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Birth Defects in Infants Born to Employees of a Microelectronics and Business Machine Manufacturing Facility

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Abstract

Background—Concerns about solvent releases from a microelectronics/business machine manufacturing facility in upstate New York led to interest in the health of former workers, including this investigation of birth defects in children of male and female employees.

Methods—Children born 1983 to 2001 to facility employees were enumerated and matched to New York State's Congenital Malformations Registry. Reported structural birth defects were compared with numbers expected from state rates (excluding New York City), generating standardized prevalence ratios (SPRs). Exposure assessors classified employees as ever/never potentially exposed at the facility to metals, chlorinated hydrocarbons, and other hydrocarbons during windows critical to organogenesis (female workers) or spermatogenesis (male workers). Among workers, adjusted prevalence ratios were generated to evaluate associations between potential exposures and specific birth defects.

Results—External comparisons for structural defects were at expectation for infants of male workers (SPR = 1.01; 95% confidence interval [CI], 0.77–1.29; $n = 60$) and lower for births to female workers (SPR = 0.84; 95% CI, 0.50–1.33; $n = 18$). Among full-term infants of male workers, ventricular septal defects (VSDs) were somewhat elevated compared with the general population (SPR = 1.58; 95% CI, 0.99–2.39; $n = 22$). Within the cohort, potential paternal metal exposure was associated with increased VSD risk (adjusted prevalence ratio = 2.70; 95% CI, = 1.09–6.67; $n = 7$).

Conclusion—While overall SPRs were near expectation, paternal exposure to metals (primarily lead) appeared to be associated with increased VSD risk in infants. Take-home of occupational exposures, nonoccupational exposures, and chance could not be ruled out as causes. Case numbers for many defects were small, limiting assessment of the role of occupational exposures.

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Keywords

occupational exposure; metals; lead; chlorinated hydrocarbons; congenital heart defects; paternal exposure

Introduction

In response to community concerns about solvent releases from industrial operations in a town in upstate New York, the New York State Department of Health (NYSDOH) and the Agency for Toxic Substances and Disease Registry (ATSDR) conducted a series of studies of area residents (ATSDR, 2006a, 2006b, 2007, 2008; Forand et al., 2012). The community studies included an evaluation of birth defects, which found no statistically significant increase in total birth defects but did observe statistically significant increases in total heart defects and conotruncal heart defects (with only three cases of the latter) in an area affected by trichloroethylene (TCE) releases (Forand et al., 2012).

Community concerns also led the NYSDOH and Congressional representatives from New York State (NYS) to request that the National Institute for Occupational Safety and Health (NIOSH) study current and former employees of the area's microelectronics and business machine facility. Mortality and cancer morbidity among the workers, and birth defects in their infants, were of interest.

The NIOSH study cohort comprised 34,494 former workers employed at the facility for at least 91 days between 1969 (when electronic personnel records became more reliable for determining workers' locations within the facility) and 2001 (the last full calendar year the facility was wholly owned by the founding company). Details of the overall study and results of the former worker mortality evaluation have been published elsewhere (Silver et al., 2014).

Numerous studies have examined the reproductive health effects of working in semiconductor facilities. However, the facility discussed here was engaged in microelectronics manufacturing, with production ranging from printed circuit boards to bank machines, and many manufacturing processes differed from those commonly used in the semiconductor industry, which were primarily focused on chip design and manufacture during the study period. Therefore, exposure assessments from semiconductor facilities were not applicable to this workplace. Instead, exposure assessors used facility documentation and job histories (Fleming et al., 2014) to identify chemical classes and specific chemical agents of particular concern: chlorinated hydrocarbons (TCE, perchloroethylene [PCE], methyl chloroform, and methylene chloride); metals (lead, chromium, nickel, arsenic, cadmium, beryllium, and mercury); and other hydrocarbons (e.g., isopropyl alcohol and other alcohols, epoxy resin and hardener, ethylene glycol mono-methyl ether [EGME] and other glycol ethers, methyl ethyl ketone, formaldehyde, and/or oil mist).

Exposures to TCE and PCE were of concern to the community because of environmental releases of these substances. Lead was in widespread use at the facility as the soldering material for circuit board manufacture and repair, and in associated maintenance, testing,

research & development, recovery, and analytical work. Other hydrocarbons were also used in a range of operations at the facility. While TCE use was largely phased out by 1986, the use of PCE did not decline markedly until the mid-1990s. Lead use was prevalent throughout the study period, but likely peaked during the 1986 to 1993 time-frame (Fleming et al., 2014).

The literature on teratogenic effects of many of the aforementioned chemicals is limited. Briefly, several chlorinated hydrocarbons have been associated with birth defects in a small group of studies. Human environmental exposure to TCE has been linked to neural tube defects, orofacial clefts, and in some studies, cardiac defects (Bove et al., 1995, 2002). Results for developmental cardiac toxicity in animals have varied (Johnson et al., 1998; Rufer et al., 2010; Chiu et al., 2013). PCE has been linked to orofacial clefts and neural tube defects (Aschengrau et al., 2009). Two other chlorinated hydrocarbons used at the facility, methyl chloroform and methylene chloride, have been linked to neural tube defects and conotruncal heart defects, respectively (Brender et al., 2014).

Although lead's neurobehavioral effects on children are well-known, investigations of the teratogenicity of lead and other metals have been limited. An increased risk that was not statistically significant was previously reported for parental (male and female) occupational lead exposure and total anomalous pulmonary venous return (Jackson et al., 2004). In another study, maternal lead exposure was associated with statistically significant increases in conotruncal defects, right and left ventricular outflow track obstruction, anomalous pulmonary venous return, septal defects, and other heart defects (Liu et al., 2015). Studies of lead and orofacial clefts (isolated cleft palate and cleft lip with or without cleft palate) have reported mixed results (Lorente et al., 2000; Vinceti et al., 2001).

While lead was by far the predominant metal used at the facility, several other metals were also used: chromium, nickel, arsenic, cadmium, beryllium, and mercury. The sparse research on the teratogenicity of these metals has not produced consistent results in humans or animals (Goldberg et al., 1990; El-Tawil and Morgan, 2000; Eizaguirre-Garcia et al., 2000). A study of paternal occupational exposures reported positive associations that did not attain statistical significance between heavy metal exposure and some cardiac defects (perimembranous ventricular septal defects [VSDs], tetralogy of Fallot, and coarctation of the aorta), but observed no elevations for two other cardiac defects (atrioventricular septal defects [AVSD] and transposition of the great arteries [TGA]; Snijder et al., 2012).

Studies of associations between chemicals in the "other hydrocarbons" grouping and birth defects in humans are scarce. Ethylene glycol and other glycol ethers were associated with orofacial clefts, urinary tract malformations, and male genital malformations in births to occupationally exposed women (Cordier et al., 2012); EGME with increased incidence of VSD and right ductus arteriosus in rodents (Toraason et al., 1985); and formaldehyde with increased risk for all birth defects combined in some studies, along with increased cardiac malformations in the infants of environmentally exposed women (Duong et al., 2011).

Most epidemiologic studies evaluating associations between the aforementioned chemicals and birth defects have focused on maternal exposure. The potential effects of paternal

occupational and environmental exposures on fetal development have received much less attention. However, because of the possibility of chemical effects on sperm quality, as well as the possibility of fathers exposing mothers who did not work at the facility through take-home of workplace exposures, we examined birth defects among infants born to both men and women who were employed at the facility.

Materials and Methods

This birth defect evaluation was performed in partnership with the NYSDOH. NIOSH investigators enumerated the former worker cohort, compiled work histories, and conducted exposure assessments. Assembly of the worker cohort (Silver et al., 2014) and the exposure assessment process (Fleming et al., 2014) have been described in detail elsewhere. As birth defect data could not be shared with NIOSH due to privacy restrictions, NYSDOH personnel enumerated births to former workers, identified birth defects among those births by matching to the NYSDOH Congenital Malformations Registry (CMR), and performed the statistical analyses. NIOSH reviewed and interpreted the results with input from NYSDOH. The study was approved by the NIOSH and NYSDOH Institutional Review Boards.

ASCERTAINMENT OF BIRTHS AND BIRTH DEFECTS

Because the NYSDOH CMR achieved statewide coverage in 1983, the birth defects evaluation was restricted to births occurring in the worker cohort from 1983 through 2001 (the year part of the facility was sold). In addition to the general study inclusion criteria (at least 91 days employed at the facility 1969–2001), workers had to have been employed at least 1 day at the facility between 1 January 1983 and 31 December 2001, with at least one biological child born during this period, to be eligible for this component of the study. Births to facility employees were enumerated by matching identifying information from employee records to the birth certificate records in the NYSDOH Vital Records database; live births identified in the cohort were then matched to the NYSDOH CMR to identify birth defects. The CMR is a population-based registry that records congenital defects, chromosomal anomalies, and persistent metabolic defects identified in children from birth to age two. Birth defects are reported to the CMR using ICD-9-CM codes; since 1992, they have been recoded into the expanded BPA coding system by CMR staff. To calculate the prevalence of defects for the reference population, birth records for residents of NYS (excluding NYC) were linked to CMR records for the years 1983 to 2001. Infants with chromosomal disorders and birth defects/syndromes of known origin were excluded from the calculations for births to facility workers and births in the reference population.

BIRTH DEFECTS OF INTEREST

Birth defects considered in this analysis were selected from the defects systematically ascertained by the NYS-DOH CMR. Defects eligible for selection comprised all structural birth defects included in the case definition of the National Birth Defects Prevention Network (NBDPN) Guidelines for Conducting Birth Defects Surveillance (NBDPN, 2004) with some modifications. Of the 45 defects, 9 were excluded from the analyses because they fell into the following categories: (1) those attributed to known etiologies (fetal alcohol syndrome); (2) those attributed to chromosomal abnormalities (Down syndrome, trisomy 13,

trisomy 18); and (3) defects with poor ascertainment in the CMR (microcephaly, atrial septal defect, patent ductus arteriosus, congenital hip dislocation, and amniotic bands).

Collectively, the 36 remaining defects were used for an overall summary of birth defects and are referred to herein as "structural defects." Because many of the eligible defects are rare and occurred infrequently among the cohort's infants, risks were evaluated for defects grouped by affected body system (central nervous, eye, cardiac, orofacial, gastrointestinal, genitourinary, and musculoskeletal systems). The International Classification of Disease, Ninth Revision, Clinical Modification Code (ICD-9-CM) and the corresponding expanded British Paediatric Association (BPA) codes used for individual defects and groupings are found in Appendix A.

Specific defects and defect groupings of a priori interest were identified based on the literature on exposures of concern at the facility and the results of the community birth defects investigations described above (ATSDR, 2006a, 2007, 2008): cardiac defects (particularly conotruncal heart defects), neural tube defects, choanal atresia, and orofacial clefts.

To align with the community studies (ATSDR, 2006a, 2008), both a larger "cardiac" defect grouping and a "major cardiac" subset of that defect grouping were assessed. The "cardiac" defect group comprises conotruncal heart defects, VSDs, AVSDs, pulmonary valve stenosis/atresia, tricuspid atresia/stenosis, Ebstein's anomaly, aortic valve stenosis, hypoplastic left heart syndrome, and coarctation of the aorta. Because this grouping encompasses a wide range of defects, both major and minor, we also considered a more restrictive subgroup of cardiac defects designated "major cardiac" defects because their severity makes their detection less likely to be influenced by screening practices (ATSDR, 2006a). This category excludes VSDs, AVSDs, and Ebstein's anomaly.

Some cardiac defects, including VSDs, tend to resolve without external intervention as a fetus or infant matures and are, therefore, more commonly ascertained in premature infants than in infants born at term (Ekici et al., 2008). In addition, some VSDs co-occur with other cardiac defects or as part of multi-defects syndromes. Because of these VSD ascertainment issues, the structural and cardiac defect groups were analyzed with and without inclusion of VSDs. VSDs were also analyzed separately for full-term versus preterm births and for isolated VSD cases (vs. those co-occurring with other defects) when numbers allowed.

EXPOSURE ASSESSMENT

The exposure assessment used in the current study was conducted as part of the mortality and morbidity study of former facility employees (Fleming et al., 2014). Briefly, information sources included industrial hygiene monitoring results (1980–2002); industrial hygiene department documents (1974–2002); a subset of company environmental impact assessments (1974–1980 and 1985–2002); discussions with employees who formerly worked at the facility; and an ATSDR study evaluating outdoor chemical air emissions in the community around the facility (ATSDR, 2006b). The exposure database was based on work departments and time periods and was completed using binary assignments of usage (likely used/not used) for each chemical class and agent for each department-year combination.

Work histories were constructed from the company's electronic databases, the department-exposure matrix matched to the detailed work history for each worker, and potential (ever/never) for exposure at the facility to each chemical class and agent, based on assigned department, evaluated. Exposure-based analyses considered whether the worker was ever/never potentially exposed to a class or agent at the facility during specific time windows of interest. In addition, two modifying factors, a position factor indicating, based on job-title, whether a worker was likely a "hands-on" worker and a frequency factor indicating whether departmental exposures to chemicals in general (rather than to any specific agent) were intermittent or routine, were available for sensitivity analyses.

EMPLOYMENT AND EXPOSURE WINDOWS

Based on probable mechanisms, we identified "critical periods" of exposure: for male workers, approximately 3 months before the estimated date of conception (EDC) through 1 month after the EDC to capture spermatogenesis and periconceptional exposures (Desrosiers et al., 2012); for female workers, approximately 1 month before the EDC through 3 months after the EDC to capture fetal organogenesis (Selevan et al., 2000). Because stored lead can be mobilized from bone during pregnancy or other physical changes, we also examined potential lead or metals exposure in a "long window" defined as any time during employment at the facility through 1 month after the EDC (for fathers) or 3 months after the EDC (for mothers).

DATA ANALYSIS

Birth defects in this cohort were evaluated through both external and internal comparisons. The external analyses compared the prevalence of selected birth defects in the infants of former workers with the prevalence in the infants of the general population of NYS (excluding NYC). Internal comparisons were used to evaluate whether specific birth defects or birth defect groupings were more likely to have occurred in the infants of workers who had potential for occupational exposure to certain chemicals than in the infants of workers without that potential exposure.

STANDARDIZED PREVALENCE RATIOS

Standardized prevalence ratios (SPRs) were calculated using indirect standardization to compare the prevalence of selected birth defects in infants born to facility workers with the prevalence of birth defects in infants born to NYS residents (excluding NYC residents) from 1983 to 2001. Both CMR and birth certificate data were restricted to live births occurring in NYS (excluding NYC).

Defects among infants of male and female workers were assessed separately. In addition, paycode (salaried ["exempt" in company parlance] or hourly ["nonexempt"]) was of interest because of potential associations with both occupational exposures and lifestyle factors, like smoking (Fujishiro et al., 2012). Smoking status and alcohol use information for employees was not readily available from the facility. On birth certificates, smoking status was not collected from fathers and was frequently missing from mothers. To adjust in part for these factors, separate SPRs were also generated for births to hourly and salaried employees of each sex.

For the SPR calculations, data were stratified on covariates of interest, using information obtained from the NYS birth certificates. Stratifiers included maternal age group (15–19, 20–29, 30–34, 35–39, ≥40), maternal education (less than high school, high school and some college, college degree or higher), infant's sex, maternal race/ethnicity (non-Hispanic white vs. all other), and infant's year of birth divided into 5-year intervals starting with the study begin date (1983–1987–1988–1992–1993–1997–1998–2002). For each birth defect or birth defect group examined, the expected number of defects in the study cohort was calculated by summing the product of the number of births in each stratum and the NYS (excluding NYC) rate of the birth defect for each stratum. SPRs were generated by dividing the number of observed birth defects by the number of expected birth defects, and 95% confidence intervals were calculated (Ulm, 1990).

REGRESSION ANALYSES

Regression analyses were conducted to compute adjusted prevalence ratios (PRs) for internal comparisons of birth defects in the infants of workers with and without potential for exposure to each chemical agent or class evaluated. The regression analyses used generalized estimated equations to perform modified Poisson regression with repeated measures; this approach produces adjusted PRs without requiring a Poisson distribution (Spiegelman and Hertzmark, 2005) and also accounts for the correlation between siblings born to the same parents with respect to shared genetic risk factors, parental covariates, and exposures. The regression analyses included adjustments for maternal age, maternal education, year of birth, and infant sex. As the cohort was largely white and case numbers were small, race was not considered in the internal analyses. Small case numbers necessitated recategorization of three covariates for the regression analyses: maternal education (high school diploma/equivalent or less, more than high school diploma); year of birth (1983–1986–1987–1992–1993–2001); and maternal age (<24, 25–34, ≥35).

For the long windows, we also accounted for whether the other parent was exposed to the agent being analyzed (metals or lead) where numbers permitted (structural defects in analyses of infants of male workers and of female workers, and VSDs in analyses of infants born to female workers). Observations with missing covariates were excluded from the analyses. For metals and lead, we also performed sensitivity analyses reclassifying as unexposed workers who, during the relevant time period, were never considered hands-on and who worked only in departments assessed as either unexposed or as having only intermittent chemical exposures. Data analyses were performed using SAS 9.3 (Statistical Analysis Software, Cary, NC, 2012).

Results

A total of 27,744 workers, 9288 female (33.5%) and 18,456 male (66.5%), met the study inclusion criteria. Most members of this group were white (87.2%). Of these workers, 7302 had a live-born infant during the full study period (without consideration of the exposure window), with 5633 (77%) of births occurring during the critical exposure period. Maternal education was available for 88% of births; mothers of infants born to facility workers tended to have more formal education at the time of birth than mothers in the population of NYS

(excluding NYC). Most births to facility workers occurred during the early years of follow-up, reflecting in part facility downsizing and reduced hiring of younger workers in later years.

During the study period, totals of 4164 infants of male workers and 1469 births to female workers who were employed at the facility during the respective critical periods were identified (Table 1); 591 birth records matched to both a male and a female worker. Apart from 67 pairs of twins, a worker matched to no more than one birth record in a given year. Over the entire study period, workers matched to records for one to eight different births (data not shown).

The number of workers potentially exposed to “other hydrocarbons” was more than fourfold the number potentially exposed to PCE and more than 10-fold the number potentially exposed to TCE, which was the least common of the exposures evaluated during the study period (Table 1).

SPR RESULTS

After excluding 19 infants with chromosomal disorders or birth defects/syndromes of known origin, 60 infants of men and 18 infants of women employed at the facility during the respective critical periods were identified as having at least one structural birth defect that fit the study definition. Fewer than five of the infants had multiple structural defects. The SPR for all structural defects was very close to expectation (based on prevalence in the NYS population, excluding NYC) in children born to male workers, and slightly below expectation in children born to female workers (Table 2).

Cardiac defects as a group showed a modest elevation approaching statistical significance in the infants of male employees and were just below expectation in the infants of female employees (Table 2). The majority of these cases were VSDs, which were significantly elevated in births to male workers (SPR = 1.77; 95% CI, 1.18–2.56; $n = 28$); the risk was higher for preterm births (SPR = 3.29; 95% CI, 1.21–7.16; $n = 6$) than for full-term births (SPR = 1.58; 95% CI, 0.99–2.39; $n = 22$). Conotruncal heart defects were close to expectation in births to male workers but had a nonstatistically significant elevation in births to female workers, due primarily to <5 observed cases of TGA. Although case numbers were small, TGA showed nonsignificant elevations in the infants of both men and women, with elevations higher in women.

SPRs for the overall structural defect grouping were similar in the infants of hourly and salaried male workers (SPR = 1.08; 95% CI, 0.72–1.54; $n = 29$ hourly; SPR = 0.95, 95% CI, 0.64–1.34; $n = 31$ salaried; data not shown). Differences between infants of hourly and salaried workers were observed in SPRs for some specific heart defects (hypoplastic left heart syndrome was observed only in the infants of hourly males and tricuspid atresia/stenosis only in the infants of salaried males), but numbers of these specific defects were quite small and SPRs for the summary cardiac grouping were quite similar (SPR =1.49; 95% CI, 0.83–2.46; $n = 15$ hourly; SPR = 1.43; 95% CI, 0.85–2.26; $n = 18$ salaried). Risk estimates for VSDs were similar in the two groups, but attained statistical significance only

in salaried workers (SPR = 1.71; 95% CI, 0.88–2.98; *n* = 12 hourly; SPR = 1.82; 95% CI, 1.04–2.96; *n* = 16 salaried).

While elevations were observed for some defects that were not of a priori interest, such as congenital cataracts (Table 2), cases were sparse (<5), and the elevations were not statistically significant. A number of specific structural defects did not occur in this cohort (see footnote to Table 2); some of the outcomes are rare, and few cases would be expected.

INTERNAL COMPARISONS

Most regression analyses were restricted to the infants of male workers because of the scarcity of exposed cases among the infants of female workers. Among infants of male workers, only the structural defect grouping, all cardiac defects, and VSDs had at least five cases (Table 3) born to workers potentially exposed to metals, chlorinated hydrocarbons, and/or other hydrocarbons during the critical period. Among infants born to these potentially exposed men, VSD cases comprised all or almost all (depending on the exposure) of the infants with cardiac defects. Therefore, regression results for the critical period are presented only for structural defects (including and excluding VSDs) and for VSDs alone.

In births to male workers during the critical period, potential exposure to metals was associated with statistically significant increases for structural defects and for VSDs. Results were very similar when only lead was considered, although confidence intervals were a bit wider (a small subset of workers was exposed only to other metals). With restriction to full-term VSDs, the point estimates were somewhat lower but remained statistically significant, with adjusted PRs above 2.5.

Sensitivity analyses again examined ever/never exposure to metals but reclassified as unexposed non–hands-on workers from departments with intermittent exposures to chemicals in general. Results for structural defects with VSDs were attenuated slightly but remained statistically significant (data not shown); structural defects excluding VSDs were unaffected, as no parents of cases were reclassified. For VSDs in the infants of fathers exposed to metals, the results remained statistically significant (adjusted PR = 2.86; 95% CI, 1.26–6.19; *n* = 9). With restriction to full-term VSDs, the adjusted PR remained elevated but was no longer statistically significant (adjusted PR = 2.31; 95% CI, 0.90–5.36; *n* = 6). The effects of reclassification were similar for lead, with an adjusted PR for VSDs of 2.71 (95% CI, 1.17–6.30; *n* = 7) and for full-term VSDs, 2.48 (0.92–6.65; *n* = 5).

When the longer exposure window was considered, adjusted PRs for infants of male workers exposed to metals were lower than for the critical period. Additional adjustment for maternal exposure during the long window produced little change in these risk estimates for infants of exposed males. Risks for exposure to lead during the long window were similar to those for metals as a class; 14 of the 17 VSD cases with potential metal exposures were identified as potentially exposed to lead. Restricting VSDs to isolated cases (those not observed in combination with other cardiac malformations or syndromes) did not lead to substantial changes in the risk estimates. For the major cardiac defects group, the adjusted PR was elevated for the longer exposure window, but cases born to male workers with potential metal exposure were sparse and the CI spanned the null (adjusted PR = 1.81; 95% CI, 0.59–

5.55; $n = 6$). Consideration of the job and department modifiers did not lead to any reclassifications for the long window.

For births to female workers exposed during the long window (data not shown), the point estimate for structural defects (including VSDs) was higher for all metals (adjusted PR = 1.23; 95% CI, 0.63–2.42; $n = 14$) than for lead specifically (adjusted PR = 1.05; 95 CI, 0.50–2.19; $n = 10$) although the confidence intervals overlapped; the same was true for structural defects excluding VSDs (adjusted PR = 1.26; 95% CI, 0.62–2.56; $n = 12$ for all metals and adjusted PR = 0.96; 95% CI, 0.44–2.13; $n = 8$ for lead). VSDs were not analyzed separately, as fewer than five cases were observed among births to female workers potentially exposed to metals.

Chlorinated hydrocarbons were evaluated only for the critical exposure period and only for men (few exposed cases were observed in the infants of female workers). The effects of two specific hydrocarbons of concern, TCE and PCE, could not be evaluated because there were too few exposed cases. For chlorinated hydrocarbons as a class, elevations were modest and not statistically significant for overall birth defects. The adjusted PRs for VSDs were approximately 50% higher than expectation, but with only five exposed cases, confidence intervals were wide and included the null. Restricting the analyses to full-term VSDs did not change the results.

Similar findings were observed for the “other hydrocarbon” class. However, for this exposure grouping, restricting VSDs to full-term cases reduced the adjusted PR, although confidence intervals were wide and overlapped those of the unrestricted analysis.

Discussion

Overall, the rates of birth defects examined in infants born to members of this occupational cohort were close to expectation from rates in the population of NYS (excluding NYC). As a group, major cardiac defects, which were of interest based on studies in the part of the surrounding community where TCE was a concern, had rates near expectation. However, a cardiac outcome outside this grouping, VSDs, showed an increase that was statistically significant when prematurity was not considered and had an elevation approaching statistical significance in full-term infants of male workers compared with full-term infants in the general population. Furthermore, the adjusted PRs for VSDs were elevated for infants of male workers potentially exposed to metals (and to lead specifically) compared with infants born to workers without this potential exposure.

The VSD finding is somewhat difficult to interpret, given the very sparse literature on metals and birth defects, as well as the limited pool of studies on the role of paternal exposure in birth defects. The risk factors for cardiac defects vary by defect and have not been fully elucidated; the etiology of VSDs, which comprise the majority of the cardiac defects observed in this cohort, is largely unknown.

Paternal exposure to lead has been associated with abnormal sperm mobility and decreased fertility (Trasler and Doerksen, 1999), but whether lead exposure is associated with birth defects has been little studied in humans. A recent report noted a significant increase in

septal defects (subtype not specified) in births to lead-exposed mothers after adjusting for factors including maternal age, gestational age, and parental smoking (Liu et al., 2015). One hypothesized mechanism for birth defects following lead exposure involves DNA methylation changes (Senut et al., 2012). Take-home exposure of lead or other metals by male workers to their female partners is a potential route of exposure, although the teratogenicity of lead and other metals in pregnant women has received little attention.

Information on the severity of the VSDs observed in this study was not available. Without this information, increased ascertainment of VSDs in a medically insured occupational cohort is a potential explanation for the VSD results in comparison with the general population rates. However, differential ascertainment does not explain the positive relations observed between VSDs and potential chemical exposures, particularly the statistically significant increase observed for metals.

Prematurity is associated with increased risk for VSDs (Tanner et al., 2005). Some, but not all, of this elevation is due to ascertainment in premature infants of defects that will resolve without intervention as the infant matures. However, recent review articles have noted studies suggesting possible associations between preterm birth and (a) parental lead exposure (Ferguson et al., 2013), (b) maternal smoking (Leonardi-Bee et al., 2008), and (c) environmental (second-hand) parental tobacco exposure (Banderali et al., 2015). Furthermore, maternal smoking during pregnancy has been found to increase maternal blood lead levels (Chelchowska et al., 2013). To assess the effects of lead exposure independent of prematurity, we conducted analyses restricted to full-term births. Point estimates were reduced but remained greater than 2.0, suggesting the observed relation between lead exposure and VSDs is not completely explained by prematurity.

Analyses reclassifying as unexposed non–hands-on workers from departments with exposures judged to be intermittent also attenuated the point estimates somewhat, but the adjusted PRs still exceeded 2.0. Restricting analyses to isolated VSDs had little effect, weighing against the likelihood of increased ascertainment in the context of infants with multiple defects as an explanation for the observed elevation. Collectively, ascertainment and exposure classification issues do not appear to completely explain the observed link between VSDs and metal exposure. Many fathers of infants with VSDs who were exposed to metals were also exposed to chlorinated hydrocarbons and/or other hydrocarbons, although the associations between these groupings and VSDs were weaker. The role of multiple exposures in the observed health outcomes could not be apportioned due to limitations in the exposure data and case scarcity.

One noncardiac outcome, congenital cataract, had elevated SPRs that did not attain statistical significance and had too few cases to permit exposure analyses. Congenital cataracts are usually syndromic, familial, or result from congenital infections (Angra, 1987; Mahalakshmi et al., 2010); we could not evaluate whether the observed cases could be attributed to these causes or were idiopathic.

In the community studies of infants born to residents of the TCE-affected areas near the facility, risks were elevated for all cardiac defects evaluated, major cardiac defects, and

conotruncal malformations, with the elevations statistically significant or nearly so. In the current study, VSDs comprised the majority of all cardiac defects; results for VSDs alone were not reported in the community study and so cannot be compared directly. Defects of the common truncus in infants of male workers and TGA in infants of female workers, both defects belonging to the conotruncal grouping, showed non-significant SPRs above 3, but cases were sparse, precluding analyses by parental exposure. None of the infants with major cardiac defects or conotruncal defects were born to mothers or fathers considered potentially occupationally exposed to chlorinated hydrocarbons during the critical period.

Some possible explanations for the discrepancies between the community and occupational studies include: differences in chemicals the groups were exposed to; different routes, intensity, and duration of residential versus occupational exposures; differential ascertainment (for less serious defects, more of which were included in the “all cardiac defects” used by the community study); and residual confounding. Fewer than five births to this occupational cohort with defects meeting the criteria for “structural defects” were also part of the community study; all of these cases had an occupationally exposed parent. The community study was focused on assessing results in areas primarily affected by TCE or PCE, although exposures in both areas were likely mixed. In the current study, individual substances within the chlorinated hydrocarbon class could not be evaluated because exposed birth defect cases were sparse; this is particularly true for TCE and PCE. No conclusion can be drawn about whether TCE or PCE exposures in this occupational cohort conferred increased risk for birth defects.

The study has some additional limitations. Many birth defects have a familial component, and family history has been established as a risk factor for several birth defects (Romitti, 2007). In NYS (excluding NYC), all children from a family with malformations are included in the CMR, so for SPR analyses, all cases born to occupational cohort members who met employment criteria were retained, regardless of familial relationship. In the regression analyses, generalized estimated equation models were used to account for children in the same family. Family history of specific birth defects was known only when multiple infants with malformations were born to a single family during the study period.

Information was not available for other risk factors that have been associated with adverse birth outcomes such as parental smoking and alcohol consumption, maternal illness, and medication use. Studies examining the effects of parental smoking and/or alcohol use on VSD risk have been sparse. Paternal alcohol use and cigarette smoking were associated with increased VSD risk in one study, although the analysis did not account for prematurity (Savitz et al., 1991; Williams et al., 2004). Studies of maternal smoking and VSD risk have been mixed, with both positive (Malik et al. 2008) and negative (Williams et al., 2004) results. In the absence of data on these covariates, maternal education was considered in all analyses to account, in part, for confounding by lifestyle factors. However, covariates such as maternal illness and medication use are less likely to be adequately addressed by such adjustment.

Overall, more hourly than salaried workers at the facility had hands-on jobs, but some types of salaried employees worked in areas where chemicals were used and performed some

hands-on tasks. The finding of similar SPRs for VSDs in hourly and salaried workers may reflect (a) VSDs in the offspring of salaried workers who had exposures, (b) better ascertainment of VSDs in salaried workers due to increased screening, and/or (c) differences in risk factors leading to VSDs in the offspring of hourly and salaried workers.

In addition, the facility is close to the border with another state, but only births in New York State were included, as other states are not mandated to report defects to New York's CMR. If the infant received care for the defect in NY before the age of 2, the defect would then be included in the CMR. However, missed out-of-state diagnoses could affect comparisons between facility workers and NYS residents or among groups of workers if some groups are more likely than others to seek out-of-state care.

Case numbers were very small for many outcomes, precluding assessment of associations with exposure relations in births to female workers and full assessment of the role of the less common exposures of interest, such as TCE and PCE, in birth defects in infants of male workers. Moreover, levels of many occupational exposures were likely highest in the 1960s, but the birth defects component of the study had a start date of 1983, the year the CMR began. Manufacturing use of TCE, specifically, ended in 1985; therefore, any effects observed for "chlorinated hydrocarbons" likely reflect exposures to the other chlorinated hydrocarbons that continued to be used in later years. Also, the primary internal analyses were based on binary (ever/never) exposure potential, and whether risk of defects increased at higher levels of exposure was not evaluated.

To provide an overall grouping of defects useful for comparing defects in the infants of this occupational cohort to defects in the NYS population (excluding NYC), we used a modification of the NBDPN grouping recommendations. As understanding of birth defects progresses, defects included in this listing changes (NBDPN, 2015). Results for another overall grouping could differ from those presented in this study. Finally, this study was limited to live-born infants. Pregnancies affected by birth defects can end in miscarriages, stillbirths, or therapeutic abortions if defects are diagnosed prenatally. As a consequence, all effect estimates are based on birth prevalence rather than true incidence.

Among the advantages of the study are inclusion of births to both male and female workers and enhanced reporting to and coding of birth defects by the CMR. In addition, the exposure assessment included evaluation of changes in chemical usage at the facility over time and assessed potential exposures to both male and female workers, facilitating evaluation of associations between outcomes and chemical exposures.

In summary, no overall excess was observed in the group of structural defects examined in the offspring of this occupational cohort, but exposures to metals (and specifically lead) appear to be associated with increased risk for VSDs, an outcome that was not specifically of a priori interest. While a previous study reported an association between all septal defects and maternal hair lead levels (Liu et al., 2015), to our knowledge this is the first epidemiologic study to report an increased prevalence of VSDs in infants of men potentially exposed to lead. Numbers of all defects were small, and data on other factors such as take-home exposure, exposures at other worksites, nonwork exposures, family history of birth

defects, and parental smoking were not available, hindering definitive assessment of the role of direct occupational exposures at the facility in VSDs and other health outcomes. Targeted study of VSDs in the infants of other metal/lead-exposed occupational cohorts, including study of paternal exposures, is warranted.

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TABLE 1

Distribution of Selected Characteristics of Live Births to Facility Employees and the New York State (Excluding New York City) Live Birth Population, 1983 to 2001

Characteristic	Live-born infants of men employed at facility during critical period[a] Number (%)	Live-born infants of women employed at facility during critical period Number (%)	New York State live births Number (%)
Total	4,164 (100)	1,469 (100)	2,777,654 (100)
Maternal age[b]			
<20	32 (0.77)	20 (1.36)	224,467 (8.08)
20–29	2,086 (50.1)	723 (49.2)	1,430,362 (51.5)
30–34	1,459 (35.0)	538 (36.6)	758,841 (27.3)
35–39	527 (12.7)	168 (11.4)	306,915 (11.0)
40+	59 (1.42)	20 (1.36)	51,697 (1.86)
Missing	1 (0.02)	0	5,373 (0.19)
Maternal race/ethnicity			
Non-Hispanic white	3,491 (83.8)	1,245 (84.8)	1,828,357 (65.8)
Non-Hispanic black	63 (1.51)	36 (2.45)	236,255 (8.51)
Hispanic	338 (8.12)	91 (6.19)	345,996 (12.5)
Other	136 (3.27)	42 (2.86)	32,443 (1.17)
Missing	136 (3.27)	55 (3.74)	334,603 (12.0)
Maternal education			
<High school	75 (1.80)	25 (1.70)	486,476 (17.5)
High school or some college	2,091 (50.2)	742 (50.5)	1,341,180 (48.3)
College degree +	1,626 (39.0)	589 (40.1)	599,082 (21.6)
Missing	372 (8.93)	113 (7.69)	350,916 (12.6)
Maternal year of birth			
1983–1987	1,778 (42.7)	577 (39.3)	720,046 (25.9)
1988–1992	1,440 (34.6)	531 (36.2)	787,261 (28.3)
1993–1997	637 (15.3)	219 (14.9)	724,996 (26.1)
1998–2002	309 (7.42)	142 (9.67)	545,351 (19.6)
Infant sex			
Male	2,167 (52.0)	789 (53.7)	1,423,569 (51.2)
Female	1,997 (48.0)	680 (46.3)	1,354,064 (48.8)
Indeterminate	0	0	20 (0.00)
Pay status			
Hourly	1,847 (44.4)	895 (60.9)	n/a
Salaried	2,317 (55.6)	574 (39.0)	n/a
Potential for exposure[c]			
Metals	669 (16.1)	181 (12.3)	n/a
Lead	505 (12.1)	143 (9.73)	n/a

Characteristic	Live-born infants of men employed at facility during critical period[a] Number (%)	Live-born infants of women employed at facility during critical period Number (%)	New York State live births Number (%)
Chlorinated hydrocarbons	534 (12.8)	170 (11.6)	n/a
Trichloroethylene	63 (1.51)	8 (0.54)	n/a
Perchloroethylene	205 (4.92)	50 (3.40)	n/a
Other hydrocarbons	953 (22.9)	332 (22.6)	n/a

[a]Critical period: 3 months prior to estimated conception date (EDC) through 1 month after EDC for males and 1 month prior to EDC through 3 months after EDC for females.

[b]For regression analyses, maternal age was collapsed to <24 (approximately 11% of live births to facility workers), 25–34 (75%), and > = 35 (14%) and infant year of birth was categorized as 1983–1986 (33%), 1987–1992 (43%) and 1993–2001 (23%).

[c]Potential exposure to the facility employee. Because some employees had multiple potential exposures, the distributions are not cumulative. n/a = not applicable.

TABLE 2

SPRs[a] for Birth Defects among Live-Born Infants[b] of Men and Women Employed at the Facility during Critical Periods[b]

	Infants of male workers		Infants of female workers	
Defect or defect grouping	**SPR (95% CI)**	***n***	**SPR (95% CI)**	***n***
Structural defects	1.01 (0.77–1.29)	*60*	0.84 (0.50–1.33)	*18*
Structural defects (excluding VSD)	0.82 (0.58–1.12)	*38*	0.89 (0.50–1.46)	*15*
Central nervous system defects	0.42 (0.05–1.52)	*<5*	*0*	*0*
Spina bifida	0.72 (0.02–4.04)	*<5*	*0*	*0*
Hydrocephaly	0.36 (0.01–2.02)	*<5*	*0*	*0*
Eye defects	2.29 (0.47–6.68)	*<5*	2.21 (0.06–12.3)	*<5*
Congenital cataract	3.83 (0.79–11.2)	*<5*[a]	3.89 (0.10–21.7)	*<5*[a]
Cardiac defects	1.43 (0.99–2.01)	*33*	0.87 (0.35–1.78)	7
Ventricular septal defect	1.77 (1.18–2.56)	*28*[a]	0.91 (0.29–2.11)	*5*[a]
VSD – preterm births	3.29 (1.21–7.16)	*6*	1.23 (0.03–6.83)	*<5*
VSD – full-term births	1.58 (0.99–2.39)	*22*	0.84 (0.23–2.15)	*<5*
Atrioventricular septal defect	1.35 (0.03–7.55)	*<5*	*0*	*0*
Major cardiac defects	1.00 (0.46–1.89)	*9*	1.26 (0.34–3.22)	*<5*
Pulmonary valve stenosis/atresia	0.98 (0.20–2.88)	<5	*0*	*0*
Tricuspid atresia/stenosis	2.72 (0.07–15.1)	*<5*	*0*	*0*
Hypoplastic left heart syndrome	2.34 (0.28–8.46)	*<5*	*0*	*0*
Coarctation of the aorta	0.57 (0.01–3.17)	*<5*	3.20 (0.39–11.6)	*<5*
Conotruncal heart defects	1.15 (0.31–2.94)	*<5*	2.47 (0.51–7.21)	*<5*
Common truncus	3.48 (0.09–19.4)	*<5*	*0*	*0*
Tetralogy of Fallot	0.65 (0.02–3.60)	*<5*	1.84 (0.05–10.3)	*<5*
Transposition of the great arteries	1.66 (0.34–4.86)	*<5*	4.76 (0.98–13.9)	*<5*
Orofacial defects	0.74 (0.24–1.72)	*5*	*0*	*0*
Clefts	0.83 (0.27–1.93)	*5*	*0*	*0*
Cleft palate	0.74 (0.09–2.68)	*<5*	*0*	*0*

	Infants of male workers		Infants of female workers	
Defect or defect grouping	**SPR (95% CI)**	***n***	**SPR (95% CI)**	***n***
Cleft lip with and without cleft palate	0.85 (0.18–2.50)	*<5*	*0*	*0*
Gastrointestinal defects	0.64 (0.28–1.27)	*8*	1.12 (0.36–2.62)	*5*
Esophageal atresia/tracheoesophageal Fistula	1.02 (0.03–5.68)	*<5*	*0*	*0*
Pyloric stenosis	0.79 (0.32–1.64)	*7*[a]	1.57 (0.51–3.67)	*5*[a]
Genitourinary defects	1.16 (0.53–2.21)	*9*	1.72 (0.56–4.01)	*5*
Renal agenesis	1.52 (0.18–5.48)	*<5*	0	0
Obstructive genitourinary defect	1.08 (0.44–2.23)	*7*[a]	2.05 (0.67–4.78)	*5*[a]
Hypospadias	0.67 (0.18–1.72)	*<5*	0	0
Musculoskeletal defects	0.94 (0.19–2.73)	*<5*	*0*	*0*
Upper limb reduction	2.64 (0.54–7.70)	*<5*	*0*	*0*

Component counts (indented) may exceed grouping totals as each infant is only counted once in each group/subgroup total even if the infant has multiple defects within the grouping. Structural defects: selected defects of the central nervous system, eye, ear, heart, gastrointestinal system, genitourinary system, musculoskeletal system, and orofacial defects. Major cardiac defects: common truncus, transposition of the great arteries, tetralogy of Fallot, pulmonary valve atresia/stenosis, tricuspid valve atresia/stenosis, aortic valve stenosis, hypoplastic left heart syndrome, and coarctation of the aorta. The following eligible outcomes had 0 cases in this cohort: anencephaly; encephalocele; anotia/microtia; anophthalmia/microphthalmia; aniridia; biliary atresia; bladder exstrophy; lower limb reduction; gastroschisis; omphalocele; choanal atresia; rectal and large intestinal atresia/stenosis; Hirschprung's disease; diaphragmatic hernia; Ebstein's Anomaly; aortic valve stenosis.

[a]Standardized for maternal age (15–19, 20–29, 30–34, 35–39, > = 40), year of birth (1983–1987–1988–1992–1993–1997–1998–2002), maternal education (less than high school, high school or some college, college degree or higher), race/ethnicity (non-Hispanic white; other), and sex of infant.

[b]Birth defects diagnosed by age 2 in biological offspring of male and female workers.

[c]Critical period: 3 months prior to estimated conception date (EDC) through 1 month after EDC for male workers and 1 month prior to EDC through 3 months after EDC for female workers.

[d]Fewer than five cases had both parents employed during the critical period.

SPR, standardized prevalence ratio; CI, confidence interval; VSD, ventricular septal defect.

TABLE 3

Adjusted Prevalence Ratios for Selected[a] Birth Defect Groups among Live-Born Infants of Male Workers Ever vs. Never Potentially Exposed to Certain Chemicals at the Facility during Specified Exposure Periods[b]

Exposure	Outcome	Adjusted prevalence ratio (95% confidence interval), # potentially exposed cases
Metals – critical period	Structural defects	2.39 (1.38–4.13), 18
	Structural defects excluding VSD	1.65 (0.78–3.49), 9
	VSD	3.13 (1.44–6.82), 10
	VSD (full-term only)	2.70 (1.09–6.67), 7
Lead – critical period	Structural defects	2.28 (1.26–4.10), 14
	Structural defects excluding VSD	1.62 (0.71–3.68), 7
	VSD	3.07 (1.36–6.93), 8
	VSD (full-term only)	2.92 (1.15–7.39), 6
Metals – long window	Structural defects	1.44 (0.95–2.19), 41
	Structural defects excluding VSD	1.39 (0.83–2.31), 28
	VSD	1.61 (0.85–3.06), 17
	VSD (full-term only)	1.47 (0.72–3.02), 13
Lead – long window	Structural defects	1.34 (0.87–2.06), 32
	Structural defects excluding VSD	1.30 (0.77–2.20), 22
	VSD	1.62 (0.84–3.14), 14
	VSD (full-term only)	1.57 (0.75–3.30), 11
Chlorinated hydrocarbons – critical period	Structural defects	1.30 (0.62–2.74), 9
	Structural defects excluding VSD	0.80 (0.27–2.42), <5
	VSD	1.53 (0.55–4.22), 5
	VSD (full-term only)	1.55 (0.52–4.65), <5
Other hydrocarbons – critical period	Structural defects	1.24 (0.69–2.25), 15
	Structural defects excluding VSD	0.78 (0.33–1.81), 7
	VSD	1.75 (0.78–3.94), 9
	VSD (full-term only)	1.18 (0.42–3.34), 5

Chlorinated hydrocarbons (e.g. trichloroethylene, perchloroethylene, methylene chloride, methyl chloroform). Other hydrocarbons (e.g. isopropyl alcohol and other alcohols, epoxy resin and hardener, ethylene glycol monomethyl ether and other glycol ethers, methyl ethyl ketone, formaldehyde, oil mist). Structural defects: selected defects of the central nervous system, eye, ear, heart, gastrointestinal system, genitourinary system, musculoskeletal system, and orofacial defects. Total defects in subcategories may exceed number of defects in the parent category because some infants had multiple defects. Critical period: 3 months prior to estimated conception date (EDC) through 1 month after EDC for male workers. Long windows any time during employment at the facility through 1 month after the EDC for male workers.

[a]All models adjusted for year of birth (1983–86, 1987–92, 1993–2001), maternal age (15-<24, 25–34, > = 35), maternal education (< = high school, > high school), and infant sex.

[b]Birth defects with at least five cases diagnosed by age 2 in infants fathered by potentially exposed male workers.

VSD, ventricular septal defect