Isocyanates and Work-Related Asthma: Findings From California, Massachusetts, Michigan, and New Jersey, 1993–2008

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Background *Isocyanates remain a leading cause of work-related asthma (WRA).*
Methods *Two independent data systems were analyzed for the period 1993–2008: (1) State-based WRA case surveillance data on persons with isocyanate-induced WRA from four states, and (2) Occupational Safety and Health Administration (OSHA) Integrated Management Information System (IMIS) isocyanate air sampling results.*
Results *We identified 368 cases of isocyanate-induced WRA from 32 industries and 678 OSHA isocyanate air samples with detectable levels from 31 industries. Seventeen industries were unique to one or the other dataset.*
Conclusion *Isocyanate-induced WRA continues to occur in a wide variety of industries. Two data systems uncovered industries with isocyanate exposures and/or illness. Improved control measures and standards, including medical surveillance, are needed. More emphasis is needed on task-specific guidance, spill clean-up procedures, skin and respiratory protection, and targeted medical monitoring to mitigate the hazards of isocyanate use.* Am. J. Ind. Med. 58:1138–1149, 2015. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

The respiratory hazards of isocyanates were first reported in the 1950s and isocyanates were recognized as a cause of work-related asthma (WRA) by the end of that decade [Woodbury, 1956; Hama, 1957; Walworth and Virchow, 1959; Elkins et al., 1962; Brugsch and Elkins, 1963; Gandevia, 1963; Longley, 1964]. Today, isocyanates remain a leading cause of WRA in industrialized countries [Meredith et al., 2000; Bello et al., 2004; Redlich et al., 2006; Vandenplas 2011], inducing asthma in 1–30% of exposed workers [Wisnewski et al., 2006; Bello et al., 2007; Lockey et al., 2015]. WRA includes both new-onset asthma induced by exposure to irritants or sensitizers in the workplace and pre-existing asthma exacerbated by workplace exposure [Jajosky et al., 1999]. Exposure to isocyanates may occur through inhalation or dermal contact [Bello et al., 2007; Redlich and Herrick, 2008;

Liu, 2009; Redlich, 2010]. In individuals who are sensitized to isocyanates, asthma attacks with immediate, delayed, or dual-onset symptoms may be triggered by exposures to concentrations of isocyanates well below occupational exposure limits [Wegman et al., 1974; Banks et al., 1989; Lemiere et al., 2002]. The physiologic mechanism of how isocyanates cause asthma is not fully understood. Nevertheless, the lag between exposure and symptom onset along with the recurrence of asthma attacks from re-exposure to low concentrations are consistent with an immune-mediated model [Woodbury, 1956; Wisnewski and Jones, 2010].

Isocyanates are a group of highly reactive, low molecular weight compounds containing the functional group —N=C=O, and are classified as aliphatic or aromatic [Bello et al., 2004]. Common forms include the aromatic methylene bisphenyl diisocyanate (MDI) and toluene diisocyanate (TDI); and the aliphatic hexamethlyene diisocyanate (HDI). Polyisocyanates are a mixture of diisocyanate monomers and other diisocyanate reaction products; prepolymers are created from the reaction of polyols with di- or polyisocyanates [Vandenplas et al., 1992; Redlich et al., 2006]. Both polyisocyanates and prepolymers have free isocyanate groups (—N=C=O), and can therefore undergo further reactions.

Isocyanates are used in a number of products, including paints, coatings, polyurethane products, foams (rigid and flexible), adhesives, and sealants, across a variety of industries [Wisnewski et al., 2006]. The American Chemistry Council reported that 4,143 million pounds of isocyanate-containing polyurethane products were used in the United States in 2010, with the building and construction industry accounting for more than one-third of that total [American Chemistry Council, 2011].

The objective of this study was to use data from state-based WRA surveillance and Occupational Safety and Health Administration (OSHA) Integrated Management Information System (IMIS) isocyanate air sampling to identify industries in the four states where workers have become ill, or may be at risk of exposure to potentially hazardous levels of isocyanates. In California, Massachusetts, and New Jersey, the WRA surveillance systems and the IMIS data system are independent sources of information about isocyanates in the workplace. In Michigan, data from the WRA surveillance system and the IMIS data system can be linked, as many isocyanate inspections were based on referrals from the WRA surveillance program.

MATERIALS AND METHODS

State-Based WRA Surveillance Data

From 1993 through 2008, the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention funded surveillance of WRA in four states: California, Massachusetts, Michigan, and New Jersey. The states used multiple data sources to identify persons with WRA and compile demographic, industry, and exposure information. The methods for WRA surveillance case identification, confirmation, and classification have been previously described [Rosenman et al., 1997; Henneberger et al., 1999; Jajosky et al., 1999; Rosenman et al., 2003 Pechter et al., 2005; Mazurek et al., 2008]. The surveillance case definition for WRA required a health-care professional's diagnosis consistent with asthma and an association between symptoms of asthma and work [Jajosky et al., 1999]. Each case was classified into one of the following categories: work-aggravated asthma (WAA) defined as pre-existing asthma exacerbated by workplace exposures, or new-onset asthma (NOA) defined as asthma in a person with no history of asthma or preexisting asthma that has been asymptomatic for at least two years prior to the onset of work-related symptoms. NOA included reactive airways dysfunction syndrome (RADS), a non-immunologic asthma lasting at least three months typically caused by a single exposure to high levels of an irritating vapor, gas, fume, or smoke; and occupational asthma (OA), which developed after a period of asymptomatic exposure to an etiologic agent. Surveillance data also included WRA cases for which there was insufficient information to classify into the above categories.

Industry was coded according to the 1987 Standard Industrial Classification (SIC). Reported exposures were coded according to the Association of Occupational and Environmental Clinics (AOEC) Exposure Codes. The AOEC exposure codes 221.00–221.06 were used to identify cases of WRA associated with isocyanate exposure [AOEC, 2014]. We analyzed all WRA cases for the period January 1, 1993 through December 31, 2008 for which an isocyanate was reported as at least one of the three possible exposures associated with the WRA. We analyzed the frequency and proportion of isocyanate-induced WRA cases by industry, age, gender, race and ethnicity using SAS® version 9.2 (SAS Institute, Cary, NC). Use of workers' compensation (WC) by cases, as reported on interview or medical record review, was also examined.

OSHA IMIS Sampling Data

The Occupational Safety and Health Administration (OSHA) launched the Integrated Management Information System (IMIS) database in 1984. The IMIS database contained information on inspection history for inspected establishments, any citations issued, standards cited, complaints investigated, employer-requested consultation evaluations, and air sampling results [USDOL, 2012]. Air sampling for isocyanates was conducted using standard protocols, as specified in OSHA's Sampling and Analytical Methods [OSHA, 2015].

Through an agreement with OSHA, access was granted to use the IMIS database of air-sampling results for 1993 through 2008 from the four states. Methods used in analyzing the IMIS data were based on Henn et al. [2011]. Nationwide air sampling data were extracted for the following isocyanates: MDI, TDI, HDI and its biuret, isophorone diisocyanate (IPDI), 1,5 naphthalene diisocyanate (NDI), and methylene bis (4-cyclohexylisocyanate). There were 9,379 air samples collected for all isocyanates in the United States over the 16-year period, of which 1,908 were in the four states under study. These included results collected by federal OSHA in Massachusetts and New Jersey, California OSHA (Cal/OSHA) and Michigan OSHA (MIOSHA) to evaluate exposures to isocyanates as part of either enforcement or employer consultation worksite visits. Sampling results were excluded if they were coded as not detected, not found or not valid, where the exposure level was zero, or where units for the sample were missing. The remaining samples were considered "detectable" and retained for analysis. Detectable samples were used as a proxy for worker exposure. Industry information in the IMIS data was coded according to 1987 SIC. Data were analyzed by state and by SIC to identify industries with potential worker exposure to isocyanates.

Detectable samples were compared to the relevant Permissible Exposure Limits (PELs) as promulgated by OSHA, Cal/OSHA, and MIOSHA. Sample results that were greater than the respective federal or state standard were considered overexposures (Supplemental Material: Table I: A summary of the enforceable PELs and guidelines set by NIOSH, the Recommended Exposure Limits [RELs], and the American Conference of Governmental Industrial Hygienists [ACGIH] Threshold Limit Values [TLVs]). It is important to note that federal OSHA has PELs only for MDI and 2,4-TDI and that these are ceiling exposure limits, not 8 hr time-weighted averages (TWAs). NIOSH and ACGIH recommended guidelines and state regulations also include 8 hr TWAs and Short Term Exposure Limits (STELs), as well as "skin" designations for some of the isocyanates.

Protection of Human Subjects

As part of requirements for the NIOSH funded grants, the following Institutional Review Boards reviewed and approved the respective asthma projects including approval of obtaining informed verbal consent from participating subjects: State of California Committee for the Protection of Human Subjects; Massachusetts Department of Public Health Institutional Review Board; Michigan State University Human Subjects Review Board; and New Jersey Department of Health's Institutional Review Board.

RESULTS

State-Based WRA Surveillance Data

A total of 368 cases of WRA associated with isocyanate exposure were identified by the four states. Examples of case reports from each state are included (Supplemental Material: Case Reports). Demographics, including age, gender, race, and ethnicity are presented in Table I. Cases ranged in age from 19 to 78 years (mean: 42.5 years). Most cases were male (n = 225, 61%), white (n = 280, 76%), and non-Hispanic/Latino (n = 295, 80%). Michigan had the greatest total number of cases (n = 268).

Of the 368 WRA cases, 347 (94%) were classified as NOA, 14 (4%) were classified as WAA, and for seven (2%) there was insufficient information to classify. The NOA cases included 18 (5% of 368) cases of RADS and 329 (89% of 368) cases of OA (Table II).

Among the 312 cases for which WC filing status was known, a total of 173 (56%) reported filing a claim; California 63%, Massachusetts 74%, Michigan 52%, and New Jersey 57%. Of the 173 who had filed a claim, 171 (99%) had a known outcome; 62 (36%) reported having received WC benefits, 86 (50%) claims were pending at the time of the interview, and 23 (13%) individuals were denied WC benefits.

The types of isocyanate exposures reported by isocyanate-induced WRA cases by state are listed in Table III. Half (n = 195, 50%) of the reported exposures were coded for a specific isocyanate, and the most common isocyanates reported were MDI (n = 88, 24%) and TDI (n = 86, 23%).

Isocyanates are frequently used with other chemicals. We examined additional non-isocyanate chemical exposures for those persons identified with isocyanate-induced WRA. In total, 101 non-isocyanate exposures were identified. The most frequent agent categories were: solvents (n = 24), glues/resins (n = 14), nonmetal dusts (n = 11), paints (n = 10), metals/metal dusts (n = 7), and cleaning chemicals (n = 6).

OSHA Sampling Data

Of the 1,908 air samples for isocyanates collected from California, Massachusetts, Michigan, and New Jersey from 1993 through 2008, 678 (36%) had detectable levels. The detectable samples were evenly divided between consultation site visit samples (n = 343, 51%) and enforcement site visit samples (n = 335, 49%). Because industry sectors may have contained data from only one worksite, we examined the distribution of detectable samples by worksite using enforcement data (information on worksite was not sufficient in consultation data). The number of detectable samples per worksite varied. We found, using enforcement data, that the distribution of the number of detectable samples per worksite

TABLE I. Number and Percentage of Isocyanate Work-Related Asthma Cases by Select Demographic Characteristics and State, 1993–2008

	California		Massachusetts		Michigan		New Jersey		Total	
	Number	%	Number	%	Number	%	Number	%	Number	%
Total[a]	44	12	43	12	268	73	13	4	368	100
Age										
18–34	12	27	11	26	55	21	3	23	81	22
35–49	24	55	22	51	143	53	6	46	195	53
50–64	8	18	10	23	67	25	3	23	88	24
65+	—	—	—	—	3	1	1	8	4	1
Gender										
Female	14	32	8	19	117	44	4	31	143	39
Male	30	68	35	81	151	56	9	69	225	61
Race										
American Indian, Alaska Native	3	7	2	5	3	1	—	—	8	2
Asian	2	5	1	2	2	1	—	—	5	1
African American	3	7	2	5	39	15	1	8	45	12
White	19	43	32	75	219	82	10	77	280	76
Other (including more than one race)	4	9	5	12	2	1	1	8	12	3
Dont know[b]	13	30	1	2	3	1	1	8	18	5
Ethnicity										
Hispanic or Latino	10	23	3	7	2	1	3	23	18	5
Not Hispanic or Latino	22	50	38	89	228	85	7	54	295	80
Dont Know[b]	12	27	2	5	38	14	3	23	55	15

– Indicates no cases ascertained.
[a]Total may not add to 100% due to rounding.
[b]Includes unknown and missing responses.

was similar to the distribution of detectable samples by industry sector (data not shown). Notably, only 80 (12%) of the sample results exceeded their respective PELs.

Industry Findings

Data from both sources were analyzed to detect similarities and differences by industry. The industries with the most isocyanate-induced WRA cases were *Transportation Equipment Manufacturing* (SIC 37, n = 155); *Rubber and Miscellaneous Plastics Manufacturing* (SIC 30, n = 27); and *Chemicals and Allied Products Manufacturing* (SIC 28, n = 26). The industries with the largest numbers of detectable air samples were *Auto Repair Services* (SIC 75, n = 155 with 40 samples greater than the respective PEL [40>PEL]), *Rubber and Miscellaneous Plastics Manufacturing* (SIC 30, n = 100; 8>PEL), and *Transportation Equipment Manufacturing* (SIC 37, n = 80; 15>PEL). Overall, state-based WRA surveillance identified eight industries where 27 cases of isocyanate-induced WRA worked and no detectable samples were reported in the OSHA IMIS database. In turn, IMIS identified eight industries in which there were no cases of WRA (Table IV).

TABLE II. Classification of Isocyanate Work-Related Asthma Cases—California, Massachusetts, Michigan, and New Jersey, 1993–2008

	Isocyanate Cases		Total WRA Cases	
Classification of work-related asthma	Number	%	Number	%
Work-aggravated asthma	14	4	1,654	20
New onset asthma	347	94	4,230	51
Reactive airways dysfunction syndrome	18	5	609	7
Occupational asthma	329	89	3,621	44
Insufficient data to classify	7	2	2,355	29
Total	368	100	8,239	100

DISCUSSION

Identification of Industries Associated With Isocyanates in the Two Systems

Potentially hazardous exposures to isocyanates, as indicated by the presence of a case of isocyanate-induced WRA, an air sample with detectable level of isocyanate, or both, continue in a wide variety of industries. In this report,

TABLE III. Number and Percentage of Reported Diisocyanate Exposures Among Isocyanate Work-Related Asthma Cases by State, 1993–2008

		California		Massachusetts		Michigan		New Jersey		Total	
Agent	**AOEC code[a]**	**Number**	**%**	**Number**	**%**	**Number**	**%**	**Number**	**%**	**Number**	**%**
Diisocyanates, NOS	221.00	30	64	30	63	132	47	3	23	195	50
Toluene diisocyanate	221.01	9	19	10	21	64	23	3	23	86	22
Methylene bisphenyl diisocyanate	221.02	8	17	6	13	68	24	6	46	88	23
Napthalene diisocyanate	221.03	—	—	—	—	6	2	—	—	6	2
Hexamethylene diisocyanate	221.04	—	—	1	2	13	5	1	8	15	4
Polymethylene polyphenylisocyanate	221.06	—	—	1	2	—	—	—	—	1	0.3
Total[b,c]		47	100	48	100	283	100	13	100	391	100

AOEC, Association of Occupational and Environmental Clinics; NOS, not otherwise specified. – indicates no cases ascertained.
[a]AOEC exposure codes as of June 2012.
[b]Total exceeds 368 because each case may be associated with up to three putative agents.
[c]Total may not add to 100% due to rounding.

many of the industries identified using both data sources such as *Transportation Equipment Manufacturing, Auto Repair Services* and *Rubber and Miscellaneous Plastics Manufacturing* are well recognized as industries that use isocyanates and where workers develop isocyanate-induced WRA [Bonauto et al., 2005; OSHA, 2013a].

We identified industries where the potential for isocyanate exposure is not widely recognized. For example, there were four cases of WRA in the *Textile Mill Products* (SIC 22) industry where isocyanates were used in the lamination process (Supplemental Material: Case Report #1) and three cases in the *Stone*,*Clay*, *Glass*, *and Concrete Products* (SIC 32) industry where isocyanates were used in coatings. We also identified 12 cases of isocyanate-induced WRA in *Sporting and Athletic Goods Manufacturing* (SIC 39) where isocyanates were used in the manufacturing of products such as golf balls (Supplemental Material: Case Report #2). Despite the finding of WRA cases, there were limited numbers of detectable isocyanate samples by OSHA in each of these three SIC codes (40 samples in SIC 22, 10 in SIC 32, and 2 in SIC 39). Several other industries less commonly recognized as posing risks of exposure to isocyanates for workers were found through the presence of WRA cases alone. Isocyanate-induced WRA cases occurred in *Educational Services* (SIC 82) where cases were exposed during school building renovations, *Public Administration* (SIC 92, 97) where, for example, a police officer developed WRA after responding to an isocyanate spill, and *Food and Kindred Products* (SIC 20) where an individual had a secondary exposure to an isocyanate product used in a floor coating in a commercial bakery. To our knowledge, isocyanate-induced WRA cases have not been previously documented in these industries.

The exposures in these industries (SIC 20, 82, 92, 97) are secondary to other activities, and are different from the well-documented process exposures in the *Transportation Equipment Manufacturing* and *Auto Repair Services* industries. For these types of secondary exposures, recognition of isocyanate use, risk anticipation, and exposure avoidance are key to WRA prevention. A number of cases arose from construction and repair activities, in which isocyanates were ingredients in materials used as sealants, roofing or floor and wall coatings. Such secondary exposures may be prevented by careful review of materials to be used, communication about ingredients and necessary cautions, including avoiding bystander exposure and observing reentry protocols.

In addition, there were seven cases of WRA in the *Health Services* (SIC 80) industry where exposure to MDI-containing synthetic orthopedic casting and immobilization cradles have been previously documented [MDPH, 1999; Donnelly et al., 2004; Suojalehto et al., 2011].

It is not surprising that there were cases of WRA in industries with no detectable samples. OSHA does not investigate all isocyanate-using workplaces, nor does it conduct air sampling on every isocyanate-related investigation. More importantly, isocyanates may not be airborne at consistent levels during all work hours. Isocyanate use may be intermittent (e.g., spill cleanup), product-specific, related to infrequent maintenance, or exposure may be indirect [Petsonk et al., 2000; Reeb-Whitaker et al., 2013]. In addition, accurate air sampling for isocyanates is difficult, imprecise, and dependent on whether isocyanates are in gas or aerosol form, the size of the particles, the extraction and laboratory analysis methods used and the effectiveness in capturing monomers and polymers [Streicher et al., 2000; Bello et al., 2004; Lesage et al., 2007; Henneken et al., 2007; Booth et al., 2009; Thomasen et al., 2011; Reeb-Whitaker et al., 2012; Schaeffer et al., 2013; Lockey et al., 2015]. For example, Thomasen et al. [2011] found differential capture of monomer and polymer of HDI and variation depending on whether autobody paint was fast-drying or slow-drying; Lesage et al. [2007] found that filter sampling method results

TABLE IV. Number and Percentage of Isocyanate Work-related Asthma, OSHA Air Samples With Detectable Isocyanates, and Detectable Samples Over the PEL, by Industry—California, Massachusetts, Michigan, and New Jersey, 1993–2008

	WRA cases 1993–2008		OSHA air samples 1993–2008	
Industry (SIC Code)	**Number**	**%**	**Number of detectable samples**	**Number of samples over PEL (/detectables × 100)**
Manufacturing (20, 22–26, 28, 30, 32–39)	289	79	443	35 (8%)
Transportation equipment (37)	155	42	80	15 (19%)
Rubber and miscellaneous plastics (30)	27	7	100	8 (8%)
Chemicals and allied products (28)	26	7	21	1 (5%)
Industrial and commercial machinery (35)	24	7	47	4 (9%)
Miscellaneous manufacturing/sporting and athletic goods (39)	15	4	2	—
Primary metal industries (33)	13	4	22	1 (5%)
Fabricated metal products, except machinery, and transportation (34)	6	2	39	0
Electronic and other electrical equipment and components, except computer equipment (36)	6	2	16	2 (12%)
Lumber and wood products (except furniture) (24)	5	1	6	—
Textile mill products (22)	4	1	40	1 (2%)
Measuring, analyzing, and controlling instruments (38)	3	1	26	2 (8%)
Stone, clay, glass, and concrete products (32)	3	1	10	1 (10%)
Food & kindred products (20)	1	—	—	—
Apparel and other finished products made from fabrics and similar materials (23)	1	—	5	—
Paper and allied products (26)	—	—	18	—
Furniture and fixtures (25)	—	—	9	—
Services (70, 75, 76, 78, 80, 82, 87, 89)	48	13	174	41 (24%)
Auto repair services (75)	23	6	155	40 (26%)
Health services (80)	7	2	—	—
Educational services (82)	6	2	—	—
Engineering, accounting, research, management, and related services (87)	5	1	2	—
Business services (73)	4	1	2	—
Miscellaneous repair services (76)	2	1	2	1 (50%)
Hotels, rooming houses, camps, and other lodging places (70)	1	—	—	—
Services, not elsewhere classified (89)	—	—	12	—
Motion pictures (78)	—	—	1	—
Construction (15–17)	8	2	37	2 (5%)
Special trade contractors: masonry, stonework, plaster (17)	7	2	23	—
Heavy construction, except building (16)	1	—	13	—
Building construction—general contractors and operative builders (15)	—	—	1	—
Transportation, communication, electricity, gas, sanitation services (41, 42, 44, 45, 47, 49)	6	2	15	—
Air transport (45)	2	1	14	—
Motor freight transportation and warehousing (42)	2	1	—	—
Local and suburban transit and interurban highway passenger transportation (41)	1	—	1	—
Electric, gas, and sanitary services (49)	1	—	—	—
Water transport (44)	—	—	3	—
Transportation services (47)	—	—	1	—
Wholesale trade (50, 51)	6	2	3	—
Wholesale trade—nondurable goods (51)	3	1	2	—

(*Continued*)

TABLE IV. (*Continued*)

Industry (SIC Code)	WRA cases 1993–2008 Number	%	OSHA air samples 1993–2008 Number of detectable samples	Number of samples over PEL (/detectables × 100)
Wholesale trade—durable goods (50)	3	1	1	—
Public administration (92, 97)	5	1	—	—
Justice, public order, and safety (92)	4	1	—	—
National security and international affairs (97)	1	—	—	—
Retail trade (52, 55)	4	1	6	2 (33%)
Automotive dealers and gas service stations (55)	4	1	—	—
Building materials, hardware, garden supply, and mobile home dealers (52)	—	—	6	—
Total[a]	366	100	678	80 (12%)

OSHA, Occupational Safety and Health Administration; PEL, Permissible Exposure Limit; SIC, Standard Industrial Classification; WRA, Work-related Asthma. – indicates no cases/samples ascertained.
[a]Two cases were missing an industry code.

were up to 40% lower than results from impinger methods. OSHA has since altered their filter handling methods to improve accuracy by requiring field extraction [OSHA, 2013a]. In addition, the primary route of exposure that caused respiratory sensitization may have been dermal [Bello et al., 2007] and some workers may develop WRA from exposure to airborne isocyanates at levels below the limit of detection [Banks et al., 1989].

We did, however, identify additional industries with detectable levels of isocyanates where workers may be at risk, but no isocyanate-induced WRA cases were ascertained, for example: *Paper and Allied Products Manufacturing* (SIC 26), *Services Not Elsewhere Classified* (SIC 89), *Furniture and Fixtures Manufacturing* (SIC 25), and *Building Materials, Hardware, Garden Supply and Mobile Home Dealers* (SIC 52). Not all cases of WRA are identified and reported (see Limitations of Data Systems).

Michigan was the only state in which OSHA IMIS data could be linked with state-based WRA surveillance data. Of the 268 isocyanate-induced WRA cases ascertained in Michigan, 194 (72%) were associated with 106 MIOSHA inspections. Although MIOSHA sampling was conducted in 84 (79%) of the 106 inspections, none of the air samples collected were above the PEL for the respective isocyanate (data not shown). WRA developed despite isocyanate air concentrations found to be less than the PEL subsequent to diagnosis of WRA, as described in Case Report # 3 (Supplemental Material). While it is possible that some workers with WRA had previously experienced higher levels of exposure, these findings suggest that compliance with MIOSHA PELs was not sufficient to prevent WRA.

Workers' Compensation

The finding that only 56% of individuals with isocyanate-induced WRA had filed for WC benefits to which they may be entitled is consistent with prior reports that individuals with WRA may never apply for WC [Azaroff et al., 2002; Luckhaupt and Calvert, 2010]. It is not known why individuals with isocyanate-induced WRA did not file WC claims, which could have covered the medical treatment for asthma, including asthma medication, job retraining, and provided lost income coverage [Biddle et al., 1998]. The denial of benefits for 13% of claims for this well-recognized hazard is of concern. A better understanding of methods to overcome barriers to filing WC claims and receiving benefits by both workers and healthcare providers is needed [Azaroff et al., 2002].

Limitations of Data Systems

Limitations of state-based WRA surveillance have been discussed previously [Rosenman et al., 1997; Henneberger et al., 1999; Jajosky et al., 1999; Rosenman et al., 2003; Pechter et al., 2005; Mazurek et al., 2008]. The number of WRA cases ascertained by state-based surveillance underestimates the true number of cases, and cases ascertained may not be representative of all WRA in the underlying population [Jajosky et al., 1999]. In a capture-recapture analysis conducted in Michigan, the surveillance system was shown to have missed 53–87% of WRA cases in the state [Henneberger et al., 1999]. This was largely due to underreporting, despite the fact that healthcare providers were legally mandated to report WRA. Sama et al.

[2003] found that only 7% of adult New England Health Maintenance Organization (HMO) members with new-onset asthma had medical record documentation that they were asked about workplace exposures by their health care providers. Mazurek and Storey [2012] found that only 13.5% of adults with asthma had ever discussed with their healthcare provider whether their asthma could be work related. Diagnosis of WRA may be challenging due to difficulty in linking workplace exposures with disease, especially in cases of delayed symptoms and delayed onset of disease [Tarlo et al., 2008].

The work-related asthma cases in this study are based on a physicians' diagnosis of asthma, clinical and occupational information, including exposures, onset, timing, severity related to work [Jajosky et al., 1999; Tarlo et al., 2008]. Less than 10% of cases in the WRA surveillance system have peak flow or spirometry performed in relationship to work, and none had specific antigen challenge testing. This reflects the standard of medical care for diagnosing WRA in the United States [Tarlo et al., 2008]. The lack of breathing tests performed in relationship to work and specific antigen challenge testing may lead to over diagnosis of WRA. In addition, cases may have been attributed to isocyanate exposures when other exposures were the etiologic agents. This may also be true for RADS, where although individual case reports of RADS after isocyanate exposure have been reported [Luo et al., 1990; Shakeri et al., 2008; Baur et al., 2012], it is possible that some of the RADS cases we have included may have been from spills/leaks of other chemicals present with the isocyanates.

The IMIS data are a valuable indicator of potential worker exposure in various workplaces, but this database was not designed as an exposure surveillance system. The presence of detectable air samples of isocyanates in the OSHA IMIS dataset was selected as the most conservative indicator of potential airborne exposure to isocyanates, with possible risk of development of disease. Workers might also be at risk from dermal contact, intermittent exposures not captured in the sampling, and exposure to very low concentrations, below the limit of detection. However, the detectable levels recorded are tangible evidence that isocyanates were in the workplace air at the time of sampling.

The OSHA IMIS data may not be representative of all workplace isocyanate exposures; they reflect only the exposures in worksites either inspected for compliance, or visited in response to employer requests. In the four states, over the 16-year period, 356 worksites had federal OSHA, Cal/OSHA or MIOSHA enforcement visits that included air sampling for isocyanates. A report from Michigan showed that of the 103 companies known to use large quantities of isocyanates in that state, 32 (31%) had a MIOSHA enforcement inspection, and in 21 of the 32 the inspector proceeded to conduct air sampling [MSUDOM, 2013]. It is not possible to determine the percentage of all companies using isocyanates that MIOSHA investigated, as no comprehensive list of companies that use isocyanates exists in Michigan or any other state.

The data in IMIS were incomplete and had errors. There is likely differential underreporting of non-detectable samples [Lavoue et al., 2013a] and likely underreporting of detectable samples for isocyanates without PELs, adding to barriers to retrieving complete data [Lavoue et al., 2013b; Williams 2014]. IMIS nondetectable results could not be used to estimate isocyanate air concentrations. Without documented data about the duration of sampling or the limit of detection (LOD), a midpoint between zero and the LOD could not be used to calculate an estimated concentration for non-detectable results. The absence of detectable levels is not equivalent to no exposure. Skin exposures were not considered in these data even though skin absorption may be a significant exposure source [Liu et al., 2009; Redlich, 2010]. Moreover, no information was available to assess the validity of the OSHA IMIS data.

Prevention

Strategies to replace isocyanates with safer products and to prevent WRA are important in all industries where isocyanates are used. Since reducing exposure to isocyanates helps prevent the development of new cases and exacerbations of WRA in existing cases [Walworth and Virchow, 1959], effective use of engineering controls to minimize exposure to isocyanates is necessary. Ventilation systems (e.g., spray booths) and personal protective equipment (PPE) to prevent inhalation and dermal contact should be used together [Heederik et al., 2012]. Poor exposure controls and poorly managed PPE use can result in the development of WRA (Supplemental Material: Case Report #4). For example, Washington's Safety and Health Assessment and Research for Prevention (SHARP) program determined that substitution or respiratory protection was needed for paint spray applications on large objects that cannot be accommodated in a spray booth (e.g., aircraft parts, boats, fire engines) [Reeb-Whitaker, 2013].

Respiratory protection programs must include a comprehensive written program and medical evaluation for fitness to wear respirators, as well as proper selection, training, use, and fit testing of respirators [OSHA, 2014a]. In one isocyanate-induced WRA case where the worker subsequently died, the worker was wearing a positive-pressure supplied-air respirator while applying a spray-on truck bed liner. However, the supply line was too long for the pump, and the worker had not been fit-tested, trained on the hazards of isocyanates, nor provided a medical evaluation or periodic screening [Michigan FACE, 2003; Chester et al., 2005].

Periodic medical screening of all isocyanate exposed workers with removal of those who develop isocyanate-induced WRA, especially in the early years of work, is vital to reduce morbidity [Chan-Yeung, 1986; Wild et al., 2005; Labrecque et al., 2011; Tarlo and Lemiere, 2014]. Preplacement screening has not been shown to be effective in identifying individuals who should be excluded from being hired [Tarlo et al., 2008; Wilken et al., 2012]. An example of the benefits of early removal from exposure can be found in Case Report #3 (Supplemental Material: Case Reports), where a worker with isocyanate-induced WRA became asymptomatic after being removed from the workplace.

A decline in isocyanate-induced asthma cases has been described in the UK and Canada [Ribeiro 2014; Walters et al., 2015]. The number of isocyanate-induced WRA cases has declined from 1993 to 2008 in all four states (data not shown). Postulated reasons for the decline are many, including health care provider reporter fatigue, absence of medical surveillance of exposed workers, improved controls and the substitute of less volatile isocyanates such as prepolymers [Lockey et al 2015; Walters et al., 2015]. Despite the apparent decline, measures should be implemented to further reduce this preventable disease.

Adequacy of Existing PELs

Currently, PELs for many isocyanates, including new variations of isocyanates, do not exist. Moreover, OSHA, MIOSHA, and CalOSHA did not issue many citations for exposures over the existing PELs. However, companies inspected for isocyanate issues were cited for failure to do a hazard assessment, provide hazard communication and use PPE, indicating lapses in worker protection. The PELs in place do not protect those who are already sensitized, since exposures below the PELs can trigger symptoms [Lemiere et al., 2002]. Additionally, exposures below the PELs may induce sensitization, with dermal contact as a contributory element. [Reilly et al., 2001; Matheson et.al, 2005]. Significantly, in its 1989 proposed standard (Health Effects Discussion and Determination of Final PEL), OSHA cited multiple studies stating that workers can develop sensitization reactions to TDI at exposure levels below the 0.02 ppm level [OSHA, 1989]. Also, the current sampling methods may underestimate exposures for many reasons, as described above. Therefore, PELs should be updated where they exist and a comprehensive standard should be developed for all isocyanates that addresses task-specific guidance, spill clean-up procedures, skin and respiratory protection, and targeted medical surveillance and medical removal protection [Tarlo et al., 2002; Pronk et al., 2006; Booth et al., 2009; Cocker 2011; Baur et al., 2012; Wisnewski et al., 2012; Pearson et al., 2013; Williams, 2014].

In June 2013, OSHA developed a National Emphasis Program (NEP) to reduce or eliminate the incidence of adverse health effects, including asthma, associated with workplace exposure to isocyanates [OSHA, 2013a]. The OSHA NEP on isocyanates includes field enforcement guidance, and suggested industries where isocyanate exposures were known or likely to occur and encouraged communication with state-based WRA surveillance programs to identify industries where isocyanate induced WRA had occurred. OSHA developed a fact sheet for workers and clinicians to use to assist in early health assessments of WRA [OSHA, 2014b]. In addition, OSHA recognized that many of the adopted PELs are inadequate, and developed annotated PEL tables to aid employers in evaluating the best way to protect workers [OSHA, 2013b].

CONCLUSION

Detectable isocyanate exposures and isocyanate-induced WRA cases were found across many industries. Examining sentinel case data from state surveillance systems and exposure data collected by OSHA gives a more comprehensive picture of the widespread use and health consequences of isocyanates than either system alone.

Employers should be vigilant about reducing or eliminating worker exposure to isocyanates. Substitution, engineering controls, administrative changes, personal protective equipment, hazard awareness and education, medical monitoring, and best practices in product usage are recommended. OSHA's current NEP for isocyanates is an important first step in both increasing awareness of the ongoing hazards of isocyanates and identifying solutions to reduce the risk from their use. Additional consideration should be given to the development of a comprehensive standard for isocyanates that also promotes education, medical monitoring, and worksite evaluation and control. Finally, cases of WRA identified by health care providers should trigger evaluation of the workplace by health and safety professionals to protect coworkers, provide insight about exposures, and promote the development of asthma prevention strategies.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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