Miller, Diane M. (CDC/NIOSH/EID)

From: Weinberg, Justine (CDPH-OHB) [Justine.Weinberg@cdph.ca.gov]
Sent: Thursday, October 22, 2009 7:16 PM
To: NIOSH Docket Office (CDC)
Cc: Flattery, Jennifer (CDPH-OHB)
Subject: Docket Number NIOSH-186 - Request for information on Glutaradehyde
Attachments: hcw.pdf; glutaraldehyde.pdf; glutaraldehydeJOEH.pdf

NIOSH:

I understand that you are requesting information on workplaces in which glutaraldehyde can be found, health effects observed in workers exposed to glutaraldehyde, a description of work tasks and scenarios with a potential for exposure to glutaraldehyde, workplace exposure data, and information on control measures.

Our Work-Related Asthma Prevention Program at the California Department of Public Health Occupational Health Branch conducts surveillance and investigates workplaces, aiming to identify industries, occupations and exposures that put workers at risk for work-related asthma. We have investigated the use of glutaraldehyde in the heart valve industry in California. I am both attaching and including links to our report and journal article regarding this work that provide information along the lines that you are requesting.

Report: http://www.cdph.ca.gov/programs/ohsep/Documents/glutaraldehyde.pdf
Journal of Occupational and Environmental Health article:
http://www.cdph.ca.gov/programs/ohsep/Documents/glutaraldehydeJOEH.pdf

In addition, our program along with three other state programs that conduct work-related asthma surveillance (Michigan, Massachusetts, and New Jersey) have also identified glutaraldehyde as an exposure among health care industry workers with work-related asthma. This was reported in the American Journal of Industrial Medicine: http://www.cdph.ca.gov/programs/ohsep/Documents/hcw.pdf

For information about our program: http://www.cdph.ca.gov/programs/ohsep/Pages/Asthma.aspx

Please contact me if you have any questions.

Sincerely,

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Work-Related Asthma Among Health Care Workers: Surveillance Data From California, Massachusetts, Michigan, and New Jersey, 1993–1997

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Background *Asthma morbidity has increased, posing a public health burden. Work-related asthma (WRA) accounts for a significant proportion of adult asthma that causes serious personal and economic consequences.*

Methods *Cases were identified using physician reports and hospital discharge data, as part of four state-based surveillance systems. We used structured interviews to confirm cases and identify occupations and exposures associated with WRA.*

Results *Health care workers (HCWs) accounted for 16% (n = 305) of the 1,879 confirmed WRA cases, but only 8% of the states' workforce. Cases primarily were employed in hospitals and were nurses. The most commonly reported exposures were cleaning products, latex, and poor air quality.*

Conclusions *Health care workers are at risk for work-related asthma. Health care providers need to recognize this risk of WRA, as early diagnosis will decrease the morbidity associated with WRA. Careful product purchasing and facility maintenance by health care institutions will decrease the risk.* Am. J. Ind. Med. 47:265–275, 2005.

KEY WORDS: asthma; surveillance; occupational; work-related; health care; hospital; cleaning products

INTRODUCTION

Asthma is a serious, chronic disease recognized as a critical public health problem in the United States. Morbidity and mortality associated with asthma has increased markedly during the last several decades [Chan-Yeung, 1995; Mannino et al., 1988, 2002; Arif et al., 2002; Oguntomilade et al., 2002]. The proportion of adult new-onset asthma that is work-related has been estimated between 5% and 29% [Milton et al., 1998; Blanc and Toren, 1999; Blanc et al., 1999; Kogevinas et al., 1999; Bakke and Gulsvik, 2000; Mannino, 2000, Karjalainen et al., 2001]. The American Thoracic Society estimated the occupational contribution to the population burden of adult asthma as 15% [American Thoracic Society, 2003].

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Work-related asthma (WRA) may have serious consequences for those affected. In a Canadian study, persons with new-onset asthma associated with work were more likely to be hospitalized than other workers [Liss et al., 2000]. Individuals with WRA may become sensitive to a variety of exposures that may exacerbate breathing problems even when away from work, and some change or leave careers with serious personal and economic ramifications [Cannon et al., 1995]. Direct and indirect costs attributable to WRA in the United States were estimated at $1.6 billion per year [Leigh et al., 2002].

As an industry, health services is growing at twice the rate of the overall economy and the number of health care workers (HCWs) continues to increase. This sector's projected 2.5% average annual employment growth rate will yield 2.8 million new jobs by 2010 [Berman, 2001]. The Bureau of Labor Statistics projects big increases among home health care aides (62%), medical assistants (57%), and nurses (26%) [Bureau of Labor Statistics, 2000].

Information about biological, chemical, and ergonomic hazards for HCWs has become more available in the last 20 years [Bermel, 1983; Omenn and Morris, 1984; Patterson et al., 1985; Emmett and Baetz, 1987; NIOSH, 1988; Behrens and Brackbill, 1993; Collins and Owen, 1996; Aiken et al., 1997; Messing, 1998; Slattery, 1998; Charney, 1999; Lipscomb and Borwegen, 2000; Quinn et al., 2000; Simpson and Severson, 2000; Tait et al., 2000; Clarke et al., 2002; NIOSH, 2002; Nygren et al., 2002]. Occupational injuries and illnesses have increased in health care while they have continued to decline in the workforce as a whole [NIOSH, 2002]. However, WRA among HCWs has not been well documented in the United States, with the exception of asthma associated with latex allergy [Bubak et al., 1992; Kelly et al., 1996; Charous et al., 2002; Dillard et al., 2002].

To characterize WRA cases among HCWs and identify prevention opportunities, we present data in this study from four states (California, Massachusetts, Michigan, and New Jersey) that conduct WRA surveillance as part of the Sentinel Event Notification Systems for Occupational Risks (SENSOR) Program.

METHODS

In 1988, Massachusetts, New Jersey, and Michigan received funding from the National Institute for Occupational Safety and Health (NIOSH) to establish statewide surveillance systems for WRA using the SENSOR model. In 1992, California also received funding. Although New Jersey was not funded for the third 5-year funding cycle beginning in 1997, it continued to participate. The SENSOR model is based on the concept of the sentinel health event which is "a preventable disease, disability or untimely death whose occurrence serves as a warning signal that prevention efforts have failed and others may be at risk [Rutstein et al., 1983]." Using surveillance data, industries, occupations, worksites, and exposures can be identified and targeted for intervention.

Case Ascertainment

The primary source of data for all four states was physician reports. In these states physicians are required by state laws to report cases of asthma caused or aggravated by workplace exposures. In addition to patient demographic information, physicians provide information on the employer and suspected asthma-causing agent. Physician reports were actively solicited through newsletters and ongoing education for the medical community. In California, cases of WRA were identified through Doctor's First Reports (DFRs) of Occupational Injury or Illness, a statewide reporting system tied to physician reimbursement. California labor code mandates that physicians report medical services for known or suspected occupational illnesses or injuries within 5 days of providing care.

In addition to physician reports, Massachusetts, Michigan, and New Jersey periodically reviewed hospital discharge data for cases of WRA and states' workers' compensation systems data for claims filed for WRA. Michigan and New Jersey, but not Massachusetts, identified significant proportions of cases using hospital discharge data for the time period reported in this paper (18% and 13%, respectively). Michigan also queried coworkers of index cases to identify additional cases. Workers' compensation data have not been useful for identifying WRA cases because there is no specific code for asthma in the workers' compensation system data.

Case Follow-up

Each state conducted telephone interviews using standardized questionnaires to confirm and obtain more information on reported cases. In addition, Michigan and New Jersey reviewed medical records. Information collected was also used to distinguish between work-related exacerbations of preexisting asthma (work-aggravated asthma) and asthma induced by workplace exposures (new-onset asthma). New-onset asthma was further classified as occupational asthma (with known or unknown inducer) or reactive airways dysfunction syndrome (RADS), a condition involving persistent asthma symptoms following a one-time acute exposure to irritants; this classification scheme has been presented previously [Jajosky et al., 1999]. The exposure(s) identified by the cases were considered known asthma inducers if they had been previously documented in the scientific literature to cause asthma [Chan-Yeung, 1995], and were coded as asthmagens in the Association of Occupational and Environmental Clinics (AOEC) database [Hunting and McDonald, 1995]. Up to three suspected agents were coded and included for each case.

Analysis

All confirmed cases of WRA from 1993 to 1997 were included in the analysis. Industry data were coded using the 1987 Standard Industrial Classification (SIC) codes and occupation data were coded using the 1990 US Bureau of the Census (COC) codes. Industry and occupation information was reviewed to identify HCWs. Our definition of "health care worker" included all cases employed in the health care industry (SIC = 8000–8099), and cases with occupation codes identifying HCWs regardless of industry (COC = 084–089, 095–099, 105, 203–208, 445–447). These codes were selected because they represented the wide variety of occupations and industries in which HCWs were employed, including schools (SIC = 8211), ambulance services (SIC = 4119), and manufacturing. This ensures that the definition of "health care worker" is not limited to physician or nurse.

Comparisons between HCWs and non-HCWs were performed using chi-square statistics. A significance level of $P = 0.01$ was used. As a proxy for relative risk, we compared the proportional distribution of HCWs among the confirmed cases to the proportion of HCWs within the general workforce in the four states.

RESULTS

Between January 1, 1993 and December 31, 1997, the four SENSOR states confirmed 1,879 cases of WRA. Of these, 305 (16%) were identified as HCWs based on our definition. All but 8 cases (n = 297, 97%) worked in settings classified as Health Services, SIC 80, with the greatest number (n = 192, 63%) working in hospitals (Table I).

HCWs accounted for the greatest number of cases in three of the four states: 32% (n = 92) of all the WRA cases in Massachusetts, 18% (n = 29) in New Jersey, and 17% (n = 112) in California. In Michigan, HCWs were second, comprising 9% (n = 72) of the cases (Table II). For comparison purposes, the last column of Table II also presents the number of workers employed in the health sector in each of the four states in 1995, the mid-year of the 5-year analysis. In all four states, the percentage of cases that were HCWs exceeded the percentage of health sector workers in each state (1995, SIC = 80) [Bureau of Labor Statistics, 2002].

Almost 91% of the cases (n = 279) were reported to the state surveillance systems by physicians. Eight percent (n = 23) were identified by review of hospital discharge data. The three remaining cases were identified from either workers compensation records (n = 1) or index case follow-up (n = 2).

Characteristics of the 305 HCWs may be compared to those of the 1,574 non-HCWs reported to the surveillance systems during this period. The median age of HCWs was 41 years compared to 42 years for non-HCWs. The HCWs were significantly more likely to be female (n = 284, 93%, $P \leq 0.01$) and white (n = 241, 79%, $P \leq 0.01$) compared to non-HCWs (n = 788, 50% female and n = 1,134, 72% white). More than half (n = 160, 52%) of the HCWs filed workers' compensation claims, significantly higher than non-HCWs (n = 598, 38% ($P \leq 0.01$)). Of those who filed claims, HCWs were significantly more likely than non-HCWs to be awarded benefits (46% vs. 35%, ($P \leq 0.01$)).

The HCW cases were also reviewed regarding exposures associated with their symptoms; the frequencies of exposures reported by ten or more cases are shown in Table III. At least one agent was coded for each case. Thirty percent of cases reported multiple exposures. Overall, the most commonly reported exposure was cleaning products (24%). Cleaning

TABLE I. Number and Percent of Work-Related Asthma Cases Among Health Care Workers by SIC* Code—California, Massachusetts, Michigan, and New Jersey, 1993–1997

SIC code	Industry	Number of cases	Percent (%)
806	Hospitals	192	63
8011, 8049	Offices and clinics of doctors and health practitioners	44	14
805	Skilled nursing care facilities	17	6
8021	Offices and clinics of dentists	12	4
8071	Medical laboratories	7	2
8082	Home health care services	7	2
8211	Elementary and secondary schools	4	1
4119	Local passenger transportation (ambulance)	4	1
8093	Specialty outpatient facilities	4	1
8092	Kidney dialysis centers	2	<1
	Other[a]	12	4
Total		305	100

*SIC—Standard Industrial Classification.

[a]Includes universities, research institutions, veterinary services, medical service plans, etc.

TABLE II. Number and Percent of Work-Related Asthma Cases by State—California, Massachusetts, Michigan, and New Jersey, 1993–1997

State	Total number of WRA cases	Number of health care workers	Health care workers as a percent of cases (%)	Health care workers[a] as a percent of workforce (%) (and number)
California	663	112	17	7 (851,300)
Massachusetts	292	92	32	11 (315,700)
Michigan	759	72	9	8 (350,700)
New Jersey	165	29	18	9 (307,700)
Totals	1,879	305	16	8 (1,825,400)

[a]Health care workers defined as employed in SIC = 80, Health Services (97% of all cases in this analysis).

products (exposures coded 322.00–322.33 in the AOEC coding, http://www.aoec.org/aoeccode.htm) included ammonia, bleach, carpet cleaners, disinfectants, floor strippers, and several recognized asthmagens (e.g., quaternary ammonium compounds). Exposure to latex, a known asthma inducer, accounted for 20% of the case reports. Other known asthma inducers reported by HCWs included glutaraldehyde (9%) and formaldehyde (5%). Indoor air pollution was reported by 12% of cases. Indoor air pollution was coded if the case reported poor indoor air quality or lack of ventilation. Specific agents associated with poor indoor air quality such as molds, chemical fumes or vapors, or smoke, were coded separately if this information was provided. Molds, some of which are known asthma inducers, were the reported exposure for 5% of cases. Exposures identified by HCWs differed from non-HCWs. Non-HCWs most frequently reported exposures to (in order of frequency) miscellaneous chemicals, cutting oils, indoor air pollution, dust, and smoke.

Table IV lists the most frequently reported exposures by occupation. Frequencies in each agent category represent the number of HCWs with WRA that reported that particular agent. Nurses were most affected by latex (33%), cleaning products (21%), and glutaraldehyde and formaldehyde, together (19%). Office workers and aides/therapists, respectively, identified miscellaneous chemicals, paints, solvents, and glues (31%, 29%), followed by cleaning products (28%, 27%) and new carpet, dust, molds, smoke, and perfume (21%, 10%), which included dust from construction/renovation. Laboratory workers and technicians reported glutaraldehyde and formaldehyde (26%) and dental HCWs reported latex exposures (75%). The "other exposures" category accounted for 27% of all exposures (117/440), and reflects the broad range of products used in health care settings that may induce or exacerbate asthma. Some of the reported exposures were: nitrogen oxides, ethylene glycol, ethyl ether, laboratory animals, freon, isocyanates, pharmaceuticals, and pesticides.

TABLE III. Number and Percent Of Work-Related Asthma Cases Among Health Care Workers by Agent,* Reported by 10 or More Cases—California, Massachusetts, Michigan, and New Jersey, 1993–1997

Exposure	Number of cases	Percent (%)
Cleaning products	74	24
Latex	61	20
Indoor air pollution	37	12
Glutaraldehyde	27	9
Miscellaneous chemicals	27	9
Paints, solvents	21	7
Formaldehyde	15	5
Molds	14	5
Dust	14	5

*Each case may report up to three exposures; each case reported at least one exposure.

The case classification for 305 confirmed HCW cases were compared to the 1,574 confirmed non-HCW cases. Proportionately more non-HCW cases were categorized as new-onset, with unknown inducer compared to HCW (45% vs. 38%) ($P \leq 0.01$). HCW were slightly more likely to be categorized as new onset with known inducer (30% vs. 27%), and more likely to be categorized as work-aggravated (23% vs. 18%). Ten percent of cases were identified as RADS in both groups.

During the interview, cases were asked several questions about their medical history including whether they had ever smoked and whether they had a history of allergies. Forty-five percent (n = 136) answered "yes" to the question, "Have you ever smoked cigarettes?" This may be compared to a population-based estimate of 48% (91.2 million people "ever smoked," of 190.3 million people), in the 1995 National Health Interview Survey (CDC, 1997). More than one-third of the respondents (n = 116, 38%) reported having a history of allergies. Although not directly comparable, estimates of allergic rhinitis among the adult population range from 10% to 30% (AAAAI, 2002).

The HCWs were queried whether they were still exposed to the agents that triggered their asthma. In California,

TABLE IV. Distribution of Exposures* Among Health Care Workers With Work-Related Asthma by Occupation†—California, Massachusetts, Michigan, and New Jersey, 1993–1997, n = 305

Occupation (number of cases)	Cleaning products	Latex	Glutaraldehyde and formaldehyde	Indoor air	Miscellaneous chemicals, paints/solvents, glues	New carpet, dust, molds, smoke, perfume	Other[a] exposures	Total exposures identified
Nurses[b] (123)	26	41	23	22	20	19	39	190
Office workers[c] (61)	17	2	3	6	19	13	22	82
Aides and therapists[d] (41)	11	8	3	3	12	4	17	58
Lab workers and technicians[e] (34)	4	1	9	2	2	8	17	43
Housekeeping and food prep[f] (19)	8	0	0	1	2	3	10	24
Dental health care workers[g] (12)	2	9	1	1	0	0	3	16
Other professional health care[h] (5)	3	0	1	1	0	1	2	8
Others[i] (10)	3	0	2	1	2	4	7	19
Totals (305)	74	61	42	37	57	52	117	440

*Up to three exposures may be coded for every case; each case reported at least one exposure.

†Occupation according to 1990 Census Occupation Code.

[a]Among other exposures are: Toluene, nitrogen oxides, ethylene glycol, ethyl ether, acrylate, laboratory animals, freon, isocyanates, pharmaceuticals, pesticides.

[b]Nurses include RNs (095) and LPNs (207).

[c]Office workers include administrators (014), managers (015, 022), psychologists (167), social workers (174), lawyers (178), health records technician (205), office supervisors (303), secretaries (313), stenographers (314), interviewers (316), receptionists (319), file, record, office and statistical clerks (335, 336, 379, 386), bookkeepers (337), billing clerks (339), telephone operators (348), bill collectors (378), administrative support (389), and welfare service aides (465).

[d]Aides and therapists include respiratory therapists (098), physical therapists (103), health aides (446), and nursing aides (447).

[e]Lab workers and technicians include chemists (073), clinical lab technologists (203), radiologic technicians (206), health technologist (208), biological technicians (223), science technicians (225), technicians, nec (235), and dental lab technicians (678).

[f]Housekeeping and food prep include cooks (436), miscellaneous food prep (444), supervisors, cleaning and building services (448), maids and housemen (449), janitors (453), baggage porters (464), and laundry operators (748).

[g]Dental health care workers include dentists (085), dental hygienists (204), and dental assistants (445).

[h]Other professional health care includes doctors (084), health diagnosing practitioners (089), and physician assistants (106).

[i]Others include inspectors (036), engineers (059), veterinarians (086), speech therapists (104), therapists nec (105), recreation workers (175), firefighting supervisors (413), photographic process operators (774), and miscellaneous machine operators (777).

Michigan, and Massachusetts, 43%, 28%, and 21%, respectively, of the cases (data not available from New Jersey) reported they were still exposed in the same facility to the identified agent(s). In some of the remaining cases, changes were made to reduce exposure, or transfer the affected worker to another area. In other cases, HCWs left employment. In Massachusetts, 20 workers reported they were fired or quit due to breathing problems; another 25 reportedly were still out of work on compensation at the time of the interview, for a total of 45 (48%) who were not at their usual jobs. In California, 35 (31%) reported they were fired, laid off, or stopped work on their physician's orders. In Michigan, 20 (28%) reported they were no longer working, among whom were three hospital workers who reported they were fired for "taking too much sick leave;" the sick leave was reportedly due to hospital stays and/or emergency room visits.

DISCUSSION

Surveillance findings from four states indicated that HCWs, a large and increasing worker population, are at risk for WRA. Sentinel surveillance offers opportunities for prevention by identifying populations at risk and hazards. In addition, the workplace provides opportunities for health promotion. Wellness efforts have been more effective when integrated with improved workplace protection [Walsh et al., 1991; Sorenson et al., 1996, 2002]. The disproportionate number of cases among HCWs is consistent with reports from other countries [Provencher et al., 1997; Bena et al., 1999; Ross, 1999; McDonald et al., 2000; Esterhuizen et al., 2001; Hnizdo et al., 2001; Kopferschmitt-Kubler et al., 2002], and with the use in health care settings of well documented sensitizers and exposures to agents that cause or exacerbate asthma.

The SWORD (Surveillance of Work-related and Occupational Respiratory Disease) system in the UK found that the rate of occupational asthma in the health care industry was nearly 2.5 times the overall industry rate [Ross, 1999]. SWORD also identified latex as the fourth most common asthmagen and found a high incidence of occupational asthma in laboratory technicians, nurses, and radiographers [McDonald et al., 2000]. The SORDSA (Surveillance of work related and Occupational Respiratory Diseases programme in South Africa) system in South Africa identified

the largest number of WRA cases in the health care industry (16%) and found latex to be the most frequent exposure identified among cases (24%) [Esterhuizen et al., 2001; Hnizdo et al., 2001]. SORDSA identified occupational asthma among nurses, ICU workers, laboratory workers, and radiographers. The PriOR system in Italy found the largest number of cases and the third highest rate of WRA among HCWs [Bena et al., 1999]. The Observatoire National de Asthmes Professionnels, a voluntary reporting system for WRA in France, found that the rate of WRA among French HCWs was second only to bakers. Latex was the third most likely etiologic agent identified [Kopferschmitt-Kubler et al., 2002]. Karjalainen et al. [2001] found an increased relative risk for occupational asthma among medical and nursing workers in Finland compared to workers in administrative work. On the other hand, asthma among HCWs in Quebec was too infrequently reported to merit listing among the top seven industries noted from the PROPULSE system [Provencher et al., 1997].

Data from the National Center for Health Statistics' third National Health and Nutrition Examination Survey (NHANES) of the US population indicate that the hospital industry was associated with the highest estimated asthma prevalence for nonsmokers—14.4% (95% CI = 8.1–20.7) or more than twice the estimated asthma prevalence among non-smokers overall—6.6% (95% CI = 5.8–7.4) [NIOSH, 1999b]. The NHANES Survey did not assess work-relatedness of individual cases.

Strengths and Limitations of the Data

SENSOR data cannot provide estimates of the true incidence or prevalence of WRA. Although all four states have mandatory reporting laws, WRA is both under-diagnosed and under-reported by physicians. In some cases the symptoms of asthma are not diagnosed [Deprez et al., 2002], while in others, the links to work are not made [Milton et al., 1998]. Other methods and analyses have provided better estimates of WRA incidence rates and population attributable risk [Milton et al., 1998; Henneberger et al., 1999; Bakke and Gulsvik, 2000; Karjalainen et al., 2001; Arif et al., 2002; Mannino et al., 2002].

The apparent disproportion of cases among HCWs may reflect differential diagnosis, reporting, and case confirmation among this workforce. Employees in health care probably have greater access to care and information about illness than non-HCWs. Among the 305 cases reported in the four states, 63% worked in hospitals with potential access to employee health services. In addition, approximately half were categorized as nurses, physicians, therapists, or aides, all of whom have received education about health-related issues. This factor probably increases the number of workers who recognize asthma symptoms and seek care and may contribute to the higher proportion of HCWs with work-aggravated asthma (23% vs. 18%). In addition, HCWs with new-onset WRA were more likely to have a known inducer identified than non-HCWs with new-onset WRA ($P = 0.06$), which may result from physicians' familiarity with some of the asthma inducers in their own work settings, such as latex gloves. While heightened knowledge of disease and exposures may increase the prevalence of confirmed WRA among HCWs, even with an informed work force, over half of the 206 HCW with new-onset WRA (excluding RADS) did not report a known inducer.

Also, HCWs may be more likely to respond to telephone interviews and be counted among confirmed cases. In California and Massachusetts, but not Michigan and New Jersey, case confirmation relied solely on completion of telephone interviews. Interviews were more likely to be completed by women, non-Hispanics, and professionals compared to men, Hispanics, and workers in manufacturing or construction. This differential case confirmation did not account for the whole difference in California and Massachusetts (results not presented), and data from Michigan and New Jersey were not limited in the same way.

HCWs were significantly more likely to file for and receive workers' compensation for their WRA than non-HCWs. Many eligible workers do not file for compensation, and some of the disincentives may affect non-HCWs more than HCWs [Biddle et al., 1998; Rosenman et al., 2000; Azaroff et al., 2002; Shannon and Lowe, 2002]. Factors associated with filing for workers compensation in these studies included female gender, union membership, non-immigrant status, increased length of employment, and not being self-employed. Among the factors that may contribute to HCWs' greater success in being awarded workers compensation are race and professional status of many of the claimants, and the increased proportion of known inducers.

Agents Identified by Health Care Workers

The following section describes the agents most commonly reported by HCWs. Workers with asthma will have a better prognosis if triggers are identified and controlled in their workplaces. Additional information about the selection and use of safer alternatives to hazardous chemicals in the hospital industry may be found at the Sustainable Hospitals website http://www.sustainablehospitals.org/.

Cleaning Products

Cleaning products, the predominant agent reported by cases (n = 74, 24%) in this industry, included disinfectants as well as cleaners. Quaternary ammonium compounds (e.g., benzalkonium chloride, n-alkyl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium chloride), called "quats," are commonly used disinfectants for surface clean-

ing in clinical and food preparation areas and are regulated by the US EPA as antimicrobial pesticides. Sensitization to several quaternary ammonium compounds has been documented [Bernstein et al., 1994; Burge and Richardson, 1994; Purohit et al., 2000] two of these compounds are recognized asthmagens. Cleaning products also contain many irritant chemicals, e.g., bleach, ammonia, hydrochloric acid. In a study from the same four states, cleaning products were associated with 12% of cases across all industries and occupations [Rosenman et al., 2003]

Natural Rubber Latex

Latex was the second most commonly reported exposure. Seventy-three percent of all dental worker cases and 35% of all cases who were nurses identified latex. Latex allergy has been attributed to latex protein exposure from frequent glove changes, especially in operating rooms and emergency departments, and dermal and airborne exposure [Turjanmaa et al., 1988; Berky et al., 1992; Hamann, 1993; Holzman, 1993; Swanson et al., 1994; Kelly et al., 1996; OSHA, 1999]. NIOSH [1997] issued an Alert on latex and OSHA issued a Technical Information Bulletin on latex in 1999. Adverse reactions range from localized dermatitis to anaphylaxis, including WRA. The huge increase in use of latex gloves in the 1980s, in response to requirements for universal precautions, led to shortcuts in glove manufacturing that increased the availability of latex protein. Replacing latex materials with synthetics, banning latex balloons and careful purchasing policies can reduce latex exposures.

Indoor Air Quality

Indoor air quality issues in health care are similar to those in other non-industrial workplaces. Reported exposures in these data (paints/solvents, glues, carpet, dust, mold, and miscellaneous chemicals) included bystander exposures from construction or maintenance activities. Inadequate ventilation, coupled with widespread chemical use, may be responsible [Behling and Guy, 1993].

Mold exposures were reported by 5% (n = 14) of cases. Some specific molds have been identified as asthma inducers [Hunting and McDonald, 1995; ACOEM, 2002; Zureik et al., 2002]. Recent European research reported an association between mold sensitization and severity of asthma [Zureik et al., 2002]. Preventing moisture incursion, careful facility and ventilation system maintenance, and control of air contaminants from construction/renovation, can prevent exposure to mold and ameliorate other indoor air quality hazards.

Glutaraldehyde

Glutaraldehyde, identified by 9% (n = 27) of cases, is an effective broad-spectrum anti-microbial agent, commonly used in health care facilities as a cold sterilizing agent for medical, dental, and surgical instruments, particularly endoscopes and plastic materials. It is also an ingredient in X-ray developer [Byrns et al., 2000] and is used as a tissue fixative in pathology laboratories. It is a strong irritant to the skin, eyes, and respiratory system and has been reported to cause asthma [Chan-Yeung et al., 1993; Gannon et al., 1995; DiStefano et al., 1998]. Two recent articles document new-onset asthma and respiratory symptoms among radiographers exposed to X-ray processing chemicals [Dimich-Ward et al., 2003; Liss et al., 2003]. There are alternatives to glutaraldehyde for disinfection, including peracetic acid, hydrogen peroxide and ortho-phthalaldehyde. Glutaraldehyde is still used, although special precautions, adequate ventilation, and employee training are recommended. A NIOSH [2001] pamphlet about glutaraldehyde is available, online and in print.

Formaldehyde

Formaldehyde (5% of cases) is a colorless, flammable gas with a strong, pungent, irritating odor. It is used in health care as a tissue preservative and disinfectant, especially in dialysis units. Commercially, formaldehyde is sold as formalin (usually stabilized with methanol) in a water solution of various strengths; it is also available as a solid (paraformaldehyde). Formaldehyde may also off-gas from building materials, such as plywood, particleboard and some fabrics. Formaldehyde has been recognized as an asthmagen in residential and workplace settings [Burge et al., 1985; Lemiere et al., 1995; Norback et al., 1995]; OSHA [1992] has recognized formaldehyde as a pulmonary sensitizer and carcinogen. Exposure must be minimized with engineering controls.

CONCLUSION

Four state-based surveillance systems for WRA documented that HCWs are at risk for WRA. Despite demographic and employment pattern variations across the four states, health care emerged as the first or second most frequently reported industry among all cases of WRA reported from 1993 to 1997, and in proportions exceeding their workforce representation. Because of the size and projected growth of this industry, the lessons from these surveillance data are important in reducing the burden of asthma in the US population and reducing risk factors for hundreds of thousands employed in health care.

Exposures to several of the asthma triggers identified by HCWs may be reduced, and even eliminated, from health care services by replacement with safer substitutes. To further minimize the risk, engineering controls and safe work practices are needed. Exposures may be reduced or prevented by better planning and control of construction and renovation

projects, and adequate facility maintenance to prevent inadvertent moisture incursion and mold growth. Purchasing decisions and planning should take into consideration cleaning products, disinfectants, construction materials, and gloves that have been tested for their allergenic and irritant properties.

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APPENDIX

CASE REPORTS

Four case reports are provided to demonstrate the range of agents, occupations and circumstances of exposure represented in the data. The case reports also demonstrate the limited information that may be available regarding each case.

Case Report #1, California

A 45-year-old, non-smoking, female X-ray technician sought emergency medical treatment for throat irritation, cough, chest tightness, shortness of breath, sinus congestion and hives which began within 5 min after X-ray developing tanks overflowed at work. She reported no ventilation in the room where she worked. She was treated with inhaled albuterol and oral diphenhydramine hydrochloride. She returned to the emergency room five times over the next 5 days for breathing treatments, and missed work for 7 days after the incident. She reported that her asthma symptoms continued over the following 10 months and that many different substances triggered her symptoms. (This case was classified as RADS.) She still worked in the same job, but felt her exposure had been lessened through engineering controls, including addition of a wall and ventilation. Among 10 workers with similar exposures in her workplace, she knew of two others with breathing problems.

Note: No information was available about specific exposures. X-ray developing fluids may contain glutaraldehyde and other respiratory irritants, e.g., acetic acid, potassium hydroxide, hydroquinone. X-ray processing may also release sulfur dioxide [Byrns et al., 2000].

Case Report #2, Michigan

After working at a hospital for 10 years, a male in his 40s started a 3-month rotation as a radiation therapist in the Simulation Room for the hospital's cancer center. He developed WRA from exposure to methylene bisphenyl diisocyanate (MDI), which was used to create foam immobilization cradles for radiation oncology patients. His duties included pouring a two-part MDI-containing mixture into a plastic bag, sealing it, then molding the bag to fit the patient. He wore latex gloves, a gown and sometimes a surgical mask while doing this job in a small, poorly ventilated room.

He developed sneezing, headaches and sinus problems, along with chest tightness and slight cough, but did not notice shortness of breath or wheezing. He did not have a history of asthma or allergies. He had smoked approximately a pack of

cigarettes a day for 2 years in his teens. His breathing tests were within normal limits but he had a positive methacholine challenge test. He was given an albuterol inhaler that he used periodically. Although he stopped working in the Simulation Room pursuant to his doctor's recommendation, his intermittent chest symptoms did not resolve completely until 5 months later.

A Michigan OSHA enforcement inspection was conducted in the Simulation Room, which included querying co-workers about breathing problems. Air concentrations of MDI were below the level of detection. The inspection revealed that many employees working in the Simulation Room had no knowledge or training about MDI, including the inadequacy of surgical masks. The industrial hygienist noted that latex gloves worn by the radiation therapists were not protective against isocyanates [NIOSH, 1999a], and recommended butyl, nitrile, or neoprene gloves. Among the nine co-workers interviewed, one had developed asthma and one other radiation therapist had developed breathing problems consistent with asthma since working with MDI. A medical surveillance program for workers in the area with potential exposure to MDI was recommended.

Case Report #3, Massachusetts

A 42-year-old, non-smoking, female worked as an assistant nurse manager/registered nurse in the gynecology/oncology department at a large urban hospital. She had been employed at this hospital for over 6 years when she began to notice respiratory symptoms associated with work. She reported wheezing, cough, chest tightness and shortness of breath, which were diagnosed as WRA, and was hospitalized once for her asthma. She had been diagnosed previously with asthma when she was 3-year-old, with allergies to trees, grass, dust, dogs and molds, but had been free of symptoms since she was 24 years old. Her work-related symptoms were triggered by the use of powdered latex gloves; she further reported problems with the ventilation system. She was out of work nearly 2 years after her diagnosis and had been awarded workers' compensation.

The hospital assessed latex in the environment and implemented changes to minimize exposures, replacing latex gloves with non-latex gloves and low allergen, non-powdered gloves, banning latex balloons, and correcting problems in the ventilation system. Further, the hospital administration developed a Latex Committee in collaboration with the hospital unions to provide oversight on latex use.

Case Report #4, New Jersey

A 52-year-old, non-smoking female worked for 9 years in the pulmonary function testing department of an ambulatory care facility. During that time she suffered recurrent symptoms of cough, shortness of breath, wheezing, and chest tightness, as well as episodes of sinusitis and bronchitis. Symptoms improved on weekends and resolved completely while on vacations. An evaluation of the facility revealed that the affected individual and other employees were found to be exposed to glutaraldehyde vapors released from a bucket of sterilizing solution stored in a cabinet. Her job required that she immerse certain pieces of equipment into the bucket of solution for 1 hr, then remove and rinse the equipment in water until "the smell of glutaraldehyde is gone." No ventilation system controlled the release of glutaraldehyde into the air and the odor was detectable in the workroom and adjacent hallway. Evidence of splashes and spills were visible around the bucket under the cabinet. She avoided work with glutaraldehyde for several months at the urging of her personal physician, and symptoms resolved. However, when she was required to sterilize some equipment on one occasion, symptoms returned. The bucket of glutaraldehyde has since been removed and equipment is now sent out of the department for gas sterilization. Her symptoms improved significantly.

California Department of Health Services
Occupational Health Branch

Executive Summary: Investigation of Work-Related Glutaraldehyde Exposures at Two Heart Valve Manufacturing Companies

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March 21, 2006

EXECUTIVE SUMMARY

BACKGROUND

The California Department of Health Services, Occupational Health Branch (CDHS/OHB), investigates the effects of workplace hazards on public health and makes recommendations to prevent occupational illness and injury. A key part of our prevention activities is statewide tracking of work-related asthma. In 2003, the California Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA), recommended lowering the Permissible Exposure Limit for glutaraldehyde in the workplace to prevent new cases of asthma. Subsequently, representatives of medical device manufacturers raised concerns that reducing workers' exposures could adversely affect the manufacture of bioprosthetic heart valves, which relies on the use of glutaraldehyde. CDHS/OHB initiated an investigation to learn more about workers' exposures to glutaraldehyde in this industry. We selected two companies, "Company A" and "Company B," because they are the largest heart-valve manufacturers in California.

METHODS

To investigate worker exposure to glutaraldehyde at Company A and Company B, CDHS/OHB researchers: observed the bioprosthetic heart valve manufacturing process; interviewed employer representatives; interviewed glutaraldehyde-exposed workers; reviewed employer written records; and reviewed the scientific literature.

To evaluate worker exposure to glutaraldehyde at these two companies we: assessed the potential for one or more routes of worker exposure to glutaraldehyde; compared employer glutaraldehyde air-monitoring data to current and proposed regulatory levels and to other recommended exposure levels;[a] assessed the presence, use, and efficacy of measures to limit workers' exposures; and assessed the presence of worker training and hazard communication about glutaraldehyde exposure.

Field visits were conducted on February 6, 2004 at Company A and on April 21, 2004 at Company B.

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[a] The current Cal/OSHA Ceiling Limit for glutaraldehyde is **0.2 parts per million (ppm)**. This means that, legally, exposures must never exceed this Ceiling Limit for any period of time. In 2003, the Cal/OSHA Airborne Contaminants Advisory Committee recommended a lower Ceiling Limit of **0.015 ppm** to protect workers from developing asthma. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends that glutaraldehyde exposures do not exceed a Threshold Limit Value (TLV) Ceiling of **0.05 ppm**. As of September 2005, the Cal/OSHA Permissible Exposure Level for glutaraldehyde is proposed to be lowered to a Ceiling Limit of **0.05 ppm**.

CONCLUSIONS

- **The approximately 400 predominantly female employees at Company A and 200 predominantly female employees at Company B making bioprosthetic heart valves have continuous airborne exposure to glutaraldehyde over the course of every workshift. Workers also have routine potential for skin and eye contact with glutaraldehyde.**

  In general, to manufacture heart valves, workers fix fresh bovine and/or porcine tissue in glutaraldehyde solutions ranging from 0.2% to 2.5%. Workers then manually size, cut, evaluate, sew, and package each glutaraldehyde-treated valve at various workstations.

  At Company A, between January 1999 and December 2003, a total of seven cases of health care provider-diagnosed glutaraldehyde-related illness were recorded on the OSHA 300 Logs: one case of contact dermatitis, two cases of allergic rhinitis, one case with both allergic rhinitis and allergic contact dermatitis, one case of chemical rhinitis (allergic or irritant not specified), and two cases of asthma. Reports of asthma were evaluated according to the National Institute for Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR) surveillance case definition and classification scheme.[1] The two cases of asthma were classified by CDHS/OHB as new-onset, work-related asthma associated with a known asthma inducer.

  At Company B, between January 1999 and April 2004, six cases of glutaraldehyde-related injury or illness were recorded on the OSHA 200 (1999-2001) and 300 (2002-2004) Logs: five reports of glutaraldehyde exposure to the eyes, and one report of eye and skin irritation. One case of latex allergy was also recorded during this time period.

- **Both companies had implemented many exposure monitoring and control measures that have decreased workers' glutaraldehyde exposures over time, including:**

  Company A: a closed system to minimize handling of large volumes of glutaraldehyde, and dilution and local exhaust ventilation. No respiratory protection is in use for routine glutaraldehyde-related manufacturing tasks. Workers responsible for cleanup of glutaraldehyde spills are reportedly part of a respiratory protection program.

  Company B: the use of a less toxic alternative to glutaraldehyde to sterilize the fixation rigs; a closed system to minimize handling of large volumes of glutaraldehyde; local exhaust ventilation for certain tasks; and reducing the fill volume of storage containers, using "no-drip" nozzles to fill the storage

containers, and changing to a storage container model with a gasket snap-lid. Exposures were also reduced through the implementation of administrative controls and respiratory protection.

- **Measured employee glutaraldehyde exposures were all well below current Cal/OSHA regulatory levels (0.2 ppm) at both companies.** At Company A, this conclusion is based on the results of 61 samples collected over an approximately six-week period in 2003. To describe workers' current exposures at Company B, 147 personal air-monitoring samples collected between 1999 and 2004 were categorized by job task over time. The highest and most recent measured exposure for each of the 30 glutaraldehyde-related tasks was selected to represent the current exposure of workers performing that task. As of April 2004, workers' documented glutaraldehyde personal exposure levels were all below 0.20 ppm.

- **Health effects can occur at current levels of glutaraldehyde exposure at both companies.** Glutaraldehyde vapor in the air can cause tearing of the eyes, burning nose, sore throat, cough, nausea, and headache. Symptoms may occur even when the amount of glutaraldehyde in the air is below 0.05 ppm.[2,3,4] At Company A, over 16% (10/61) of the individual personal samples collected, and 21% (6/28) of the monitored job tasks (i.e., the highest measured exposure for the worker performing that task) involved exposures greater than 0.05 ppm. The six tasks with the highest exposures to glutaraldehyde involved sterilizing, fixing, and preparing the tissue. At Company B, the majority of all personal glutaraldehyde exposures monitored (55%; 81/147), all 2004 exposures monitored (60%; 42/60), and all job tasks monitored (57%; 17/30), involved exposures greater than 0.05 ppm. Of the 75 samples collected in 2004, 42 (56%) were greater than 0.05 ppm; 11 of 15 (73%) collected in Fixation/Post Fixation were greater than 0.05 ppm.

- **Repeated exposure to glutaraldehyde can cause asthma.** Glutaraldehyde vapor can irritate the lungs, causing chest pain and shortness of breath. Repeated exposure to glutaraldehyde can cause asthma, which in some individuals may cause serious morbidity.[5-16] Symptoms of asthma include chest tightness, shortness of breath, wheezing, and cough. A person who has developed asthma can have symptoms when exposed to even very small amounts of glutaraldehyde or other irritant chemicals, making it impossible for them to continue working where glutaraldehyde exposure can occur. The current Threshold Limit Value and proposed Cal/OSHA regulatory level of 0.05 ppm are not based on protecting workers against asthma. Asthma has occurred in individuals exposed to low levels of glutaraldehyde, probably below 0.05 ppm.[17,18] One study reported the development of asthma in workers whose short-term exposures ranged from 0.015 ppm to 0.21 ppm.[19] At Company A, almost two-thirds (40/61) of all measured exposures and 71% (20/28) of glutaraldehyde-related job tasks involve exposure above 0.015 ppm. At

Company B, almost 92% (135/147) of all measured personal exposures and 83% (25/30) of current glutaraldehyde-related job tasks involve exposure above 0.015 ppm.

- **Workers making bioprosthetic heart valves are at risk for asthma.** In California over a ten-year period (1993-2003), CDHS/OHB's tracking system identified 20 cases of work-related asthma associated with exposure to glutaraldehyde. Of these 20 cases, two (10%) occurred in workers at Company A. No cases of asthma were identified at Company B. Paradoxically, the large proportion of asthma cases reported from Company A is likely a measure that the health and safety program at the company may be *effective* relative to other employers, i.e., because they had medical staff on-site to evaluate employees who reported problems. Effective health and safety programs identify problems and attempt to correct them. In general, cases reported by physicians of work-related asthma are likely to be an underestimate of the true incidence.

- **The potential chronic effects of long-term glutaraldehyde exposure have not been well studied.** Whether glutaraldehyde can cause cancer in humans and whether it can affect the reproductive system have not been well studied. Glutaraldehyde is believed to be unlikely to affect pregnancy or male or female reproductive function so long as exposure levels are below those that cause irritation or other obvious symptoms.

- **Many factors that will contribute to worker exposure to glutaraldehyde persist at both companies, including:** (1) the presence of large exposed surface areas of glutaraldehyde. (Nine of the ten most highly exposed tasks at Company A occur in the fixation area where the tissue is placed in, and where workers manipulate, open containers of glutaraldehyde. Many other containers of glutaraldehyde are simultaneously uncovered in all the work areas.); (2) working with glutaraldehyde-treated tissue in close proximity to workers' breathing zones; (3) manual pouring and disposal of glutaraldehyde solutions without local exhaust ventilation, eye protection, and waste neutralization; and (4) prolonged use of latex gloves. Exposure reductions can be achieved by enclosing and/or capturing glutaraldehyde vapors prior to entering a worker's breathing zone. Therefore, industry concerns that legally mandating further reductions in worker exposure would lead to modifying the work process in such a way as to warrant new clinical trials, and would place patient care in jeopardy, appear to be unwarranted.

- **Both companies provide workers with many valuable opportunities for training and communication about hazards.** However, in general, and specifically in light of the wide range of language and literacy skills and cultures represented by the workforce, Company A's sole reliance on employees to come forward as individuals, to ask questions, provide their

hands-on observations and knowledge of the work process, and raise concerns, even anonymously, is unlikely to effectively support its health and safety objectives. An important strength of Company B's program is its ongoing maintenance of an active, cross-departmental Health and Safety Committee including managerial and non-managerial representatives.

- **Company A's policy that requires employees to report pregnancy is not an effective health and safety measure to protect against reproductive/developmental toxicity in the workplace.** Consistent with the requirements of the Cal/OSHA Hazard Communication Standard, workplace reproductive hazards, including hazards to pregnancy, should be identified, and the prevention measures employed to protect against the hazards should be discussed proactively with all employees as a part of health and safety training.

LIMITATIONS

For both companies, we did not take independent measurements of potential physical, biological, or chemical hazards. Results of air monitoring may have underestimated workers' "Ceiling" or instantaneous exposure levels. We did not verify the efficacy of the written respiratory protection program at either company. We did not independently verify the efficacy of worker training and hazard communication. Language barriers and the lack of a pre-established mechanism for direct worker input limited our ability to gather workers' perspectives on health and safety. The limited nature of our investigation was resource-driven and does not imply there are, or are not, other health and safety issues at these workplaces.

In addition, for Company A, we did not validate the assumption that the level of glutaraldehyde exposure was below 0.015 ppm in areas that were not sampled. For Company B, the grouping of various job tasks for the purpose of this analysis may have obscured differences in exposures among individual workers performing the same task, or differences in similar tasks; workers should refer to their personal monitoring results for the most precise assessment of their exposure.

RECOMMENDATIONS

CDHS/OHB recommends that both heart valve manufacturing companies:

1. Implement additional engineering controls to minimize workers' exposures to glutaraldehyde.

Although Company B has successfully eliminated the use of glutaraldehyde for some tasks, at the present time, there does not appear to be a less toxic, commercially available alternative to the use of glutaraldehyde for manufacturing bioprosthetic heart valves. Engineering controls should be implemented to minimize workers' exposures, to at least below a level of 0.015 ppm. Exposure reductions can be achieved by enclosing and/or capturing glutaraldehyde vapors prior to entering a worker's breathing zone. Heart valve manufacturers should involve directly-exposed production workers in the planning and implementation of recommended engineering controls and monitor exposures after changes are made.

Company A and Company B should:

- Separate procedures such as fixation that require handling large volumes of the chemical from other work areas;

- Put tight-fitting lids on fixation tanks, trays, jars, and all other glutaraldehyde containers to reduce the exposed surface area of glutaraldehyde;

- Consider re-designing the fixation tanks to increase their depth (i.e., allow for vertical submersion of the tissue, rather than horizontal submersion, to reduce the size of the opening of the tanks) to further minimize the exposed surface area;

- In all areas, when container lids must be breached to manipulate the tissue or solution, reduce glutaraldehyde vapor in the air by installing local exhaust ventilation located at the point of discharge to prevent the vapor from escaping into the room air;

- Depending on the task, pour glutaraldehyde under local exhaust ventilation using automatic dispensing systems and/or splash-resistant safety nozzles; and

- Neutralize glutaraldehyde solutions before disposal.

Company B should also:

- Implement the recommendations made previously by a Certified Industrial Hygienist consultant to Company B to reduce exposures through the use of engineering controls;

- Place the Solutions area under negative pressure relative to the hallway, to prevent any glutaraldehyde vapors in the Solutions area from migrating into the hallway and other adjacent work areas; and

- Provide local exhaust ventilation in the Solutions area to obviate the need for respiratory protection while measuring out dry chemicals.

2. **Identify and implement the use of an appropriate glove to prevent worker skin exposure to glutaraldehyde and latex.** Latex gloves should not be used to control worker skin exposure to glutaraldehyde. Chemicals can permeate gloves without visibly affecting the materials and thus gain access to the skin in an insidious manner. Latex gloves are suitable in situations where only short-term, incidental contact with glutaraldehyde is expected. Moreover, latex gloves themselves present their own hazards, including dermatitis and asthma.

3. **Require the use of safety glasses when handling glutaraldehyde solutions.** There is a large amount of glutaraldehyde poured and dispensed by hand without eye protection. Eye contact with glutaraldehyde is harmful and easily prevented. As it may be difficult to identify all situations with potential for a "splash," workers should <u>always</u> use safety glasses when working with glutaraldehyde.

4. **Implement a medical surveillance program for glutaraldehyde-exposed workers.** Early diagnosis of asthma and early removal from exposure are key to ensuring a favorable outcome for workers who develop asthma. In the event of removal from work due to work-related respiratory problems, a Medical Removal Protection Program should be in place to protect the workers from loss of salary and benefits. The medical surveillance program in the Cal/OSHA Formaldehyde Standard is designed to address sensitization, and could be used as a template to implement medical surveillance among glutaraldehyde-exposed workers.

5. **Integrate worker health and safety considerations into the assessment of alternatives to glutaraldehyde-fixation at the onset of process redesign.** Almost all commercially available tissue valves are currently fixed in glutaraldehyde. However, the development of alternative fixation techniques is an area of great interest to the heart valve industry because glutaraldehyde-fixed tissue has limited durability. Future use of an

alternative to glutaraldehyde in the manufacture of bioprosthetic heart valves will not obviate the need to monitor and control worker exposure. Worker health and safety considerations should be anticipated by employers and regulatory agencies and integrated into the assessment of alternatives to glutaraldehyde fixation at the onset of process redesign.

In addition,

Company A should:

Hire an industrial hygienist. Company A's stated policy is that "health and safety will be given equal importance with production, quality, and other facility functions." The capacity for carrying out this policy would be greatly strengthened by hiring a full-time industrial hygiene professional to support the efforts of the occupational health nurse and ventilation engineering professional in finding creative solutions to exposure control consistent with the needs of production.

Establish a Health and Safety Committee. Exclusive reliance on individual-based mechanisms for employee input on health and safety is a critical weakness of Company A's employee communication efforts. A cross-departmental Health and Safety Committee composed of manufacturing and health and safety managers and line staff would provide an opportunity for employees to work together to meet the goals and objectives of Company A's health and safety policies.

Revise the mandatory reporting of pregnancy policy. Mandatory reporting of pregnancy is not an effective health and safety measure. This policy should be revised such that workers are protected from potential reproductive hazards by preventing hazardous exposures for all employees, training and communicating reproductive hazard information to all workers (so they will have this information in time to ensure they are adequately protected), and establishing a voluntary mechanism for workers to report *any* disability for which they may need accommodation.

Company B should:

Hire on-site health care provider support of the Environmental Health and Safety Program. The capacity for carrying out the health and safety program at Company B would be greatly strengthened by hiring a full-time occupational health nurse to support the efforts of the Facilities Environmental Health and Safety Manager in finding creative solutions to exposure control consistent with the needs of production, and to coordinate a medical surveillance program.

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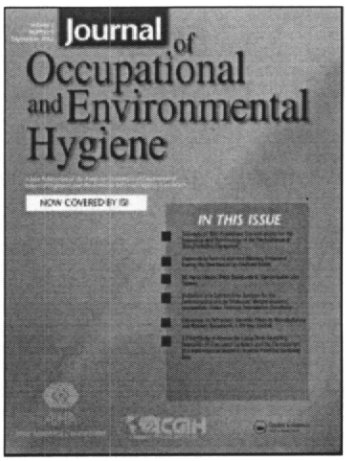

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Glutaraldehyde Exposures Among Workers Making Bioprosthetic Heart Valves

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Glutaraldehyde Exposures Among Workers Making Bioprosthetic Heart Valves

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Exposure to glutaraldehyde is a recognized cause of work-related asthma. An investigation was undertaken to describe exposure to glutaraldehyde among workers making bioprosthetic heart valves and to make recommendations for prevention. At the two largest heart valve manufacturing facilities in California, the work process was observed; employer representatives and glutaraldehyde-exposed workers were interviewed; and employer written records, including company-generated industrial hygiene data, were analyzed. Approximately 600 female workers had continuous airborne exposure to glutaraldehyde over the course of every work shift and the routine potential for skin and eye contact with glutaraldehyde while making heart valves. Employee short-term (15-min) glutaraldehyde exposures were all well below the current regulatory ceiling level (0.20 ppm). Overall, approximately 40% of the glutaraldehyde-related job tasks involved exposures above the American Conference of Industrial Hygienists threshold limit value ceiling of 0.05 ppm; the majority (71.4% and 83.3%, depending on the company) involved exposures greater than 0.015 ppm. At one company, two cases of physician-diagnosed asthma were recorded by the employer in the previous 5-year period; these reports met the surveillance case definition for new-onset, work-related asthma associated with a known asthma inducer. Factors that contributed to worker exposure included large exposed surface areas of glutaraldehyde under agitation; working with glutaraldehyde-treated tissue in proximity to workers' breathing zones; manual pouring and disposal of glutaraldehyde solutions without local exhaust ventilation, eye protection, and waste neutralization; and prolonged use of latex gloves. Workers making bioprosthetic heart valves are at risk for occupationally acquired asthma. Employers should implement additional engineering controls to minimize workers' exposures to at least below a level of 0.015 ppm, an appropriate glove to prevent workers' skin exposure to glutaraldehyde, consistent and universal use of eye protection, and a medical surveillance program for glutaraldehyde-exposed workers.

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Keywords bioprosthetic heart valves, glutaraldehyde, permissible exposure limit, work-related asthma

INTRODUCTION

Glutaraldehyde is widely used in the health care industry as a cold sterilant of medical and surgical instruments. Glutaraldehyde vapor in the air can cause tearing of the eyes, burning nose, sore throat, cough, nausea, and headache; symptoms may occur even when the amount of glutaraldehyde in the air is below the current California Department of Industrial Relations, Division of Occupational Safety and Health (Cal/OSHA) permissible exposure Limit (PEL) of 0.20 ppm ceiling[1–3] and the American Conference of Industrial Hygienists (ACGIH®) threshold limit value ceiling (TLV®–C) of 0.05 ppm.[4–6] Exposure to glutaraldehyde is a recognized cause of work-related asthma;[7–19] asthma has occurred in individuals exposed to low levels of glutaraldehyde, probably below 0.05 ppm.[20,21] One study reported the development of asthma in workers whose short-term exposures ranged from 0.015 ppm to 0.21 ppm.[22]

In 2003, Cal/OSHA recommended lowering the PEL for glutaraldehyde in the workplace to 0.015 ppm ceiling to protect workers from developing asthma. The 0.015 ppm level was based on the recommendation of the Cal/OSHA Airborne Contaminants Advisory Committee. In 2004, Cal/OSHA held three supplemental Glutaraldehyde Advisory Committee meetings to consider the impacts of the proposed change for glutaraldehyde; in late 2005, public hearings were held. In April 2006, the California Occupational Safety and Health Standards Board adopted a PEL of 0.05 ppm ceiling for glutaraldehyde. The 0.05 ppm ceiling becomes effective on July 8, 2008; until that time, the following Cal/OSHA exposure limits are currently in effect: a ceiling limit of 0.20 ppm and a PEL of 0.05 ppm (8-hour time-weighted average). There is no federal PEL for glutaraldehyde at present.

Subsequent to the 2003 Cal/OSHA proposal, representatives of medical device manufacturers raised concerns that

reducing workers' exposures could adversely affect the manufacture of bioprosthetic heart valves (i.e., heart valves made from porcine or bovine tissue). Specifically, industry representatives anticipated that lowering workers' glutaraldehyde exposures would involve modifying the heart valve manufacturing work process, lead to costly clinical trials, and jeopardize patient access to heart valves. Glutaraldehyde has been used in the manufacture of bioprosthetic heart valves for more 30 years, and almost all commercially available tissue valves are currently fixed in glutaraldehyde.[23]

The development of alternative fixation techniques is an area of great interest to the heart valve industry. This is because glutaraldehyde-fixed tissue tends to calcify, which limits the durability of the bioprosthetic.[24] However, at the present time, there does not appear to be a less toxic, commercially available, alternative to the use of low concentrations (0.5% to less than 3%) of glutaraldehyde for manufacturing bioprosthetic heart valves.[25,26] The industry reports that the facilities of two California companies, with more than 6000 employees in the state, produce 90% of the more than 100,000 bioprosthetic heart valves used annually throughout the world.

The National Institute for Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risks (SENSOR) program provides funding to California and three other states to conduct surveillance for work-related asthma. The California SENSOR asthma program aims to identify industries, occupations, and exposures that put workers at risk for work-related asthma to develop prevention measures. At the time of Cal/OSHA's initial proposal to lower the PEL for glutaraldehyde, California's SENSOR asthma program had documented one case of work-related asthma associated with exposure to glutaraldehyde in the manufacture of bioprosthetic heart valves. However, there were no published reports of asthma among workers in this industry, nor had the nature and extent of worker exposure to glutaraldehyde in heart valve manufacturing been documented in the scientific literature. Therefore, an investigation was undertaken to describe exposure to glutaraldehyde among workers making bioprosthetic heart valves and make recommendations for prevention.

METHODS

Selection Criteria

The facilities were selected because they were the two largest heart valve manufacturers in California.

Investigation Protocol

The California Department of Health Services' (CDHS) SENSOR surveillance program collects existing health and hazard data pursuant to legislative authority of the CDHS (California Health and Safety Code 105175). The protocol for data collection and investigation for the SENSOR asthma surveillance program has been approved by the California Health and Human Services Agency Committee for the Protection of Human Subjects.

At each facility, the investigation protocol included:

- *A worksite walkthrough of the bioprosthetic heart valve manufacturing process.* An occupational health physician and industrial hygienist walked through the facility and directly observed the glutaraldehyde-related work processes and the presence and use of glutaraldehyde exposure control measures; at one facility, a toxicologist also observed the workplace.
- *Employer and worker interviews.* Using a detailed industrial hygiene checklist, employer representatives were queried about the heart valve work process, job tasks, glutaraldehyde exposure control measures, and the employer's health and safety program. Worker interviews were conducted by CDHS researchers during the on-site investigation. A convenience sample of English-speaking workers, selected by the employer, was interviewed privately as a group, in a room at the facility. Workers were provided with a description of the scope and purpose of the investigation, and researchers answered employee questions, asked employees about their work, exposure to glutaraldehyde, and any health problems they may have experienced.
- *A review of employer exposure monitoring and other related health and safety records.* All written glutaraldehyde-related health and safety materials were requested from each employer including, but not limited to: Injury and Illness Prevention Program (a written plan for illness and injury prevention that is required for every California employer by California Code of Regulations, Title 8, Section 3203), Hazard Communication Program, and glutaraldehyde-related Material Safety Data Sheets currently in use; employer glutaraldehyde air monitoring protocols and results descriptive of workers' current exposure levels; ventilation records that documented the most recent maintenance activities; and Employer's Reports of Occupational Injury or Illness and OSHA 200 and 300 Logs for the previous 5 years.

Data Analysis

Available medical and other records for all glutaraldehyde-related illness and injury reports recorded on employer OSHA logs were reviewed by two occupational health physicians and an epidemiologist. Reports of asthma were evaluated according to the NIOSH SENSOR surveillance case definition and classification scheme.[27] The NIOSH case definition of work-related asthma requires a health care professional's diagnosis consistent with asthma and an association between symptoms of asthma and work. The NIOSH definition further distinguishes between cases of work-related asthma as either "new-onset" or "work-aggravated" asthma.

Observational and records-based data were compiled by CDHS researchers separately for each facility; all summarized data regarding the work process, glutaraldehyde exposure levels, and exposure control measures were reviewed by the employer for accuracy and trade secrets. A company-specific report of findings and recommendations for illness prevention

was disseminated to each employer and its glutaraldehyde-exposed employees.

At Company A, personal exposure monitoring had been recently performed for all tasks involving glutaraldehyde exposure at a time when the highest exposures were deemed likely for each task. For tasks having multiple samples, the highest measured level was selected to represent the ceiling level of exposure for that task. For Company B, workers' current exposures by job task were analyzed as follows: all personal air monitoring samples collected between 1999 and 2004 were categorized by job task over time. Related departments and job tasks were grouped, and the most recent measured exposure for each of the glutaraldehyde-related tasks was selected to represent the current ceiling level of exposure of workers performing that task; where multiple samples were taken for a task on the most recent sampling date, the highest measured exposure from that date was selected to represent the current ceiling level of exposure of workers performing that task.

Our decision to report maximum measured exposure levels by task (rather than, for example, mean exposure) is to promote comparison with a ceiling regulatory limit, which is not allowed to be exceeded at any time. Samples collected with passive diffusion badges that had values of "not detectable" were assigned a value of 0.01 ppm. Descriptive statistics were used to analyze the distribution of workers' glutaraldehyde exposures.

Evaluation Criteria

Criteria to assess worker exposure to glutaraldehyde were: (a) the potential for one or more routes of worker exposure to glutaraldehyde, i.e., skin, air, eye, and ingestion; (b) comparison of employer glutaraldehyde air monitoring data to glutaraldehyde levels of 0.20 ppm ceiling (the current Cal/OSHA PEL), 0.05 ppm ceiling (the current TLV-C and newly approved Cal/OSHA PEL that will take effect July 8, 2008), and 0.015 ppm ceiling (the level recommended by the Cal/OSHA Airborne Contaminants Advisory Committee); (c) the presence, use, and efficacy of measures to limit workers' exposures, i.e., engineering and administrative control measures and personal protective equipment; and (d) the presence of worker training and hazard communication about glutaraldehyde exposure.

RESULTS

Data Collection

A walkthrough was conducted at each facility in 2004; 7 and 15 employer representatives were present during the on-site investigation, and 12 and 11 English-speaking workers were interviewed as a group, at Companies A and B, respectively. All requested employer records were available, provided to CDHS researchers, and comprehensively reviewed. Additional records were also available and reviewed, including Doctor's First Reports of Occupational Illness or Injury (DFR) (i.e., California physicians are required to file a DFR within 5 days of initial treatment for every injury or illness that may be related to work, including first aid injuries); medical records associated with illnesses recorded on the OSHA logs; company-specific Injury/Illness Incident Analysis Reports (for selected cases); Respiratory Protection Program, health and safety training materials, spill procedures, new employee physical examination form, and job descriptions currently in use; and minutes of the monthly Health and Safety Committee meetings (January 2002–June 2004).

Work Force

There were a total of 600 employees (mostly female) with potential exposure to glutaraldehyde at the two facilities, 400 at Company A and 200 at Company B. Workers spoke up to 11 different languages/dialects, including Vietnamese, Korean, Spanish, Taiwanese, and Cambodian. Employees worked one of two 8- to 10-hour shifts, 5 days per week, and overtime as required. There was no union representing the employees at either facility.

Work Process

Tissue Staging and Fixation

At both companies, workers received bovine and/or porcine tissue at the facility, manually cleaned the fresh tissue in saline, and prepared the tissue for fixation in glutaraldehyde.

Company A. Workers submerged the tissue in uncovered tanks of glutaraldehyde for a period of time. The tissue was submerged horizontally across the tank. Workers also manually placed tissue in open containers of glutaraldehyde and put the containers in an enclosure. An automated system agitated the glutaraldehyde while the tissue was in the enclosure. Workers used a hose to manually fill and drain glutaraldehyde from the fixation containers. Workers sat at laboratory benches and sized, cut, and evaluated the tissue using hand-held tools and microscopes.

Company B. Workers manually secured the valves onto long tubes and loaded the tubes horizontally into fixation "rigs." A 0.2% solution of glutaraldehyde was pumped into and out of the fixation rigs through an enclosed system. When the valve fixation process on the rigs was finished, workers manually removed each valve from the rig and placed the valves in 5-gallon buckets of glutaraldehyde solution. A 0.2% solution of glutaraldehyde was manually dispensed into the 5-gallon buckets from a faucet. The buckets were stored on shelves. Workers removed a bucket of valves from the storage shelves, placed the bucket on a laboratory bench, and sat at the laboratory bench with an open or loosely-covered 5-gallon bucket of 0.2% glutaraldehyde solution on either side of their workstations. Workers removed each valve individually from the fixation bucket to inspect and test each valve and returned the valve to the appropriate bucket.

Manufacturing

Company A. Workers sat at laboratory benches. Tissue was stored in jars of glutaraldehyde at each workstation. Workers manually removed the tissue from the jar and sewed the tissue.

The tissue was kept wet with glutaraldehyde during the sewing process. The jars of glutaraldehyde were variably open or loosely capped with the jar's lid during the sewing process. Some workers sewed while looking at the tissue through a large magnifying glass or microscope that was attached to the bench. Workers also manually inspected, cut, selected, tested, and packaged each glutaraldehyde-treated valve at various workstations. The jars of glutaraldehyde were filled by pouring from a spigot and emptied by pouring the glutaraldehyde down a sink that led to the sanitary sewer system.

Company B. Workers sat at laboratory benches, removed a valve from a 4-oz container of 0.2% glutaraldehyde solution, and manually cut and sewed each valve onto a stent. While working, workers periodically rinsed the valve in a small aluminum bowl containing saline solution. Each stent was prepackaged in a sealed cup containing 4 oz of glutaraldehyde solution. Workers disposed of the glutaraldehyde solution in the stent cups as follows: they pulled off the heat-sealed foil cover, poured the glutaraldehyde solution into one of two sinks in the workroom, rinsed the container with water, and put the empty stent cup in the trash. At other workstations, workers removed the lid from each glutaraldehyde solution-filled container; took the valve out of its container; and manually inspected, tested, and measured the valve. To package the valves, workers manually decanted and filled cups with glutaraldehyde solution (less than 1%). Workers manually poured off the glutaraldehyde solution from each cup into a funnel that was attached to tubing that led to a 5-gallon carboy. Workers transferred valves to a container and then filled the container with new glutaraldehyde solution using an automated dispenser. Workers placed cups containing glutaraldehyde solution and a valve in an oven for the sterilization process.

Solutions

Direct observations were not made of this area. Depending on the facility, concentrated glutaraldehyde (25%) was reportedly mixed into a variety of solutions ranging from 0.2% to 2.5% glutaraldehyde, or concentrated glutaraldehyde was diluted with water to a 0.625% buffered solution. Monthly glutaraldehyde usage was in the range of thousands of liters at each company.

Exposure Control Measures

Engineering

Various types of industrial hygiene engineering controls were present at both facilities to reduce worker exposure during tissue fixation, manufacturing, and mixing and delivering glutaraldehyde solutions to the process areas (Table I).

Administrative

CDHS researchers observed the following work practices at one company: containment of glutaraldehyde-soaked towels within a sealed container, use of isopropyl alcohol instead of glutaraldehyde to clean gloves, and use of saline instead of glutaraldehyde solution to keep tissue wet during mounting.

Employee health and safety communication was accomplished at both companies through safety meetings, training programs, bulletin boards, written communication, safety

TABLE I. Engineering Controls at Two Bioprosthetic Heart Valve Manufacturing Facilities

Work Process	Company A	Company B
Fixation	Fixation tanks equipped with LEV[A] "slots" designed to pull air away from workers' breathing zones. Glutaraldehyde supplied to and removed from the tanks through an enclosed system. Tissue also fixed in a fully enclosed locally exhausted box.	Tight-fitting lids and LEV installed on the fixation rigs. LEV system a self-contained exhaust fan that drew air over the tank surface, into a charcoal filter bed, and returned the filtered air to the room. The units were not equipped with a reliable and adequately sensitive monitoring system to indicate adsorbent breakthrough. A hydrogen peroxide-based solution was used for sterilizing the fixation rigs (eliminated the use of 2.5% glutaraldehyde for this task). Valve storage container fill volume was reduced, equipment used to fill the containers used a "no drip" nozzle, and the storage containers had a gasket snap lid.
Manufacturing	LEV slots on manufacturing workstations designed to exhaust glutaraldehyde vapors out of the room before entering the workers' breathing zones.	Filling and sealing stent-filled cups of glutaraldehyde solution under LEV. Tissue carrousel under LEV. Final packaging performed in a biological safety cabinet designed to draw room air past the worker and into the cabinet.
Solutions	Glutaraldehyde solutions mixed in an enclosed system. Glutaraldehyde dispensed from the enclosed system at the various tanks and workstations through a spigot.	Glutaraldehyde solutions mixed in an enclosed system. A closed system automatically filled and delivered glutaraldehyde solutions to the process areas.

[A]LEV = local exhaust ventilation.

posters and other postings, and anonymous reporting. One company had a labor-management Health and Safety Committee. At both facilities, all new employees received 2 hours of health and safety training. The format used was an oral PowerPoint presentation in English. Material Safety Data Sheets were available in each work area.

Neither company had a medical monitoring program for glutaraldehyde-exposed employees. At one facility, the Injury and Illness Protection Program specified: "All pregnant employees must notify Health Services after confirmation of pregnancy by a physician. The Occupational Health Nurse will evaluate and determine proper placement." The employer's stated rationale for this policy was that "employees are asked to notify Health Services of pregnancy so a full disclosure of chemical exposure can be given to the employee's health care provider to determine work status."

Personal Protective Equipment

All workers wore a disposable head cover, gown, booties, and latex gloves while working with glutaraldehyde. Safety glasses were required when workers handled glutaraldehyde if there was a potential for splash or aerosolization of the chemical (Company A), and for workers entering selected areas and/or while performing selected tasks (Company B). No respiratory protection was in use for routine glutaraldehyde-related manufacturing tasks at Company A; selected workers were part of the written respiratory protection program at Company B. For tasks that required the use of a respirator, i.e., sampling glutaraldehyde by the QA technician, mixing various glutaraldehyde solutions, custodial cleaning of the fixation room during glutaraldehyde use, and cleaning of the fixation rigs, workers at Company B were required to wear a negative-pressure, full-face, air-purifying respirator with organic vapor/acid gas/cartridges.

Exposure Levels

Workers were primarily exposed to glutaraldehyde by inhalation. There was also potential for workers' skin and eyes to come into contact with glutaraldehyde.

Company A. At the time of this investigation, the most recent air sampling to evaluate worker exposure to glutaraldehyde was conducted in 2003 by a certified industrial hygienist retained by the facility. Personal exposure monitoring was performed for all tasks involving glutaraldehyde exposure at a time when the highest exposures were deemed likely for each task. Areas where the contractor presumed there was "100% confidence" that the level of glutaraldehyde was below 0.015 ppm were not sampled. The contractor consulted with supervisory staff to determine which tasks involved glutaraldehyde exposure and when the highest exposures would occur. All personal samples were collected for 15 min on treated glass fiber filters and analyzed according to the OSHA 64 method.[28]

A total of 61 personal air-monitoring samples were collected from four locations representing 28 glutaraldehyde-related tasks. Workers' glutaraldehyde exposure levels ranged from 0.003 ppm to 0.10 ppm. Of 61 air samples, 21 (34.4%) were less than 0.015 ppm, 51 (83.6%) were less than 0.05 ppm, and all were below 0.20 ppm. Of the 10 air samples greater than 0.05 ppm, 9 were collected in the Fixation area. The six tasks with the highest exposures to glutaraldehyde involved sterilizing, fixing, and preparing the tissue.

Company B. Between 1999 and April 2004, a total of 147 personal air-monitoring samples were collected from

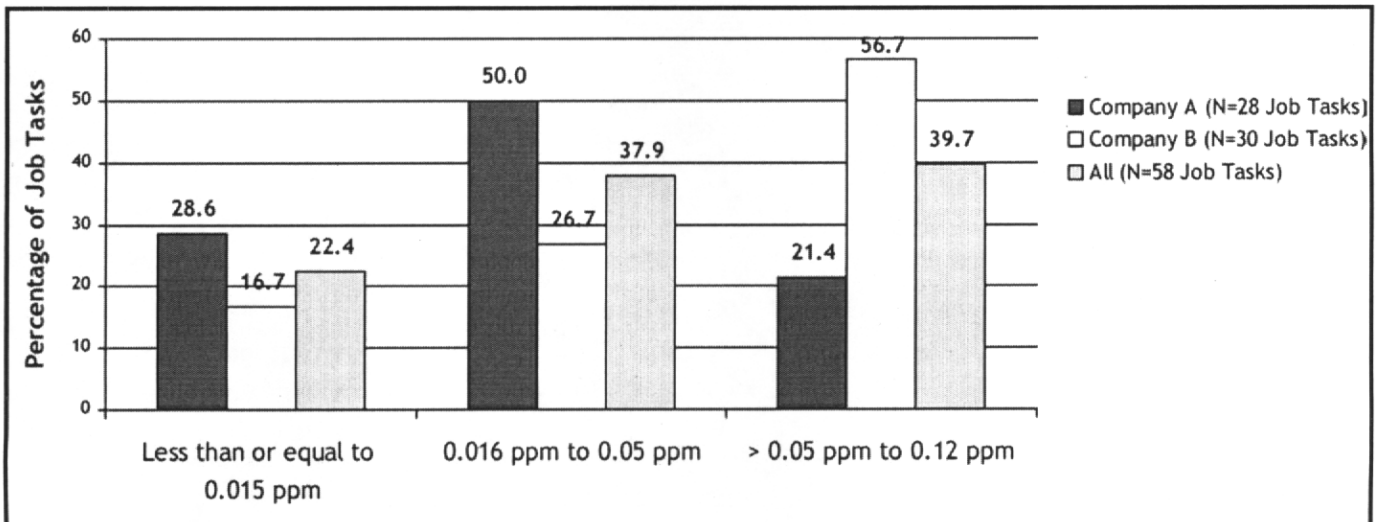

FIGURE 1. Glutaraldehyde exposures by job tasks at two heart valve manufacturing facilities. *Note:* At Company A, the results are based on 61 samples collected over an approximately 6-week period in 2003 categorized by job task. The highest exposure for each job task was selected to represent the current exposure of the worker performing that task. To describe workers' current exposures at Company B, 147 personal air monitoring samples collected between 1999 and 2004 were categorized by job task over time. The highest and most recent measured exposure for each of the 30 glutaraldehyde-related tasks was selected to represent the current exposure of workers performing that task. Exposures that are no longer relevant due to changes in the work process were excluded from this analysis.

14 departments representing at least 30 glutaraldehyde-related tasks. Of the 147 personal air samples, 103 (70%) were collected by a certified industrial hygienist consultant retained by the employer. These personal samples were collected for 15 min on treated glass fiber filters and analyzed according to the OSHA 64 method.[28] The estimate quantification limit for this method was 0.05 μg per sample (0.00044 ppm). The remaining 44 samples (30%) were personal air samples collected in-house by the Facilities Environmental Health and Safety Manager for approximately 15 min using passive diffusion badges and analyzed according to OSHA Method 64. The detection limit was 0.02 ppm for this method.

Of the 147 personal air samples, glutaraldehyde exposure levels ranged from less than detection to 0.83 ppm; 12 samples (8.2%) were less than 0.015 ppm, 66 (44.9%) were less than 0.05 ppm, 140 (95.2%) were below 0.20 ppm, and 7 (4.8%) were 0.20 ppm or greater. Of the 7 samples greater than 0.20 ppm, 3 were obviated by changes in the work process that modified or eliminated the tasks. The remaining 4 samples greater than 0.20 ppm involved tasks that were subsequently documented as having exposures reduced to below 0.20 ppm. All workers' documented current glutaraldehyde personal exposure levels were below 0.20 ppm; however, exposures exceeded 0.05 ppm for workers performing 17 of 30 tasks. The majority of the 75 personal samples collected in 2004 (56%) were greater than 0.05 ppm, up to a maximum of 0.11 ppm.

The Figure presents the percentage of documented current glutaraldehyde exposure levels among bioprosthetic heart valve workers according to the highest and most recently measured exposure for each job task. Exposure levels were greater than 0.05 ppm for 6 of 28 job tasks (21.4%) and 17 of 30 tasks (56.7%) at Companies A and B, respectively. Overall, of 58 tasks with documented current exposure to glutaraldehyde at these two companies, 39.7% were greater than 0.05 ppm.

TABLE II. Glutaraldehyde-Related Health Outcomes

Health Outcome	Number	Health Care Provider Diagnosis?
Glutaraldehyde exposure to eyes	5	No
Asthma	2	Yes
Allergic rhinitis	2	Yes
Contact dermatitis	1	Yes
Both allergic rhinitis and allergic contact dermatitis	1	Yes
Chemical rhinitis (allergic or irritant not specified)	1	Yes
Eye and skin irritation	1	No
Total	13	

Notes: Recorded in two employers' OSHA Logs among workers making bioprosthetic heart valves (January 1999 to April 2004, Company A; January 1999 to December 2003, Company B).

Glutaraldehyde-Related Health Outcomes

Between January 1999 and December 2003, seven cases of health care provider-diagnosed, glutaraldehyde-related illness were recorded on the OSHA Logs at Company A; between January 1999 and April 2004, six cases of glutaraldehyde-related injury or illness were recorded on the OSHA Logs at Company B (Table II). Workers experienced glutaraldehyde exposure to the eyes, asthma, rhinitis, dermatitis, and eye and skin irritation (Table II).

Two cases of physician-diagnosed asthma met the NIOSH surveillance case definition for new-onset, work-related asthma associated with a known asthma inducer. The two cases of asthma were diagnosed 2 and 8 months after worker exposure to glutaraldehyde began. One case of latex allergy was also recorded during this time period.

DISCUSSION

Worker Exposure to Glutaraldehyde

Worker exposure to glutaraldehyde at both facilities in this investigation occurred throughout the work process and in all manufacturing locations. No other published reports documenting exposure to glutaraldehyde among workers making bioprosthetic heart valves have been identified.

Workers had continuous airborne exposure to glutaraldehyde over the course of every work shift. Based on the most current exposure monitoring data available at the time of this investigation, short-term (15-min) employee glutaraldehyde exposures were all well below the current regulatory ceiling level (0.20 ppm). Overall, approximately 40% of the glutaraldehyde-related job tasks identified at these companies involved exposures above 0.05 ppm; the majority (71.4% and 83.3%, depending on the company) involved exposures greater than 0.015 ppm (Figure).

At these two companies, health effects can occur at current levels of airborne exposure. Occupational exposure to glutaraldehyde can cause asthma, which in some individuals may cause serious morbidity.[7–19] Symptoms of asthma include chest tightness, shortness of breath, wheezing, and cough. An individual who has developed sensitizer-induced asthma can have symptoms when exposed to even very small amounts of glutaraldehyde or other irritant chemicals, making it difficult or impossible to continue working where glutaraldehyde exposure continues to occur.

Heart valve workers also had the potential for skin and eye contact with glutaraldehyde. Glutaraldehyde can remove the skin's natural protective oils. This can irritate the skin and cause dermatitis (skin rash), with dryness, redness, flaking, and cracking of the skin. Repeated exposure can also cause an allergic skin reaction.[29] Based on animal data, there is also some concern that skin sensitization from glutaraldehyde may lead to asthma.[30,31]

Exposure Control Measures

Engineering controls were implemented at both companies, including (a) a closed system to minimize handling of large

volumes of glutaraldehyde, and (b) dilution and local exhaust ventilation (Table I). However, many factors that contribute to worker exposure to glutaraldehyde persisted, including:

- *The presence of large exposed surface areas of glutaraldehyde under agitation.* At both facilities, existing dilution and local exhaust ventilation was unable to capture and remove glutaraldehyde vapor effectively during all glutaraldehyde-related tasks. For example, at Company A, 9 of the 10 most highly exposed tasks occurred in the area where the tissue was fixed in glutaraldehyde in locally exhausted open tanks and in an enclosed box. Assuming that the local exhaust ventilation system for the fixation enclosure was maintained in working order, fixation still required that workers manipulate the open containers in and out of the box, exposing a large surface area of glutaraldehyde and treated tissue. Additionally, many other containers of glutaraldehyde were simultaneously uncovered in all the work areas, resulting in a large exposed surface area of glutaraldehyde at both facilities.
- *Working with glutaraldehyde-treated tissue in proximity to workers' breathing zones.* Although significant efforts were made at one facility to pull the flow of air away from workers' breathing zones via local exhaust ventilation slots on the workstations, the existing dilution and local exhaust ventilation systems were not designed to fully capture glutaraldehyde vapors at their source.
- *Manual pouring and disposal of glutaraldehyde solutions without local exhaust ventilation, eye protection, and waste neutralization.* Although the jars and other containers of glutaraldehyde that were manually handled were relatively small, there was a large volume of glutaraldehyde poured and dispensed by hand without local exhaust ventilation and without eye protection at both facilities. Existing policies did not result in consistent, universal use of safety glasses. Moreover, disposing of glutaraldehyde solutions down the drain without neutralization has been reported to result in extremely high vapor levels at the point of disposal.[32,33]
- *Prolonged use of latex gloves.* Latex gloves should not be used for prolonged skin protection against glutaraldehyde.[34] Chemicals can permeate gloves without visibly affecting the materials and thus gain access to the skin in an insidious manner.[35] Latex gloves are suitable in situations where only short-term, incidental contact with glutaraldehyde is expected. Tests on latex gloves against glutaraldehyde have shown breakthrough in less than 45 min with 2% to 3.4% solutions.[36] The protection afforded by latex gloves can be improved by double gloving and changing gloves every 10 to 15 min. Although the data provided by one glove manufacturer indicates that its gloves will resist permeation to glutaraldehyde for more than 480 min, this may not be fully relevant to the conditions of use while making bioprosthetic heart valves, which involves exposure to glutaraldehyde in solution with other chemicals, including the use of isopropyl alcohol to clean the gloves. Moreover, latex gloves themselves present their own hazards. They have been associated with dermatitis, sensitization, and allergic reactions, including asthma.[7,37]

Illness Reports

In California over a 10-year period (1993–2003), CDHS' tracking system identified 20 cases of work-related asthma associated with exposure to glutaraldehyde. Of these 20 cases, 2 (10%) were new-onset, work-related asthma associated with glutaraldehyde in workers making bioprosthetic heart valves. In general, cases reported by physicians of work-related asthma are likely to underestimate the true incidence for several reasons: (1) workers are not routinely required to be examined by physicians as part of medical monitoring programs for agents that cause work-related asthma; (2) physicians may not recognize symptoms and signs of work-related asthma and report these cases as work related; (3) individuals who develop symptoms of asthma may leave the workplace before physician diagnosis; and (4) workers' fear of retaliation prohibits full reporting.

Training and Hazard Communication

Workers received training and communication about hazards. However, as we did not observe any training and did not implement a validated mechanism to assess worker knowledge, we do not know whether this system overall was fully effective. For example, in light of the mix of language and literacy skills and the use of English, PowerPoint training may not be effective.

A strength of one company's program was its ongoing maintenance of an active, cross-departmental Health and Safety Committee, including managerial and nonmanagerial representatives. Documentation of the proceedings and tracking of changes suggested a transparent and accountable process. The need to monitor and control worker exposure to glutaraldehyde was routinely discussed.

A weakness of the hazard communication efforts at Company A was its policy of requiring exposed workers to report their pregnancies to the employer. Whether glutaraldehyde can affect the reproductive system has not been well studied. Glutaraldehyde is believed unlikely to affect pregnancy or male or female reproductive function so long as exposure levels are below those that cause irritation or other obvious symptoms. The mandatory reporting of pregnancy policy at Company A is not an effective health and safety measure to protect against glutaraldehyde-related or other reproductive/developmental toxicity in the workplace. Consistent with the requirements of the Cal/OSHA Hazard Communication Standard, workplace reproductive hazards, including hazards to pregnancy, should be identified, and the prevention measures employed to protect against the hazards should be discussed proactively with all employees as a part of health and safety training. If particular hazards selectively impact the outcome of pregnancies, the employer's policy for addressing these hazards, including alternative work assignments, should be

clearly stated and included as a part of health and safety training regardless of pregnancy status.

In addition, a mandatory reporting of pregnancy policy (a) breaches workers' privacy; (b) may cause workers who fear economic loss or retaliation to hide their pregnancy rather than seek care or removal from a hazardous exposure; (c) is inconsistent with the fact that the timing of exposure to toxic chemicals can have a significant impact on fetal outcomes, yet a worker may not recognize her condition in the early weeks and months of pregnancy; and (d) does not account for the potential for reproductive impacts as a result of paternal exposure to toxic substances.

Limitations

The scope of this investigation was limited to the use of glutaraldehyde at the facilities discernible through observation, record review, and worker and employer representative interviews. We did not take independent measurements of workers' glutaraldehyde exposures and did not validate the assumptions underlying the sampling strategies at these facilities. The impact of these limitations on the findings of this investigation is not known.

Sampling was conducted by three individuals, and 30% of the samples at Company B were obtained with a less sensitive sampling method. Therefore, comparisons of exposures between companies may be imprecise. The grouping of various job tasks at Company B for the purpose of this analysis may have obscured differences in exposures among individual workers performing the same task, or differences in similar tasks.

Workers' airborne exposures to glutaraldehyde were measured for 15-min periods in accordance with the recommended OSHA method. High levels of exposure that may have occurred over much shorter time periods would have been averaged into the 15-minute sample; therefore, the results of air monitoring may have underestimated workers' ceiling or instantaneous exposure levels.

The efficacy of the written respiratory protection program at Company B, and of worker training and hazard communication at both facilities, was not independently verified by CDHS researchers. Language barriers and the lack of a pre-established, independent mechanism for direct worker input limited the ability to gather information about workers' knowledge about their exposure to glutaraldehyde and the worker perspective on health and safety. The limited nature of this investigation was resource driven and did not imply there were, or were not, other health and safety issues at these workplaces.

CONCLUSIONS AND RECOMMENDATIONS

Workers making bioprosthetic heart valves are at risk for occupationally acquired asthma. Workers had continuous airborne exposure to glutaraldehyde over the course of every work shift at levels that can result in health effects, as well as potential skin and eye contact with glutaraldehyde. Reductions in worker exposure to glutaraldehyde could be achieved by implementing additional engineering controls and by making improvements in the type and use of personal protection equipment, as described in the recommendations below. Therefore, industry concerns that reductions in worker exposure would lead to modifying the work process in such a way as to warrant new clinical trials, and would place patient care in jeopardy, appear to have been unwarranted.

CDHS recommends the following measures (in italics) be implemented to prevent exposure to glutaraldehyde among workers making bioprosthetic heart valves. These recommendations are also applicable to other work processes for which a safer substitute for glutaraldehyde is not presently available.

Implement additional engineering controls to minimize workers' exposures. When it is currently not possible to substitute a toxic chemical with a safer alternative, engineering controls should be implemented to control worker exposures. The current TLV-C, equal to the newly approved Cal/OSHA PEL ceiling limit of 0.05 ppm, was not based on protecting workers against asthma. Data suggest that respiratory sensitization to glutaraldehyde is possible at a level of 0.015 ppm.[16] Therefore, engineering controls should be implemented to minimize workers' exposures to at least below a level of 0.015 ppm.

Many opportunities to further reduce exposures through the use of engineering controls remain to be implemented. At one company, procedures such as fixation that require large volumes of the chemical under pressure could be separated from other work areas. Tight-fitting lids should be put on fixation tanks, trays, jars, and all other glutaraldehyde containers to reduce the exposed surface area of glutaraldehyde. Fixation tanks could be redesigned to increase their depth (i.e., allowing for vertical submersion of the tissue, rather than horizontal submersion, to reduce the size of the opening of the tanks) to further minimize the exposed surface area.

In all areas, when container lids must be breached to manipulate the tissue or solution, release of glutaraldehyde vapor should be controlled by installing local exhaust ventilation located at the point of discharge to prevent the vapor from escaping into the room air.[34] Enclosure hoods are considered the best choice for highly toxic materials.[38]

Depending on the task, glutaraldehyde should be poured under local exhaust ventilation, and automatic dispensing systems and/or splash-resistant safety nozzles should be used. The work process should be reviewed to determine how the numerous pouring steps could be centralized and conducted under appropriate engineering controls. Research has shown that implementation of low-cost, splash-resistant safety nozzles can significantly reduce the exposure of workers pouring 2.6% glutaraldehyde solution.[32] Glutaraldehyde solutions should be neutralized before disposal. A recent study[32] demonstrated that neutralization of glutaraldehyde with sodium bisulfite for only 5 min resulted in reducing worker exposure to below 0.01 ppm.

Involving directly exposed production workers in the planning and implementation of recommended engineering controls is likely to improve the efficacy of these steps. It is essential to remonitor exposures after changes are made.

Identify and implement an appropriate glove to prevent workers' skin exposure to glutaraldehyde and latex. Latex gloves should not be used to control workers' skin exposure to glutaraldehyde. Nitrile and butyl rubber gloves are suitable for use with up to 50% glutaraldehyde, and polyethylene gloves can be used with low concentrations of glutaraldehyde (less than 3–4%). Glove manufacturers should be asked to provide documentation to support the suitability of their gloves for glutaraldehyde protection under conditions of use. Specifically, consideration should be given to the impact of buffered solutions of glutaraldehyde and alcohol on glove permeability.

Require the use of safety glasses when handling glutaraldehyde solutions. Eye contact with glutaraldehyde is harmful and easily prevented. As it may be difficult to identify all situations with potential for a "splash," workers should always use safety glasses when working with glutaraldehyde.

Implement a medical surveillance program for glutaraldehyde-exposed workers. Early diagnosis and removal from exposure significantly improves the prognosis for recovery after the development of sensitizer-induced occupational asthma.[47–49] The medical surveillance program in the Cal/OSHA Formaldehyde Standard is designed to address sensitization and could be used as a template to implement medical surveillance among glutaraldehyde-exposed workers making bioprosthetic heart valves (CCR, Title 8, Section 5217; the federal standard is 29 CFR 1910.1048). Any worker potentially exposed to glutaraldehyde should also be included in a medical surveillance program. An annual respiratory questionnaire should be administered, with medical evaluation and spirometry as indicated by work-related symptoms.

In the event of medical removal due to work-related health problems, a Medical Removal Protection Program should be in place to protect the workers from loss of salary and benefits. Medical Removal Protection is essential to the success of a medical surveillance program because it allows workers to come forward with symptoms without the fear of job loss or retaliation.

Mandatory reporting of pregnancy is not an effective health and safety measure. Workers are protected from potential reproductive hazards by preventing hazardous exposures for all employees, training and communicating reproductive hazard information to all workers (so they will have this information in time to ensure they are adequately protected), and establishing a voluntary mechanism for workers to report *any* disability for which they may need accommodation.

Integrate worker health and safety considerations into the assessment of alternatives to glutaraldehyde-fixation at the onset of process redesign. Future use of an alternative to glutaraldehyde in the manufacture of bioprosthetic heart valves will not eliminate the need to monitor and control worker exposure to other chemicals. Worker health and safety considerations should be anticipated by employers and regulatory agencies and integrated into the assessment of alternatives to glutaraldehyde-fixation at the onset of process redesign.

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