Closeout Report

Occupational Exposure to Chlorinated Solvents and Cardiovascular Malformations (5R03OH009231-02)

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List of Terms and Abbreviations

BWIS – Baltimore Washington Infant Study
CI – confidence interval
CT - carbon tetrachloride
MC - methylene chloride
NCI – National Cancer Institute
OR – odds ratio
PCE - perchloroethylene
TCE – trichloroethylene

Abstract

To date, the epidemiologic literature has been inconclusive regarding the teratogenicity of organic solvents, primarily due to small sample sizes, limited exposure assessment methods, and grouping of solvents and specific malformations. Given that only three percent of infants are born with major malformations, epidemiologic studies of birth defects are often limited to the case-control design and retrospective assessment of exposure. Many studies have relied upon self-reported occupational exposures or job titles to determine exposure, which may have led to exposure misclassification and attenuation or overestimation of risk estimates. The National Cancer Institute developed a new exposure assessment method that uses task and job exposure matrices developed after an extensive literature review. An industrial hygienist uses the matrices, as well as his/her own experience to infer exposure for each individual job. The standardized and comprehensive source of exposure information, as well as the identification of exposure determinants (location, quantity, ventilation, temperature, operation and mechanism of release) should provide more reliable, and possibly more valid exposure estimates, resulting in less biased effect estimates. Using this new methodology, we carried out a reliability study and found relatively good intra-rater agreement, however, inter-rater agreement tended to be lower, reflective of the different knowledge base of different industrial hygienists. A consensus panel review of the same jobs judged fewer jobs to be exposed than the primary industrial hygienist. These results have important implications for determining the error associated with the retrospective assessment of jobs by industrial hygienists. We are currently examining methods to correct for this measurement error in a case-control study of solvent exposure and cardiovascular malformations.

Section 1

Highlights/Significant Findings:

This research was designed: 1) to examine the reliability of industrial hygienists when retrospectively assessing occupational exposure to solvents, 2) to develop methods to correct for the error associated with the retrospective assessment of solvents, and 3) to provide error-adjusted estimates for the association between occupational solvent exposure and cardiovascular malformations. Within our reliability study, we observed relatively good intra-rater agreement, however, inter-rater agreement tended to be lower, reflective of the different knowledge base of different industrial hygienists. A consensus panel review of the same jobs judged fewer jobs to be exposed than by the primary industrial hygienist. These results have important implications for determining the error associated with the retrospective assessment of jobs by industrial hygienists. We are currently examining methods to correct for this measurement error and provide error-adjusted estimates for the association between solvent exposure and cardiovascular malformations.

Translation of Findings:

In the near term, the reliability study provides important information on the retrospective assessment of solvents, which should be considered in designing and analyzing studies using this method. In the long term, should significant effects be found with one or more of the solvents of interest (carbon tetrachloride, trichloroethylene, perchloroethylene, methylene chloride, chloroform, and 1,1,1-trichloroethane), it would provide further and more conclusive evidence that some solvents can be teratogenic. In an effort to translate research into practice, efforts to translate the results into lower occupational and environmental exposures and a reduced risk of solvent-associated malformations would be encouraged through dissemination of results at conferences and in the peer-reviewed literature. Furthermore, given the wide-use of these compounds in the home, education of parents and caregivers on the potential reproductive hazards should be undertaken.

Outcomes/Relevance/Impact:

Cardiovascular malformations are the most prevalent of all malformations with approximately six per 1,000 children being born with such a defect. Of these children, approximately 25-35% have other extracardiac defects [1,2]. Cardiovascular malformations are associated with considerable pediatric morbidity and mortality, as well as high health care costs [3-6]. While diagnosis and treatment of heart defects has improved greatly over the past 50 years, few risk factors have been identified to date. Genetics explains only a small fraction of all cardiovascular cases with approximately four percent of infants having a family history of cardiac defects, and six percent having a family history of non-cardiac defects [2]. This necessitates further investigation of potential risk factors for cardiovascular malformations so future cases may be prevented.

This investigation of solvents as a potential risk factor for cardiovascular malformations will provide important information on the teratogenicity of solvents. Given their widespread use throughout industry and in the home, as well as a contaminant in drinking water, it is essential to better understand this association. Current occupational and environmental standards are not based upon reproductive effects thereby putting both men and women at risk for adverse reproductive outcomes. As many women do not realize they are pregnant at the time of cardiac development, they may not take the necessary precautions to prevent potentially harmful exposures that may put their fetuses at greater risk for cardiac malformations. It is therefore necessary to set standards at a level that will not cause reproductive harm.

Section 2 – Scientific Report

A. Background

Men and women of reproductive age represent an overwhelming percentage of the employed population. In 2004, women aged 16-44 represented 28% and men aged 16-54 represented 45% of the employed population [7]. Occupational exposures, whether chemical, physical, or infectious, have been shown to produce adverse reproductive outcomes including infertility, miscarriage, birth defects, low birth weight, preterm delivery, and developmental disabilities. The teratogenicity of organic solvents is one area of particular concern. These agents represent a diverse group of chemicals, used in cleaners, rinsers, degreasers, paints, lacquers, glues, and adhesives, and commonly occur as mixtures. Exposures occur both in the workplace and in the home.

The investigation of the teratogenic effects of solvents and other occupational exposures in human populations is often limited to the case-control study design and retrospective assessment of exposure given the low prevalence of birth defects in the population. To date many studies have relied upon self-reported occupational exposures or job titles to determine exposure, which may have led to information bias, exposure misclassification, and attenuation or overestimation of risk estimates [8-12]. Furthermore, many studies limited by sample size have combined case groups (all cardiovascular malformations, all malformations), as well as combining all solvent exposures, which may further attenuate any associations with specific solvents or malformations. These limitations have resulted in inconclusive results across studies.

A.1 Chlorinated Solvents

Chlorinated solvents are a diverse group of chemicals. Their widespread use throughout industry results in millions of workers being exposed to chlorinated solvents each year. Exposure can also occur in the home primarily through painting, auto repair and cleaning. In addition, improper disposal of solvents can result in contamination of environmental media, leading to population exposures not related to direct use of solvent-containing products. Chlorinated solvents can leach into the groundwater contaminating drinking water and be a low-level air pollutant.

Some of the more common chlorinated solvents are methylene chloride (MC), perchloroethylene (PCE), trichloroethylene (TCE), chloroform, 1,1,1-trichlorethane, and carbon tetrachloride (CT). One of the most widespread uses of chlorinated solvents is metal degreasing with trichloroethylene, perchloroethylene and 1,1,1-tricholoethane the most commonly used degreasers. Chlorinated solvents have also been frequently used in the dry cleaning industry as a cleaning solution and spotting agent, with perchloroethylene now the primary solvent being used. Other industries or products in which chlorinated solvents are used include plastics manufacturing (MC), foam industry (MC), textile industry (PCE, TCE, 1,1,1-trichlorethane, MC, and chloroform), electronics industry (MC, PCE, TCE, 1,1,1-trichloroethane), pharmaceutical industry (MC, chloroform), rubber industry (PCE, TCE, CT, MC, chloroform, 1,1,1-trichloroethane), health care industry (chloroform, PCE, MC, CT), aerosols (MC, 1,1,1-trichloroethane, PCE), food processing (MC), paints and strippers (MC, 1,1,1-trichloroethane), printing (TCE, PCE, 1,1,1-trichloroethane), glues (MC, PCE, TCE, TC, 1,1,1-trichloroethane), and pesticides (CT, TCE, PCE, MC, 1,1,1-trichloroethance). Chloroform, methylene chloride, perchloroethylene, 1,1,1-trichloroethane, and trichloroethylene have all been identified as groundwater contaminants [13]. Low levels of chloroform, carbon tetrachloride, 1,1,1-trichloroethane have been measured in air.

Most chlorinated solvents are highly volatile with the primary route of exposure through inhalation; however, oral and dermal exposure may occur as well. Once inhaled, solvents are readily absorbed into the blood and distributed primarily to adipose tissue, liver, brain and kidney. Solvents have been shown to cross the placenta in both animal and human studies [14-16]. Dowty et al. found benzene,

carbon tetrachloride, and chloroform present in cord blood in levels equal to or higher than in maternal blood [15].

A.1.1 Organic Solvents and Cardiovascular Malformations

A limited number of studies have examined risk factors for cardiovascular malformations with the Baltimore Washington Infant Study contributing significantly to the literature [2,17]. Cardiac malformations have been shown to vary by race/ethnicity with whites being at greater risk of D-transposition of the great arteries, Ebstein anomaly, coarctation of the aorta, and aortic valve stenosis, while blacks have been shown to be at greater risk for pulmonary stenosis and patent ductus arteriosis [18,19]. Studies have found fairly consistent associations between heart defects and some diseases, lifestyle factors, and medications including: rubella [20-22], diabetes [23,24], epilepsy [25], influenza [26], fever [26], vitamin A [27,28], maternal alcohol consumption [2,29,30], maternal and paternal smoking [2,31], maternal and paternal cocaine use [2,32], and various medications [2,33].

Environmental and occupational exposures have also been explored with associations being found with herbicides [26], rodenticides [26], solvents [26,32,34], lead [2,2,34,34-40], hair dyes [2], and ionizing radiation [2,34,41]. To date the association with solvents has been inconsistent across studies, but remains a concern given the large number of exposed jobs through work, hobbies, and drinking water.

A.1.2. Maternal Solvent Exposure

Maternal exposure to solvents could result in insults to germ cells prior to pregnancy causing DNA damage or it may be a direct effect during cardiogenesis. The heart develops early in pregnancy between the third and eighth week of gestation. This is often before a woman knows she is pregnant, and therefore may not limit exposure to harmful substances.

Few studies have investigated the association between solvents and cardiovascular malformations in general, and even fewer have investigated the association with specific cardiovascular malformations. Tikkanen et al. carried out a series of case-control studies for specific cardiovascular malformations in relation to maternal occupational exposures [42-47]. They found significant associations between maternal solvent exposures during the first trimester and ventricular septal defects and conal malformations of the heart [42,44]. While not significant, a two-fold increased odds of solvent exposure was associated with conus arteriosus syndrome, atrial septal defect, hypoplastic left ventricle, and endocardial cushion defect [45]. Garcia et al. found a similar association for cardiac defects of closure among women working as assemblers in the leather industry who had potential solvent exposure compared to all other women (adjusted OR 1.78; 95% CI: 0.44-7.17) [48]. A case-control study carried out in France by Cordier et al. found an increased odds of cardiac malformations among women exposed before and during pregnancy to “pure” solvents (OR=1.7; 95% CI 0.4-7.6) [49]. Occupational solvent exposure has also been associated with malformations, in general, in several studies [50,51], as well as oral clefts and neural tube defects [52-56]. Various studies have observed an increased risk of spontaneous abortions due to occupational solvent exposure, specifically among those exposed to perchloroethylene, trichloroethylene, or glycol ethers [51,57-61]. To date epidemiologic studies investigating the teratogenicity of solvents have been limited by exposure assessment with only seven studies identified as using some type of expert assessment of occupational histories [49,50,52,53,55,60,62]. While four of these studies examined various groups of solvents (glycol ethers, oxygenated, chlorinated, petroleum, or aromatic solvents), only one examined a specific solvent (methylene chloride) [60], and none examined specific cardiac malformations.

Several studies have examined the association between contaminated drinking water (primarily TCE) and cardiovascular malformations; however, the results have been inconclusive and limited by sample size, comparison groups, and exposure assessment [63]. Yauck et al. did not note an association between living near a TCE emitting facility and cardiovascular malformations overall, but did observe

a six-fold increased odds of exposure among women 38 years of age or older who gave birth to a child having a cardiovascular malformation [64].

A.1.3. Paternal Solvent Exposure

While the mechanism by which paternal solvent exposure may lead to cardiovascular malformations is unclear, there are several potential pathways including: 1) a direct effect on germ cells or sperm DNA, or 2) an indirect effect through transmission of toxicants to the mother via seminal fluid or via paternal take-home exposures transmitted to the mother and embryo during cardiogenesis. In a meta-analysis, Logman et al. found an increased odds of major malformations (OR 1.47; 95% CI 1.18-1.83) associated with paternal exposure to solvents, as well as an increased odds of neural tube defects and anencephaly [65]. Several studies have noted an association between occupations with solvent exposure and congenital malformations. Schnitzer et al. noted an association between painting and atrial septal defects (OR 2.7; 95% CI: 1.0-7.4) and Olshan et al. noted an association with painting and patent ductus arteriosis (OR=2.34) [66,67]. Several studies have shown an association between paternal solvent exposure and spontaneous abortion or stillbirth [39,68]. Overall, studies investigating the association between paternal solvent exposure and malformations have been limited by exposure assessment, with the vast majority using job title or occupation as a means for determining exposure.

A.2. Occupational Exposure Assessment in Case-Control Studies

Etiologic studies of birth defects are generally limited to the case-control design given the low prevalence of birth defects in the population. This generally requires exposure assessment to be done retrospectively and therefore accurate assessment of exposure is difficult. Industry records are usually not available and/or it would be infeasible to collect records from each place of employment. While current exposure levels could be measured, they often are not reflective of exposures for the same task prior to the outcome of interest. Various methods have been used to assess exposures retrospectively including self-reports, job titles, job exposure matrices (JEM), and expert (industrial hygienist) assessment. These methods have their advantages and disadvantages with trade-offs between feasibility, power and cost [69]. Furthermore, the validity and reliability of these methods may vary depending on the type of agent that is being studied and the prevalence of exposure in the study population [70]. Accurate recall of self-reported occupational exposures is a common concern associated with case-control studies. Inaccurate recall may lead to an under-estimation of exposure for jobs and attenuation of the risk estimate if recall is non-differential or an under- or over-estimation of the risk if recall is differential.

Assessment by experts such as industrial hygienists is generally considered the best method of exposure assessment in the absence of true exposure measures or biological markers of exposure [69,71,72]. This method involves one or more industrial hygienists or exposure experts who review the occupational histories of jobs to infer exposure. As with job exposure matrices there is less concern about recall bias as subjects are unlikely to relate occupation to the disease of interest and hygienists are blinded to case-control status. Expert assessment provides more flexibility in assigning exposure allowing for greater detection of inter-individual differences within occupation compared to a JEM which generally assigns the same exposure to everyone with the same occupation. Furthermore, expert assessment tends to be more valid than self-reports and JEMs, thereby increasing the power to detect a difference between groups [73]. However, studies have found that expert assessment is still prone to misclassification with sensitivity ranging from 40-70% and specificity 75-90% for a study comparing expert assessment to metabolites related to solvent exposure [74]. Benke et al. found inter-rater reliability as measured by kappa varied from 0.19 for the retrospective assessment of toluene and benzene to 0.64 for cutting fluids [75]. In general, intra-rater reliability tends to be higher with Siemiatycki et al. reporting a kappa=0.75 in relation to the retrospective assessment of solvents in a population-based study [76]. Factors limiting the validity and reliability of expert assessment are the quality of the occupational history and the experience of the industrial hygienists.

In an attempt to improve the validity and reliability of expert assessment, industrial hygienists at the National Cancer Institute (NCI) developed an extension to this method, which is referred to as the "NCI Method". This method provides the industrial hygienist with task and exposure matrices based on an extensive review of the literature. The hygienist then uses the matrices, as well as his/her own experience to infer exposure for each individual job. The standardized and comprehensive source of exposure information, as well as the identification of exposure determinants (location, quantity, ventilation, temperature, operation and mechanism of release) should provide more reliable, and more valid estimates, as shown by Semple et al. [77,78].

B. Specific Aims

The purpose of this study was to examine the association between exposure to six chlorinated solvents (carbon tetrachloride, trichloroethylene, perchloroethylene (tetrachloroethylene), methylene chloride (dichloromethane), chloroform, and 1,1,1-trichloroethane) and five specific cardiovascular malformations (hypoplastic left heart syndrome, coarctation of the aorta, pulmonary valve stenosis, total anomalous pulmonary venous return, and pulmonary valve atresia) using data previously collected for the Baltimore Washington Infant Study (BWIS) which was carried out between 1981 and 1989. The BWIS represents one of the largest studies of cardiovascular malformations with high quality data including a thorough assessment of diagnostic groups, potential risk factors, confounders, and effect modifiers. In addition, we examined the reliability of the NCI exposure assessment method and associated methodologies to correct for error in exposure assessment.

The specific aims of the study were:

Specific Aim 1: To determine the association between occupational, chlorinated solvent exposure and cardiovascular malformations among families participating in the Baltimore Washington Infant Study, 1981-1989.

Specific Aim 2: To evaluate the inter- and intra-rater reliability of the NCI method in assessing chlorinated solvent exposure. A subset of jobs was assessed for exposure by two additional hygienists, as well as by the primary hygienist at a second point in time to determine inter- and intra-rater reliability of the method, respectively.

Specific Aim 3: To assess the impact of potential misclassification of chlorinated solvent exposure on the association between solvents and cardiovascular malformations. Using the reliability data as well as data from a consensus review of jobs for which there was disagreement among hygienists in Specific Aim 2, misclassification of exposure will be estimated and effect estimates corrected.

C. Methods

C.1. Baltimore Washington Infant Study

The Baltimore Washington Infant Study (BWIS) was a large, population-based case-control study of cardiovascular malformations among live-born infants (Figure 1). Recruitment of subjects and their families was carried out between January 1, 1981 and December 31, 1989. All infants were delivered in participating hospitals (n=52) within the state of Maryland, the District of Columbia, and Northern Virginia.

Cases (infants with a structural cardiovascular malformation) were identified using logbooks of clinic visits, inpatient consultations, echocardiography, cardiac catheterization, cardiac surgery, and pathology examination at six pediatric cardiology centers including the University of Maryland, Johns Hopkins University, Children's National Medical Center, Howard University Hospital, Georgetown

University, and Fairfax Hospital. In addition, community searches including review of pathology logbooks, medical examiner's logbooks (Maryland), and death certificates of infants who died before one year of age (Maryland and District of Columbia) were performed. Cases were confirmed before one year of age by echocardiography, cardiac catheterization, surgery or autopsy and their diagnosis and vital status updated at one year of age. Each infant was given a primary diagnosis based upon the cardiovascular malformation that most likely occurred the earliest according to embryogenesis [79]. Of the 3,763 cases eligible for the study, 3,377 (90%) participated.

Controls (n=3,572) were a random sample of all live-born infants without cardiovascular malformations stratified by month and year of birth and hospital of birth. The number of controls selected from each hospital was proportional to the number the hospital contributed to all regional deliveries. Participation among controls was high with 78% of first and 17% of second choices participating in the study [80]. Controls were similar to all area births during the study period by infant gender, race, birthweight and plurality, as well as season of birth and maternal age [80].

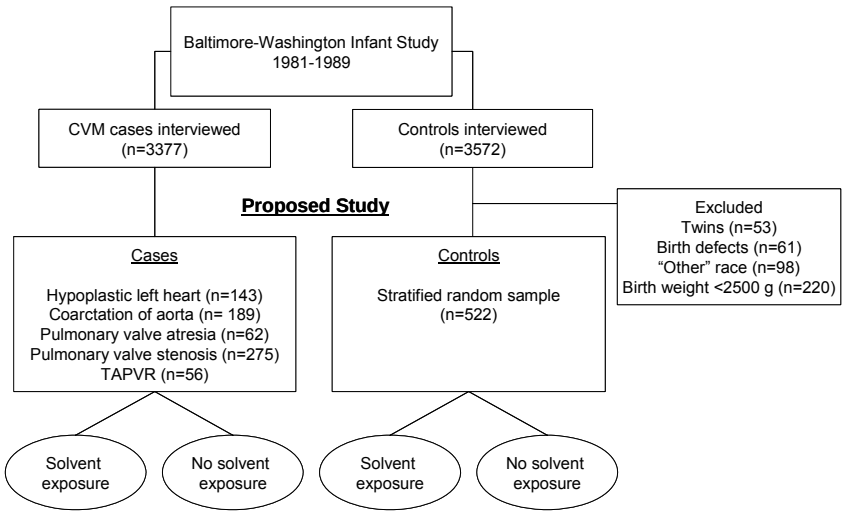
Respondents for cases and controls were administered a questionnaire including questions on infant factors, demographic and socioeconomic factors, maternal medical history, family genetic factors, therapeutic drugs, medical exposures, personal habits, occupational and avocational exposures, home environment, and occupational histories. The infant's mother was the primary respondent for 98% of all cases and 99% of all controls [81]. Fathers were either the primary or secondary respondent for 22% of all cases and 16% of all controls [81]. The BWIS was the first population-based epidemiologic study of cardiovascular malformations providing extensive insight on the epidemiology of these defects.

C.2. NIOSH Funded Study

C.2.1. Study Population

The funded project (Figure 1) included five cardiovascular malformation case groups including hypoplastic left heart syndrome (HLH; n=142), coarctation of the aorta (CoA; n=189), pulmonary valve stenosis (PVS; n=275), TAPVR (n=56), and pulmonary valve atresia (PVA; n=62). These case groups were selected due to their size and association with environmental and occupational exposures in preliminary analyses of self-reported exposures.

Figure 1. Study Design: Case-control study of parental occupational solvent exposure and cardiovascular malformations among children, Baltimore-Washington Infant Study, 1981-1989



The control population was originally sampled for a study of occupational lead exposure and low birth weight within the Baltimore Washington Infant Study [82]. They were selected from a subset (n=3,140) of the original control population (n=3,572) that excluded twins (n=53), infants with non-cardiac birth defects (n=61), infants of race other than black or white (n=98), and low birth weight infants (n=220). Stratified random sampling was used to select 522 controls stratified on year of birth from this subset. It was not possible to resample a new, and more comparable control

group for the current study as the occupational history data for the other controls were not in the database and the questionnaires were no longer available.

C.2.2. Exposure Assessment

The primary method of exposure assessment was by expert assessment using a task and exposure matrix developed by the National Cancer Institute (NCI method) as described below. Assessment was based upon data collected during the BWIS interview, which included a detailed work history for both parents of jobs held from six months prior to pregnancy through the end of pregnancy. Data collected included employer, dates of employment, time of job in relation to pregnancy, section of the workplace, type of work done, job title, job description, and whether the parent believed they were exposed to any hazardous substances on the job. Furthermore, parents were queried on 35 different exposures. If a positive response was given to any one of these exposures further information was obtained on the type of activity involved, whether they were exposed at home, work, or other place, the dates of exposure and the frequency of exposure for each three-month interval from six months prior to pregnancy through birth. Chlorinated solvents including carbon tetrachloride, trichloroethylene, perchloroethylene (tetrachloroethylene), methylene chloride (dichloromethane), chloroform, and 1,1,1-trichloroethane were the primary exposures of interest for the funded study. Assessment of these specific compounds was based upon their potential teratogenicity and the availability of NCI exposure matrices.

All jobs were assessed by a primary industrial hygienist, with a subset of jobs (n=300) reviewed by two additional industrial hygienists to determine inter-rater reliability, as well as reviewed by the primary hygienist at a second point in time to assess intra-rater reliability. The subset of 300 jobs was a stratified random sample with 20% of jobs being unexposed and 80% exposed based upon review by the primary hygienist. Any disagreement between hygienists within the reliability study was resolved through an in-person consensus panel which included four industrial hygienists: the primary industrial hygienist, one inter-rater industrial hygienists, and two of the developers of the NCI solvent matrices.

NCI Method

The exposure matrices for the six chlorinated solvents were developed through an extensive review of the literature and other resources including 1) relevant journals published from 1980 to 2003 (*American Industrial Hygiene Association Journal*, *Applied Occupational and Environmental Hygiene*, *American Journal of Industrial Medicine*, *Journal of Occupational and Environmental Medicine*, *Scandinavian Journal of Work, Environment and Health*, *Annals of Occupational Hygiene*, and *Occupational and Environmental Medicine* - note that some of these journals were published in earlier years under a different journal name.); 2) various databases including NIOSHTIC, MEDLINE, and TOXLINE; 3) NIOSH Health Hazard Evaluations; and 4) other references identified in the above articles. In all, over 500 papers were reviewed.

Qualitative and quantitative information was abstracted from each paper on the use and occurrence of solvent exposure. In addition, exposure measurement data and the accompanying documentation [i.e., duration, type of measurement (area/personal; air, dermal, wipe; peak, eight-hour time-weighted average), job, industry, task, etc.] were abstracted including over 5100 measurements. All exposure measurement data and the accompanying documentation were entered into an Excel database. For each exposure measurement, information on six determinants of exposure was assigned based on the information in the measurement report. Determinants of exposure included location (indoors/outdoors), quantity used, ventilation, temperature, operation and mechanism of release.

Task (e.g., degreasing, painting, dry cleaning) exposure matrices were developed based on the exposure matrix. Each task matrix includes estimates of the probability and frequency of exposure for

each of the six chlorinated solvents by decade (1930s-1990s). In addition, an estimate of confidence was assigned based on the source for the probability and frequency information. The current study primarily focused on the exposure data for the 1980s coinciding with the BWIS study.

For each assessed job in the funded study, the industrial hygienists used the task and exposure matrices as guidelines in assigning probability and frequency of exposure, and their confidence in their estimate, while considering job-specific information to refine their estimates. The industrial hygienists also identified the exposure determinants related to the job. The classifications for each exposure measure and determinant are provided in Tables 1 and 2.

Critical Windows of Exposure

For the purposes of the current study, jobs during the critical windows of exposure were identified. based upon the timing of embryogenesis and spermatogenesis. For mothers, the critical period was defined as the three months preceding pregnancy and the first three months of pregnancy. The heart develops between the third and eighth week of pregnancy, and therefore it is important to capture those exposures that occur during this time. Among fathers, the critical period was defined as the three months prior to pregnancy. This time period includes the 74 days of spermatogenesis and sperm maturation.

Table 1. Definitions and responses for probability, frequency and intensity of exposure

PROBABILITY	PROBABILITY CONFIDENCE IF EXPOSED	CONFIDENCE IN PROBABILITY IF UNEXPOSED
0 = unexposed **1 =** <10% **2 =** 10-49% **3 =** 50-89% **4 =** ≥90%	**1 =** Did not say, gave no other information but job is often doing that task or no probability date available on process. **2 =** Either did not say used process but provided circumstantial evidence they probably used the process and some data available on process or the converse. **3 =** Data on subject using process or product and have data but for any decade reasonable to extrapolate. **4 =** Data on both subject and use of the solvent or have used the process and data on probability for the decade and same job/industry.	**1 =** Most subjects would not have exposure but small amount could but very rare and would not meet minimum criteria (secretary from whiteout). **2 =** Some subjects with this job in this industry could have exposure but highly likely that it is less than the minimum amount (supervisor of an office from whiteout). **3 =** Unlikely that anyone with this job in this industry would have exposure (taxi driver). **4 =** Highly unlikely anyone with this job in this industry would have exposure. This will generally be white collar people (e.g., accountant).

FREQUENCY	FREQUENCY CONFIDENCE
1 = 1hr/wk (5%) **2 =** 2-10 hr/wk (5-25%) **3 =** >10-20 hrs/wk (26-50%) **4 =** >20 hrs/wk (>50%)	**1 =** Information is contradictory **2 =** Guess **3 =** Relatively confident **4 =** Confident

INTENSITY	INTENSITY CONFIDENCE
Carbon Tetrachloride (ppm) **0 =** <1 **1 =** 1-10 **2 =** 11-50 **3 =** >50	**1 =** no measurement data **2 =** no measurements available for time period or for agent but measurements are available for a different time period or other agent **3 =** <5 measurements are available for time period and agent **4 =** 5 or more measurements are available for time period and agent
Trichloroethylene (ppm) **0 =** <1 **1 =** 1-20 **2 =** 21-100 **3 =** 101-200 **4 =** >200	
Perchloroethylene (ppm) **0 =** <1 **1 =** 1-20 **2 =** 21-100 **3 =** 101-200 **4 =** >200	
Methylene Chloride (ppm) **0 =** <1 **1 =** 1-20 **2 =** 21-100 **3 =** 101-200 **4 =** >200	
1,1,1-trichloroethane (ppm) **0 =** <1 **1 =** 1-20 **2 =** 21-100 **3 =** 101-350 **4 =** >350	
Chloroform (ppm) **0 =** <1 **1 =** 1-10 **2 =** 11-50 **3 =** 51-100 **4 =** >100	

Table 2. Definitions and responses for each exposure determinant assessed

Determinant	Definition	Codes
Process Condition	The containment of the industrial operation that uses the agent.	**1 =** Closed **2 =** Both **3 =** Open
Temperature	The temperature of the operation that contains the agent.	**0 =** Room temperature **1 =** Both **2 =** Elevated
Release Mechanism	The method by which the agent is dispersed into the atmosphere where the subject comes into contact with the agent. In some ways, it represents the amount of energy being applied in the operation.	**0 =** Evaporation **1 =** Spreading **2 =** Manual agitation **3 =** Rolling **4 =** Mechanical agitation **5 =** Aerosolized
Quantity	The approximate amount of the agent in liquid form that is processed, but not necessarily used up by the operation.	**0 =** <100 gal/mo **1 =** 100-1000 gal/mo **2 =** >1000 gal/mo
Ventilation (Personal)	The type of ventilation system at the major sources of exposure for the subject. For example, in a closed system, ventilation at a sample point would be rated for a production worker taking samples.	**1 =** LEV+MechDil **2 =** LEV **3 =** Indust. Mech. Dilution **4 =** Mech. Dil +None **5 =** None present & specified **DK =** No mention of ventilation
Vent Efficiency	The ability of the ventilation system identified above (whatever type it is) to remove the agent from the breathing zone of the subject to result in a substantially lower exposure level	**Y =** Yes **N =** No **DK =** Don't know **NA =** Not applicable
Location (vent2)	The physical location of the source(s) where the subject gets his/her major exposure(s)	**1 =** Outdoor **2 =** Both **3 =** Indoor
Confined Space	The presence of a small, contained, infrequently visited area containing the agent and visited by the subject	**1 =** No **2 =** Both **3 =** Yes
Proximity	The average distance of the subject from the major source over the length of the job	**0 =** >3 feet **1 =** Both **2 =** < 3 feet
Route of Exposure	The mechanism through which the subject comes into contact with the agent	**0 =** Dermal **1 =** Inhalation **2 =** Both
Confidence in determinants	The overall relative confidence the industrial hygienist has in the determinant ratings.	**1 =** Information is contradictory **2 =** Guess **3 =** Relatively confident **4 =** Confident

D. Results

D.1. Specific Aim 1: Association between occupational solvent exposure and TAPVR

As part of Specific Aim 1, all jobs (n=2724) were assessed by the primary industrial hygienist for chlorinated solvent exposure. The prevalence of exposure among these jobs was as follows: carbon tetrachloride (12%), trichloroethylene (16%), perchloroethylene (18%), methylene chloride (16%), 1,1,1-trichloroethane (20%), and chloroform 13%). Overall, 22% of jobs had exposure to one or more of the chlorinated solvents of interest, with 7% (n=204) having exposure to all six chlorinated solvents. Further analysis of this data has been put on hold until we complete analyses for Specific Aims 2 and 3, which will allow to correct risk estimates for measurement error in the exposure assessment; however, analyses will proceed as described below.

Maternal and paternal exposure to each of the solvents will be examined by case-control status. Probability of exposure for each parent will be a weighted average over all jobs held during the critical period with the probability of exposure in each job weighted by the percent of time spent in that job during the critical period. A similar method will be used to determine the overall frequency and intensity of exposure. Determinants of exposure including ventilation, quantity etc. will be examined as well.

Odds ratios (OR) and 95% confidence intervals (CI) will be calculated to compare the odds of exposure for cases and controls for the three exposure measures (probability, frequency and intensity). Multivariable logistic regression will be employed to adjust for potential confounders. Confounders entered into the model will be identified by comparing the distribution of cases and controls for variables previously shown to be related to cardiovascular malformations, or suggestive as being a confounder in preliminary analyses. Potential confounders include: family history of malformations, infant race/ethnicity, maternal and paternal age, pregnancy history, influenza, fever, rubella, pre-pregnancy body mass index, medication use, and smoking and alcohol consumption. All variables in the final model, as well as those shown to be effect modifiers in previous studies will be tested for interactions. Evaluation of multiple solvent exposures per parent, as well as maternal versus paternal exposure or both parents exposed will be undertaken. Given that we will be making multiple comparisons we will use a Bonferroni correction to determine statistical significance.

D.2. Specific Aim 2: Reliability Study

The inter- and intra-rater assessment included 300 jobs randomly selected from all 2724 jobs and stratified on exposed (80%) and unexposed (20%) jobs as determined in the primary assessment. The primary industrial hygienist completed the intra-rater assessment, and two additional industrial hygienists (IH 1 and IH 2) with expertise in assessing occupational exposures for epidemiologic studies assessed exposure for the inter-rater assessment. A consensus panel including the primary industrial hygienist, one inter-rater industrial hygienist, and two industrial hygienists who developed the NCI solvent matrices. The consensus panel reviewed 273 out the 300 jobs assessed in the inter- and intra-rater assessment, with the remaining 27 jobs all being assessed as unexposed in the primary, intra and inter-rater assessments.

Percent agreement and Cohen's kappa statistic (κ) was used to assess agreement on the following exposure variables: exposure (yes/no), and probability, frequency, intensity and determinants of exposure. Unweighted kappa statistics were calculated for dichotomous and categorical variables (exposure yes/no; some exposure determinants) and quadratic weighted kappa statistics calculated for ordinal variables (probability, frequency and intensity of exposure and various exposure determinants). The kappa statistic is a measure of agreement taking into consideration the expected agreement due to chance alone, assuming independence of raters. Kappa provides a better estimate of agreement than percent agreement [83]. As defined by Fleiss, kappa values below 0.4 are

considered to represent poor agreement beyond chance alone, 0.40-0.75 represent fair to good agreement, and greater than 0.75 excellent agreement; kappa's less than zero represent agreement worse than which would be expected due to chance alone [84].

The results of the intra- and inter-rater assessment and consensus panel are summarized below for each. For these results, the inter-rater industrial hygienists are referred to as IH 1 and IH 2.

Chloroform

Intra-rater agreement. In the primary assessment, the hygienist determined that 168 (56.0%) of the 300 jobs were exposed to chloroform. On the repeat assessment 151 (50.3%) were considered exposed. Overall percent agreement between the two assessments was 86.3%. Of these, 139 jobs (46.3%) were classified as exposed to chloroform in both assessments. The kappa for dichotomous exposure (yes/no) was 0.73. Agreement on probability of exposure was excellent (κ=0.84), while other measures had fair to good agreement, ranging from 0.58 (location of exposure) to 0.73 (route of exposure and temperature).

Inter-rater agreement. IH1 identified 50 jobs (16.8%) and IH 2 identified 110 jobs (37.0%), out of a total of 297, as exposed to chloroform. IH 1 and IH 2 agreed on the exposed/unexposed classification of 195 jobs (65.7%), mostly in the category of unexposed. There were only 29 (9.8%) jobs that both IH 1 and IH 2 considered to be exposed. The kappa for dichotomous exposure (yes/no) was 0.17. All of the kappa statistics for this solvent were in the "poor" category (κ<0.40).

Consensus panel. Out of 273 jobs included in the consensus panel, 137 (50.1%) were identified as exposed to chloroform, as compared to 168 (61.5%) in the primary assessment. Overall percent agreement was 75.5%; 119 (43.5%) were considered exposed by both the primary hygienist and the consensus panel. Agreement for dichotomous exposure (yes/no) (κ=0.51) and probability of exposure (κ=0.65) was fair to good, while there was poor agreement on the frequency of exposure (κ=0.35).

Carbon Tetrachloride

Intra-rater agreement. The primary hygienist classified 152 (50.7%) jobs as exposed to carbon tetrachloride in the first assessment, and 130 (43.3%) in the second assessment; 119 (39.7%) were considered exposed in both assessments. The kappa for dichotomous exposure (yes/no) was (κ=0.71). All of the kappas for this solvent had "fair to good" agreement, ranging from 0.67 (location of exposure) to 0.72 (route of exposure and temperature of the operation containing the agent).

Inter-rater agreement. IH 1 identified 24 jobs (8.0%) and IH 2 identified 104 jobs (35.0%), out of a total of 297, as having exposure to carbon tetrachloride. IH 1 and IH 2 agreed on the exposed/unexposed classification of 209 jobs (70.3%), primarily as unexposed. There were only 20 (6.7%) jobs that both IH 1 and IH 2 considered to be exposed. All of the kappa statistics for this solvent indicated poor agreement. The kappa for dichotomous exposure (yes/no) was 0.21. The lowest kappas for this solvent were for frequency of exposure (κ=0.09) and secondary release mechanism (κ=0.10) and the highest were for quantity of exposure (κ=0.22) and probability of exposure (κ=0.24).

Consensus panel. The primary hygienist classified 152 (55.7%) jobs as exposed to carbon tetrachloride, and the consensus panel classified 126 (46.2%) jobs as exposed. They agreed on the exposed/unexposed status of 195 (71.4%) jobs overall. Kappa statistics for dichotomous exposure and probability of exposure were both in the fair to good range, κ=0.43 and κ=0.46, respectively. The remaining kappas that were estimated indicated poor agreement: frequency of exposure (κ=0.34).

Methylene Chloride (Dichloromethane)

Intra-rater agreement. The primary hygienist classified 202 (67.3%) jobs on the first assessment and 185 (61.7%) on the second assessment as exposed to methylene chloride; 177 (59.0%) were identified as exposed on both assessments. Overall percent agreement for dichotomous exposure was 89.0%. The kappa for dichotomous exposure (yes/no), κ=0.76, indicated excellent intra-rater agreement. Additional kappas that indicated excellent agreement were probability of exposure (κ=0.78), frequency of exposure (κ=0.76), and temperature of the operation containing the exposure (κ=0.76). All other kappas for this solvent were "fair to good", ranging from 0.60 for type of ventilation to 0.75 for route of exposure, presence of a confined space containing the agent, and containment of the industrial operation that uses the agent.

Inter-rater agreement. IH 1 identified 83 jobs (27.9%) and IH 2 identified 122 jobs (41.0%), out of a total of 297, as having exposure to methylene chloride. IH 1 and IH 2 agreed on the exposed/unexposed classification of 220 jobs (74.1%). Agreement for dichotomous exposure (yes/no) was fair to good ((κ=0.44), as was intensity of exposure (κ=0.51), containment of the industrial operation that uses the agent (κ=0.44), quantity of exposure (κ=0.41), temperature of the operation that contains the agent (κ=0.40), and presence of a confined space containing the agent (κ=0.44).

Consensus panel. Out of 273 jobs included in the consensus panel, 202 were assessed as exposed by the primary hygienist and 152 (55.7%) by the consensus panel; 148 (54.2%) were classified as exposed by both the hygienist and the panel. Overall percent agreement between the primary hygienist and panel on dichotomous exposure (yes/no) was 78.8%. The kappa statistic for dichotomous exposure was κ=0.55, in the fair to good range. Other fair to good kappas for this solvent included probability of exposure (κ=0.55) and frequency of exposure (κ=0.40).

Trichloroethylene

Intra-rater agreement. The primary hygienist classified 195 (65.0%) jobs on the first assessment and 163 (54.3%) on the second assessment as exposed to trichloroethylene; 154 (51.3%) were identified as exposed on both assessments. Overall agreement for dichotomous exposure (yes/no) was 83.3%. All of the kappas calculated for this solvent had fair to good agreement. The kappa for dichotomous exposure was κ=0.66. The lowest kappa in this area was for type of ventilation and location of exposure ((κ=0.63) and the highest kappas were for frequency of exposure (κ=0.73) and quantity of exposure (κ=0.72).

Inter-rater agreement. IH 1 identified 109 jobs (36.7%) and IH 2 identified 74 jobs (24.9%), out of a total of 297, as exposed to trichloroethylene. IH 1 and IH 2 agreed on the exposed/unexposed classification of 224 jobs (75.4%) (overall agreement for exposure). The kappa for dichotomous exposure (yes/no) was κ=0.43, in the fair range. Other kappas that were fair to good included probability of exposure (κ=0.45), intensity of exposure (κ=0.46), containment of the industrial operation that uses the agent (κ=0.41), temperature of the operation containing the agent (κ=0.40), and presence of a confined space containing the agent (κ=0.44). The remaining kappas indicated poor agreement.

Consensus panel. The panel classified 165 (60.4%) and the primary hygienist classified 195 (71.4%) jobs out of 273 as exposed to trichloroethylene. The panel and primary hygienist agreed on the overall exposure status of 193 (70.7%) jobs. Overall, there was poor agreement in this category. The kappa for dichotomous exposure (yes/no) was κ=0.36. Other kappas included probability of exposure (κ=0.38) and frequency of exposure (κ=0.38).

Perchloroethylene

Intra-rater agreement. The primary hygienist classified 223 (74.3%) jobs as exposed to perchloroethylene in the first assessment, and 161 (53.7%) in the second assessment. Overall

percent agreement for dichotomous exposure (yes/no) was 72.7% and the Kappa=0.43. All of the kappas for this solvent were in the fair to good agreement range. The highest agreement was observed for quantity of exposure (κ=0.61), and frequency of exposure (κ=0.59).

Inter-rater agreement. IH 1 identified 101 jobs (34.0%) and IH 2 identified 108 jobs (36.3%), out of a total of 297, as exposed to perchloroethylene. IH 1 and IH 2 agreed on the exposed/unexposed classification of 206 jobs (69.4%), the majority of these were unexposed. All of the kappa statistics for this section indicated poor agreement between IH 1 and IH 2. The kappa for dichotomous exposure (yes/no) was κ=0.33. The lowest agreement in this section was for secondary release mechanism (κ=0.10). The highest kappas were for intensity of exposure (concentration) (κ=0.35), presence of the exposure within a confined space (κ=0.33), and dichotomous exposure.

Consensus panel. Out of 273 jobs included in this comparison, the consensus panel identified 155 (56.8%) jobs as exposed to perchloroethylene and the primary hygienist identified 223 (81.7%) as exposed. Overall percent agreement was 72.9% with 152 (55.7%) jobs considered exposed by both the primary hygienist and the panel. The kappa statistic for dichotomous exposure showed fair agreement; κ=0.41. All other kappas calculated had poor agreement, including probability of exposure (κ=0.37) and frequency of exposure (κ=0.32).

1,1,1-Trichloroethane

Intra-rater agreement. The primary hygienist classified 252 (84%) jobs on the first assessment and 193 (0.64%) on the second assessment as exposed to 1,1,1-trichloroethane; 183 (0.61%) were identified as exposed on both assessments. Overall percent agreement on exposure status was 73.7% (n=221 jobs). The kappa for dichotomous exposure (yes/no) indicated poor agreement (κ=0.35). For this solvent, kappas ranged from having fair to good agreement to having poor agreement. The lowest kappa was for presence of the exposure within a confined space (κ=0.34), whereas the highest kappas were for probability of exposure (κ=0.59) and frequency of exposure (0.59).

Inter-rater agreement. IH 1 identified 77 jobs (25.9%) and IH 2 identified 134 jobs (45.1%), out of a total of 297, as exposed to 1,1,1-trichloroethane. IH 1 and IH 2 agreed on the exposed/unexposed classification of 210 jobs (70.7%) (overall agreement). There was borderline fair agreement on dichotomous exposure (yes/no), κ=0.39. There was fair to good agreement for intensity of exposure (κ=0.46). Other kappas ranged from 0.16 (secondary release mechanism) to 0.39 (presence of the exposure within a confined space, dichotomous exposure).

Consensus panel. Among the 273 jobs included in the consensus panel, the panel classified 182 (66.7%) and the primary hygienist classified 252 (92.3%) jobs as exposed to 1,1,1-trichloroethane; the panel and primary hygienist agreed that 177 (64.8%) jobs had exposure. The panel and the hygienist agreed on the overall exposure status of 193 (70.7%) jobs. The kappa for dichotomous exposure (yes/no) was κ=0.18. Other kappas included probability of exposure (κ=0.12), confidence in the probability of exposure (κ=0.33), and frequency of exposure (κ=0.12).

Summary

The kappas calculated here represent the intra- or inter-rater agreement between individual hygienists or the consensus panel in classifying exposure status as well as specific determinants of exposure based on the provided job description. Intra-rater agreement was best for methylene chloride followed by chloroform, and worst for 1,1,1-trichloroethane; a similar pattern was observed for agreement between the primary hygienist and consensus panel. Inter-rater agreement was highest for methylene chloride and trichloroethylene, and lowest for chloroform.

Looking at all of the solvents collectively, some variables related to exposure tended to have higher agreement than others. These included dichotomous exposure (yes/no), probability of exposure, and quantity of exposure. Frequency of exposure tended to have lower agreement.

Specific Aim 3: Assessment and Correction for Misclassification of Exposure

Using data from the reliability and consensus studies we will correct effect estimates for error in the assessment of exposure. We had originally hoped to use methods being developed by one of our investigators; however, those methods require repeated measures on the full study population. Therefore, we are attempting to develop methods that will use repeated categorical measures on a random-sample of the study population to correct for this error in logistic regression models.

E. Discussion and Conclusion

Within our reliability study, we observed relatively good intra-rater agreement, however, inter-rater agreement tended to be lower, reflective of the different knowledge base of different industrial hygienists. In general, the consensus panel judged fewer jobs to be exposed than the primary industrial hygienist. These results have important implications for determining the error associated with the retrospective assessment of jobs by industrial hygienists. We are currently examining methods to correct for this measurement error in our case-control analyses and plan to publish the results in the coming year.

F. Publications

Over the next year we hope to submit several conference abstracts and journal manuscripts for publication.

G. Inclusion of Gender and Minority Subjects

This work was based upon existing data with no participants recruited as part of the research.

H. Inclusion of Children

This work was based upon existing data with no participants recruited as part of the research.

I. Project-Generated Resources

There are no resources generated as part of this project; however, in the coming year, the results of this study will be disseminated to the public through peer-reviewed journals and scientific conferences.

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