biphenyls (PCBs), perchlorates, and plastics and polymer chemicals are not shown, because < 5 mothers were exposed to these agents.

only, and mothers and fathers combined. PROC SURVEYLOGISTIC procedures in SAS V.9.4 (2017) and SUDAAN V.11.0 (2018) were used to estimate ORs. Weighted analysis was then performed to correct for non-sociodemographically representative participation, which could result in selection bias, by using the inverse of probability of participation as weights. All tables show the weighted results. Cumulative exposure was divided into three groups: unexposed; less than or equal to the median; and above the median. Confounders were selected based on the literature and with reference to the directed acyclic graph.[25] Models evaluating mothers' exposures and ASD were adjusted for maternal age, smoking, length of breastfeeding, birthplace, regional centre, total years of education and alcohol consumption. Fathers' models were adjusted for paternal age, maternal smoking, mothers' birthplace, regional centre and total years of education. The models with mothers' and fathers' combined data were adjusted for paternal age, maternal smoking, length of breastfeeding, mothers' birthplace, regional centre, alcohol consumption and total years of education.[11 26–28]

## RESULTS

Table 1 shows the baseline characteristics of the study population, which consisted of 951 children and their parents: 56.5% of the children were diagnosed with ASD and 43.5% were TD. Demographic distributions showed that ASD and TD were similar for sex, a matching factor, as well as for race/ethnicity, mean gestational age (approximately 39 weeks) and duration of breastfeeding (table 1).

The three most common occupational exposures in mothers of both children with ASD and children with TD were disinfectants/cleaners, solvents and ethylene oxide (table 2). The least common maternal occupational exposures were perchlorates, asphalt, polychlorinated biphenyls (PCBs) and cutting/machining fluids (<0.3% each, in both diagnostic groups).

Among fathers of children with ASD and TD, the three most common exposures were disinfectants/cleaners, solvents and metals (table 2). The three least common exposures among fathers for children with both ASD and TD were perchlorates, asphalt and PCBs. Similarly, the three most common exposures when combining mothers' and fathers' data were disinfectants/cleaners, solvents and metals (table 2). The least common exposures were perchlorates, PCBs and asphalt.

When the adjusted multiple logistic regression models using binary exposure data were evaluated, the OR of ASD in the children with mothers who had occupational solvent exposure were 1.5 times more likely to have a child with ASD compared with mothers with a TD child (OR=1.50, 95% CI=1.01–2.23; figure 1). None of the other exposures were associated with ASD in either parent (figure, online supplementary figure 1), or when the parents were combined (supplementary figure 2). When cumulative exposures were evaluated, moderate cumulative exposure to solvents in the mothers was associated with ASD (OR=1.85; 95% CI=1.09, 3.15; table 3). High cumulative exposure to solvents in mothers was not associated with ASD (OR=1.20; 95% CI=0.71, 2.03; table 3). However the OR P-trend was significant, indicating an increasing risk with an increasing level of exposure (P=0.02). No other exposures were found to be associated with ASD in the mothers (table 3), fathers (table 4), or when the parents' data were combined (supplementary table 1). After correcting the P-value ($p_c$) none of the associations remained significant. Although we had a larger sample size in this study, there were still a number of agents in which only a few of the parents were exposed.



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

**Table 3** Adjusted* and unadjusted OR of ASD by mothers cumulative† occupational exposures‡ during the index period.

| | | | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|---|
| | ASD§ | TD§ | OR¶ | 95% CI | OR¶ | 95% CI |
| Anaesthetic gas | | | | | | |
| Unexposed | 410 | 312 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 9 | 6 | 1.90 | 0.64 to 5.62 | 1.67 | 0.54 to 5.16 |
| High | 7 | 6 | 0.90 | 0.27 to 3.09 | 0.70 | 0.22 to 2.18 |
| Trend of OR | | | 0.25 | | 0.38 | |
| Disinfectants/cleaners | | | | | | |
| Unexposed | 289 | 230 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 70 | 46 | 1.36 | 0.87 to 2.12 | 1.42 | 0.88 to 2.29 |
| High | 67 | 48 | 1.13 | 0.72 to 1.78 | 1.09 | 0.69 to 1.73 |
| Trend of OR | | | 0.18 | | 0.15 | |
| Ethylene oxide | | | | | | |
| Unexposed | 383 | 294 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 19 | 14 | 1.42 | 0.67 to 3.02 | 1.40 | 0.64 to 3.03 |
| High | 24 | 16 | 1.12 | 0.55 to 2.29 | 0.99 | 0.49 to 2.00 |
| Trend of OR | | | 0.36 | | 0.40 | |
| Metals | | | | | | |
| Non-exposure | 408 | 314 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 11 | 5 | 2.34 | 0.76 to 7.15 | 2.21 | 0.69 to 7.03 |
| High | 7 | 5 | 0.96 | 0.26 to 3.56 | 1.03 | 0.31 to 3.49 |
| Trend of OR | | | 0.14 | | 0.18 | |
| Pharmaceuticals/medicine | | | | | | |
| Non-exposure | 388 | 303 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 18 | 10 | 1.39 | 0.59 to 3.29 | 1.31 | 0.55 to 3.09 |
| High | 20 | 11 | 1.72 | 0.77 to 3.82 | 1.45 | 0.64 to 3.31 |
| Trend of OR | | | 0.45 | | 0.54 | |
| Phenol | | | | | | |
| Non-exposure | 395 | 306 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 10 | 7 | 1.83 | 0.65 to 5.19 | 1.51 | 0.58 to 3.96 |
| High | 21 | 11 | 1.39 | 0.62 to 3.11 | 1.27 | 0.56 to 2.88 |
| Trend of OR | | | 0.26 | | 0.40 | |
| Radiation | | | | | | |
| Non-exposure | 396 | 306 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 8 | 9 | 0.91 | 0.34 to 2.45 | 0.79 | 0.28 to 2.22 |
| High | 22 | 9 | 1.82 | 0.76 to 4.36 | 1.61 | 0.69 to 3.73 |
| Trend of OR | | | 0.84 | | 0.66 | |
| Solvents | | | | | | |
| Non-exposure | 320 | 259 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 55 | 32 | **1.83** | **1.09 to 3.07** | **1.85** | **1.09 to 3.15** |
| High | 51 | 33 | 1.34 | 0.80 to 2.22 | 1.20 | 0.71 to 2.03 |
| Trend of OR | | | **0.02** | | **0.02** | |

*¶Adjusted for maternal age, smoking, length of breastfeeding, birthplace, regional centre , total years of education and alcohol consumption.
†Cumulative exposure was divided into three groups: unexposed, less than or equal to the median, and above the median.
‡Only results for occupational exposures in which at least five parents were exposed are listed.
§ ASD = autism spectrum disorder , TD = typically developing.
¶Odd ratios (OR) and 95% confidence intervals (CI) are weighted results, the sample (n) is the exact number and is unweighted. Values in bold signify 0.0215 : adjusted p: 0.0231.

## DISCUSSION

This study indicates that maternal occupational exposure to solvents may be associated with higher rates of ASD in their children. These results should be interpreted with caution given that this association did not remain significant after correcting the P-values for multiple comparisons. However, these results are consistent with earlier reports that have identified solvents as a potential risk factor for ASD.[5 9 28] Research in the non-ASD population has found that solvents can be absorbed into the blood via skin or lungs.[29] Water-soluble solvents may be cleared out of the body in urine or faeces, but many solvents are retained in organs including the brain. Solvents can also be metabolised into more toxic secondary substances (eg, methyl-butyl ketone, n-hexane) that are associated with a number of neurological effects and changes.[29] In infants, solvents have been found to interfere with the glial guidance process which inhibits neuritic outgrowth.[30] Infants of mothers who have been exposed to occupational solvents or those who abuse solvents (eg, sniff toluene) show delayed speech and motor function as well as cognitive deficits.[12] Although these later studies did not specifically evaluate the effects of solvents and ASD, they do suggest mechanisms by which



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

**Table 4** Adjusted* and unadjusted OR of ASD by fathers' cumulative† occupational exposures‡ during the index period.

| | | | Unadjusted | | Adjusted‡ | |
|---|---|---|---|---|---|---|
| | ASD§ | TD§ | OR¶ | 95% CI | OR | 95% CI |
| Automobile/mechanic fluids | | | | | | |
| Non-exposure | 463 | 359 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 21 | 14 | 1.07 | 0.51 to 2.27 | 1.22 | 0.55 to 2.67 |
| High | 19 | 15 | 1.16 | 0.56 to 2.41 | 1.14 | 0.52 to 2.52 |
| Trend of OR | | | 0.85 | | 0.63 | |
| Cutting/machining fluids | | | | | | |
| Non-exposure | 462 | 351 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 15 | 18 | 0.52 | 0.24 to 1.12 | 0.48 | 0.21 to 1.09 |
| High | 26 | 19 | 1.06 | 0.56 to 2.02 | 1.04 | 0.52 to 2.11 |
| Trend of OR | | | 0.09 | | 0.08 | |
| Disinfectants/cleaners | | | | | | |
| Non-exposure | 292 | 223 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 112 | 80 | 0.88 | 0.61 to 1.27 | 1.00 | 0.67 to 1.47 |
| High | 99 | 85 | 0.82 | 0.56 to 1.19 | 0.80 | 0.55 to 1.19 |
| Trend of OR | | | 0.49 | | 0.96 | |
| Metals | | | | | | |
| Non-exposure | 347 | 257 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 72 | 61 | 0.89 | 0.59 to 1.35 | 0.91 | 0.60 to 1.40 |
| High | 84 | 70 | 0.84 | 0.57 to 1.24 | 0.82 | 0.54 to 1.24 |
| Trend of OR | | | 0.59 | | 0.67 | |
| Pesticides | | | | | | |
| Non-exposure | 488 | 372 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 7 | 8 | 1.00 | 0.32 to 3.10 | 1.16 | 0.37 to 3.65 |
| High | 8 | 8 | 0.71 | 0.24 to 2.10 | 0.72 | 0.20 to 2.56 |
| Trend of OR | | | 0.99 | | 0.80 | |
| Plastics/polymer chemicals | | | | | | |
| Non-exposure | 483 | 372 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 14 | 7 | 1.75 | 0.63 to 4.89 | 1.95 | 0.76 to 4.99 |
| High | 6 | 9 | 0.55 | 0.18 to 1.65 | 0.55 | 0.16 to 1.85 |
| Trend of OR | | | 0.29 | | 0.16 | |
| Solvents | | | | | | |
| Non-exposure | 268 | 191 | 1.0 | Referent | 1.0 | Referent |
| Moderate | 118 | 98 | 0.76 | 0.53 to 1.09 | 0.84 | 0.57 to 1.22 |
| High | 117 | 99 | 0.83 | 0.58 to 1.18 | 0.83 | 0.56 to 1.23 |
| Trend of OR | | | 0.13 | | 0.35 | |

*Adjusted for paternal age, maternal smoking, moms' birthplace, regional centre , total years of education.
† Cumulative exposure was divided into three groups: unexposed, less than or equal to the median, and above the median.
‡Only results for occupational exposures in which at least five parents were exposed are listed.
§ASD=autism spectrum disorder, TD=typically developing
¶Odd ratios (OR) and 95% confidence intervals (CI) are weighted results, the sample (n) is the exact number and is unweighted.

maternal occupational solvent exposure may interfere with typical brain development and hence be involved in the aetiology of ASD.

Unlike previous research, we did not find an association between metals and ASD or pesticides and ASD.[6 9] A number of metals such as lead, mercury, arsenic and manganese have been found to affect the developing brain.[13 31] Childhood lead exposure is associated with lower IQ, poor eye-hand coordination and behavioural issues.[13] Similarly, manganese levels in maternal blood or hair, cord blood or placenta have been found to be associated with nonverbal memory, attention and hand skills.[13] Exposure to heavy metals such as cadmium, arsenic and methylmercury have all been found to be neurotoxic.[31] These metals can interact with neurotransmitters, ion pumps, enzymes and amino acid functional groups resulting in cognitive dysfunction. Research indicates that metals including cadmium, lead, manganese, mercury and nickel may be associated with autism.[5 9 32] Unlike these studies of toxic air pollutants, we did not see a relationship between parental occupational exposure to metals and ASD. Our results may be due to a lack of power, given that very few parents had occupational exposure to metals, which also precluded our ability to look at individual metals. It may also be that previous findings are spurious and metals are not associated with ASD, or the risk from occupational metal exposure is different than exposure via air pollution.

A number of studies have shown a relationship between ASD and pesticide exposure, including via diet, drift from agricultural applications and exposure to tick/flea treatment.[9 10 33] As previously described, Shelton et al[11] found that commercial pesticide applications within about a mile of the residence of the mother during pregnancy was associated with ASD, adjusting for multiple confounders. Early exposure to chlorpyrifos, an organophosphate pesticide widely used in agriculture, but now banned in household products, has been shown in animal models to have long-term consequences including deficits in neuritic projections and brain cell numbers that emerge in early adolescence and continue into adulthood, affecting cognitive function that can result in behavioural anomalies.[34] We did not see a relationship between parental occupational exposure to pesticides and ASD. Again, few parents were reported to have occupational exposure to pesticides in this population, therefore the power to determine if occupational pesticide exposure was a risk factor in this population was low.

This study had both strengths and limitations. A strength of this study is the accuracy and consistency of the case definition and ascertainment procedures. All the cases were clinically evaluated at either the UC Davis MIND Institute or the UCLA Neuropsychiatric Institute by well trained staff using both ADI-R and ADOS to make final diagnoses.[16] The recruitment and analytic methods were also designed to reduce selection bias and enhance the likelihood that the study population is representative of the target population, thus increasing the generalisability of the results. While the sample size is larger than that used in our previous pilot study, it may still have been too small to see potential associations between a large number of occupational exposures and ASD, particularly where few parents were exposed to industrial chemicals at their workplaces (see table 2). After correcting for P values, none of the associations remained significant, which may have also been a problem of low statistical power due to small sample size. Obtaining accurate exposure data can be challenging. Here we used IH-assessment based on parent-reported job title, tasks and responsibilities: a methodology that is less affected by recall bias than asking parents to report their specific workplace exposures.[35] However, factors that may affect its accuracy include the industrial hygienists' familiarity with specific jobs, potential exposures within each job and the use of personal protective equipment, and, in some instances, access to accurate job information. Nonetheless, while IH generated exposure assessment is less sensitive, the specificity is generally more stable, resulting in less misclassification bias and attenuation of the ORs.[36] Misclassification bias can be further reduced if information such as responsibilities, task and duties is also available as it was in this study.[35 37] However, there may be more errors in the fathers' job histories completed by the mother as compared with those completed by the father, which could have led to misclassification of exposure and decreased precision of the measures of association. Lastly, although we did not use a panel of three or more IHs to assess occupational exposure, using more



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.

than one, which was done in this study, generally improves reliability and validity over a single IH.[38 39]

Our results contribute to a growing body of evidence supporting the role of environmental and occupational factors in the aetiology of ASD. Rather than the use of broad exposure categories as was done here, future research can extend these findings by identifying the specific types of chemical and physical agents that may be involved in the aetiology of ASD. Further advancement in this field will also come as larger study samples or more efficient designs are used for focusing on workplace exposures and as research begins to focus on gene-environment interactions, which may further clarify differences in severity, pathology and susceptibility.

**Acknowledgements** We would like to thank Pamela Schumacher at the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health/Division of Surveillance, Hazard Evaluation and Field Studies (CDC/NIOSH/DSHEFS) and Jeff Purdin (senior consultant with Attain, LLC; contract programmer at NIOSH/DSHEFS) for their work in generating the NAICs and SOC codes. We would also like to thank Drs Christina Lawson (CDC/NIOSH/DSHEFS) and Carissa Rocheleau (CDC/NIOSH/DSHEFS) for working closely with Claudia Ma in the development of the ACCESS database, which facilitated the industrial hygienists in their assessment of workplace exposures.

**Contributors** ECMcC was involved in study design, statistical analysis plan, interpretation of data and manuscript preparation. CCM was involved in cleaning and preparing the data for analysis, developing the ACCESS database for the workplace exposures and analysis plan. JKG contributed to the data analysis plan, conducted the statistical analysis and wrote the statistical analysis section of the manuscript. DF was involved in the design of the work and oversaw the statistical analysis. WTS conducted the workplace exposure assessment and contributed to manuscript preparation. YJL-R reviewed all the paper, electronic and voice records to determine how many fathers specifically responded to the work history questionnaire, and IH-P contributed 'CHARGE data' to the study design, statistical analysis plan and preparation of the manuscript.

**Funding** This study has been funded by National Institutes of Health: UL1-TR000002, UG3-OD023365. National Institute of Environmental Health Sciences: P01 ES11269, R01 ES015359, P30 ES023513. Eunice Kennedy Shriver National Institute for Child Health and Human Development: U54 HD079125. US Environmental Protection Agency through the Science to Achieve Results (STAR) program: R829388, R833292, RD83543201. National Occupational Research Agenda (NORA) funding.

**Disclaimer** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

1 Buescher AV, Cidav Z, Knapp M, *et al*. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr* 2014;168:721–8.
2 Gillberg C, Coleman M. *The Biology of the Autistic Syndromes*. London: Mac Keith Press, 2000.
3 Croen LA, Grether JK, Hoogstrate J, *et al*. The changing prevalence of autism in California. *J Autism Dev Disord* 2002;32:207–15.
4 Hertz-Picciotto I, Delwiche L. The rise in autism and the role of age at diagnosis. *Epidemiology* 2009;20:84–90.
5 Windham GC, Zhang L, Gunier R, *et al*. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San fFrancisco Bay area. *Environ Health Perspect* 2006;114:1438–44.
6 Volk HE, Lurmann F, Penfold B, *et al*. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry* 2013;70:71–7.
7 Kongtip P, Techasaensiri B, Nankongnab N, *et al*. The impact of prenatal organophosphate pesticide exposures on Thai infant neurodevelopment. *Int J Environ Res Public Health* 2017;14:570–82.
8 Colborn T. A case for revisiting the safety of pesticides: a closer look at neurodevelopment. *Environ Health Perspect* 2006;114:10–17.
9 Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. *Curr Probl Pediatr Adolesc Health Care* 2014;44:277–318.
10 Keil AP, Daniels JL, Hertz-Picciotto I. Autism spectrum disorder, flea and tick medication, and adjustments for exposure misclassification: the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. *Environ Health* 2014;13:3–13.
11 Shelton JF, Geraghty EM, Tancredi DJ, *et al*. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. *Environ Health Perspect* 2014;122:1103–9.
12 Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006;368:2167–78.
13 Wigle DT, Arbuckle TE, Turner MC, *et al*. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *J Toxicol Environ Health B Crit Rev* 2008;11:373–517.
14 Windham GC, Sumner A, Li SX, *et al*. Use of birth certificates to examine maternal occupational exposures and autism spectrum disorders in offspring. *Autism Res* 2013;6:57–63.
15 Singer AB, Burstyn I, Thygesen M, *et al*. Parental exposures to occupational asthmagens and risk of autism spectrum disorder in a Danish population-based case-control study. *Environ Health* 2017;16:31–42.
16 Hertz-Picciotto I, Croen LA, Hansen R, *et al*. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environ Health Perspect* 2006;114:1119–25.
17 Mullen EM. *Mullen's Scales of Early Learning*. Circle Pines, MN: American Guidance Services Inc, 1995.
18 Sparrow SS, Balla DA, Cicchetti DV. *Vineland Adaptive Behavior Scales*. Circle Pines, MN: American Guidance Services, Inc, 1984.
19 Lord C, Risi S, Lambrecht L, *et al*. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000;30:205–23.
20 Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994;24:659–85.
21 Rutter M, Bailey A, Berument SK, *et al*. *Social Communication 211 Questionnaire (SCQ)*. Los Angeles: Western Psychological Services, 2003.
22 Risi S, Lord C, Gotham K, *et al*. Combining information from multiple sources in the diagnosis of autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry* 2006;45:1094–103.
23 CIEC. *The Essential Chemical Industry - Online*. University of York, UK: Department of Chemistry, University of York Centre for Industry Education Collaboration, 2016.
24 Park H, Park HD, Jang JK. Exposure characteristics of construction painters to organic solvents. *Saf Health Work* 2016;7:63–71.
25 Weng HY, Hsueh YH, Messam LL, *et al*. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. *Am J Epidemiol* 2009;169:1182–90.
26 Hertz-Picciotto I, Park HY, Dostal M, *et al*. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. *Basic Clin Pharmacol Toxicol* 2008;102:146–54.
27 Schmidt RJ, Tancredi DJ, Krakowiak P, *et al*. Maternal intake of supplemental iron and risk of autism spectrum disorder. *Am J Epidemiol* 2014;180:890–900.
28 McCanlies EC, Fekedulegn D, Mnatsakanova A, *et al*. Parental occupational exposures and autism spectrum disorder. *J Autism Dev Disord* 2012;42:2323–34.
29 Hurley RA, Taber KH. Occupational exposure to solvents: neuropsychiatric and imaging features. *J Neuropsychiatry Clin Neurosci* 2015;27:1–6.
30 Bondy SC, Campbell A. Developmental neurotoxicology. *J Neurosci Res* 2005;81:605–12.
31 Karri V, Schuhmacher M, Kumar V. Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction:a general review of metal mixture mechanism in brain. *Environ Toxicol Pharmacol* 2016;48:203–13.
32 Roberts AL, Lyall K, Hart JE, *et al*. Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. *Environ Health Perspect* 2013;121:978–84.
33 Roberts EM, English PB, Grether JK, *et al*. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ Health Perspect* 2007;115:1482–9.
34 Slotkin TA. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. *Toxicol Appl Pharmacol* 2004;198:132–51.
35 Teschke K, Olshan AF, Daniels JL, *et al*. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med* 2002;59:575–94. discussion 594.
36 Benke G, Sim M, Fritschi L, *et al*. Comparison of occupational exposure using three different methods: hygiene panel, job exposure matrix (JEM), and self reports. *Appl Occup Environ Hyg* 2001;16:84–91.
37 Benke G, Sim M, Abramson M. Long-term trends in occupational exposure. *Ann Occup Hyg* 2001;45:499–500.
38 Fritschi L, Nadon L, Benke G, *et al*. Validation of expert assessment of occupational exposures. *Am J Ind Med* 2003;43:519–22.
39 Siemiatycki J, Fritschi L, Nadon L, *et al*. Reliability of an expert rating procedure for retrospective assessment of occupational exposures in community-based case-control studies. *Am J Ind Med* 1997;31:280–6.



Occup Environ Med: first published as 10.1136/oemed-2018-105395 on 27 June 2019. Downloaded from http://oem.bmj.com/ on May 17, 2021 at Stephen B. Thacker CDC Library. Protected by copyright.