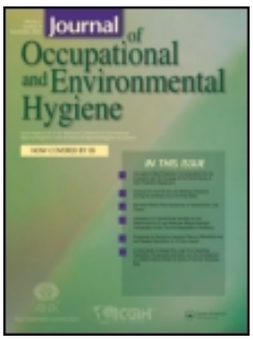

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Glutaraldehyde Exposures Among Workers Making Bioprosthetic Heart Valves

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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

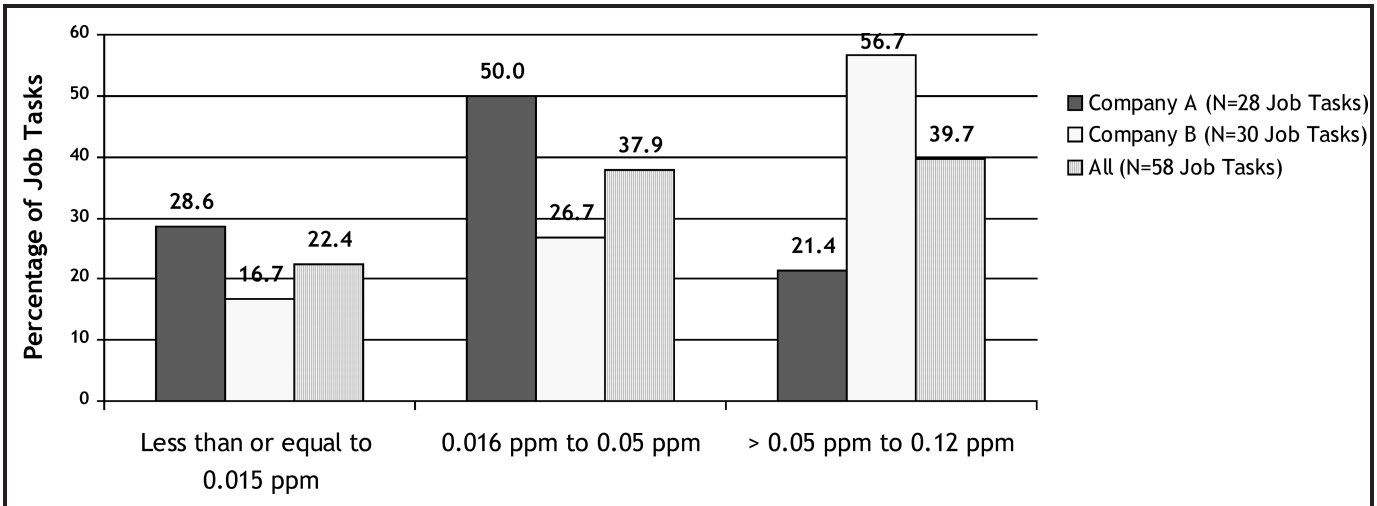

FIGURE 1. Glutaraldehyde exposures by job tasks at two heart valve manufacturing facilities. *Note:* At Company A, the results are based on 61 samples collected over an approximately 6-week period in 2003 categorized by job task. The highest exposure for each job task was selected to represent the current 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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REFERENCES

1. **Burge, P.S.:** Occupational risks of glutaraldehyde. *Br. Med. J. 299*:342 (1989).
2. **Vyas, A., C.A.C. Pickering, L.R. Oldham, et al.:** Survey of symptoms, respiratory function, and immunology and their relationship to glutaraldehyde and other occupational exposures in endoscopy nursing staff. *J. Occup. Environ. Med. 75*:752–759 (2000).
3. **Jachuck, S.J., C.L. Bound, J. Steel, and P.G. Blain:** Occupational hazard in hospital staff exposed to 2 per cent glutaraldehyde in an endoscopy unit. *J. Soc. Occup. Med. 39*:69–79 (1989).
4. **Norbäck, D.:** Skin and respiratory symptoms from exposure to alkaline glutaraldehyde in medical services. *Scand. J. Work, Environ. Health 14*:366–371 (1988).
5. **Pisaniello, D.L., R.T. Gun, M.N. Tkaczuk, M. Nitshcke, and J. Crea:** Glutaraldehyde exposures and symptoms among endoscopy nurses in South Australia. *Appl. Occup. Environ. Hyg. 12*:171–177 (1997).
6. **Leinster, P., J.M. Baum, and P.J. Baxter:** An assessment of exposure to glutaraldehyde in hospitals: Typical exposure levels and recommended control measures.*Br. J. Ind. Med. 50*:107–111 (1993).
7. "Association of Occupational and Environmental Clinics. Occupational Asthmagens on the AOEC List of Exposure Codes." [Online] Available at http://www.aoec.org/aoeccode.htm#Occupational_Asthmagen_List (Accessed February 9, 2005).
8. **Corrado, O.J., and R.J. Davies:** Asthma after exposure to glutaraldehyde in endoscopy units. *Hum. Toxicol. 5*:325–327 (1986).
9. **Benson, W.G.:** Case report: Exposure to glutaraldehyde. *J. Soc. Occup. Med. 34*:63–64 (1984).
10. **Nicewicz, J.T., D.M.F. Murphy, J.P Welsch, and H. Sirolli:** Occupational asthma caused by glutaraldehyde exposure. *Immunol. Allergy Pract. 8*:272–278 (1986).
11. **Meredith, S.K., V.M. Taylor, and J.C. McDonald:** Occupational respiratory disease in the United Kingdom, 1989. *Br. J. Ind. Med. 48*:292–298 (1991).
12. **Cullinan, P., J. Hayes, J. Cannon, D. Heap, and A. Newman Taylor:** Occupational asthma in radiographers. *Lancet 340*:1477 (1992).
13. **Waldron, H.A.:** Glutaraldehyde allergy in hospital workers. *Lancet 339*:880 (1992).
14. **Calder, H.T., L.P. Wright, and D. Grimstone:** Glutaraldehyde allergy in endoscopy units. *Lancet 339*:443 (1992).
15. **Curren, A.D., P.S. Burger, and K. Wiley:** Clinical and immunologic evaluation of workers exposed to glutaraldehyde. *Allergy 51*:826–832 (1996).
16. **DiStefano, F., S. Siriruttanapruk, J.S. McCoach, and P.S. Burge:** Occupational asthma due to glutaraldehyde. *Monaldi Arch.Chest Dis. 53*:50–55 (1998).
17. **Quirce, S., M. Gomez, C. Bombin, and J. Sastre:** Glutaraldehyde-induced asthma. *Allergy 54*:1121–1122 (1999).
18. **Ong, T.H., K.L. Tan, H.S. Lee, and P. Eng:** A case report of occupational asthma due to glutaraldehyde exposure. *Ann. Acad. Med. Singapore 33*:275–278 (2004).
19. **Chan-Yeung, M., T. McMurren, F. Catonio-Begley, and S. Lam:** Occupational asthma in a technologist exposed to glutaraldehyde. *J. Allergy Clin. Immunol. 91*:974–8 (1993).

20. **Stenton, S.C., J.R. Beach, J.H. Dennis, N.P. Keaney, and D.J. Hendrick:** Glutaraldehyde, asthma and work A cautionary tale. *J. Occup. Med. 44*:95–98 (1994).
21. **Gannon, P.F.G., P. Bright, M. Campbell, S.P. O'Hickey, and P.S. Burge:** Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x-ray departments. *Thorax 50*:156–159 (1995).
22. **Di Stefano, F., S. Siriruttanapruk, J. McCoach, and P.S. Burge:** Glutaraldehyde: An occupational hazard in the hospital setting. *Allergy 54*:1105–1109 (1999).
23. **Hendricks, M., F. Everaerts, and M. Verhoeven:** Alternative fixation of bioprostheses. *J. Long-Term Eff. Med. Implants 11(3-4)*:163–183 (2001).
24. **Schoen, F.J., and R.J. Levy:** Tissue heart valves: Current challenges and future research perspectives. *J. Biomed. Mater. Res. 47*:439–465 (1999).
25. **Khor, E.:** Methods for the treatment of collagenous tissues for bioprostheses. *Biomaterials 18(2)*:95–107 (1997).
26. **Plume, S.K., and J.H. Sanders:** The Carpentier-Edwards stented supra-annular pericardial aortic valve prosthesis: Clinical durability and hemodynamic performance. *Curr. Opin. Cardiol. 17*:183–187 (2002).
27. "State Reporting Guidelines for Asthma." [Online] Available at http://www.cdc.gov/niosh/topics/surveillance/ords/StateBasedSurveillance/SurveillanceGuidelines(WRA).html#WRACaseDefn (Accessed January 17, 2006).
28. "U.S. Department of Labor. Occupational Safety and Health Administration. Glutaraldehyde Method 64." [Online] http://www.osha.gov/dts/sltc/methods/organic/org064/org064.html (Accessed February 9, 2005).
29. **Fowler, J.F.:** Allergic contact dermatitis from glutaraldehyde exposure. *J. Occup. Med. 31(10)*:852–853 (1989).
30. **U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health**: Evidence of dermal exposure health hazards associated with isocyanates.*Current Intelligence Bulletin* 58 (January 1998).
31. **Petsonk, E.L.:** Work-related asthma and implications for the general public. *Environ. Health Perspect. 110(Suppl. 4)*:569–572 (2002).
32. **Rivers, A.M., D.J. Stephenson, K.T. Hegmann, D.R. Lillquist, and F. Derosso:** Evaluation of procedural modifications to reduce glutaraldehyde vapors during the disinfection of endoscopes using three sampling methods. *Chem. Health Saf. 9(4)*:13–20 (2002).
33. **Notarianni, G.L.:** Glutaraldehyde overexposure: Myth or reality? One hospital-wide study.*J. Healthc. Mater. Manage. 10(6)*:20,22,24 (1992).
34. **American National Standards Institute (ANSI), Association for the Advancement of Medical Instrumentation (AAMI):** *Safe use and handling of glutaraldehyde-based products in health care facilities* (ANSI/AAMI ST58:1996). [Standard] Arlington, Va.: AAMI, 1996.
35. **Mäkelä, E.A., S. Vainiotalo, and K. Peltonen:** The permeability of surgical gloves to seven chemicals commonly used in hospitals. *Ann. Occup. Hyg. 47(4)*:313–323 (2003).
36. **Jordon, S.L.P., M.F. Stowers, E.G. Trawick, and A.B. Theis:** Glutaraldehyde permeation: Choosing the proper glove. *Am. J. Infect. Control 24*:67–69 (1996).
37. **Amr, S., and M.E. Bollinger:** Latex allergy and occupational asthma in health care workers: Adverse outcomes. *Environ. Health Perspect. 112*:378–381 (2004).
38. **McDermott, H.:** *Handbook of Ventilation for Contaminant Control*, Third Edition. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2001.
39. **Tarlo, S.M., G.M. Liss, and K.S. Yeung:** Changes in rates and severity of compensation claims for asthma due to diisocyanates: A possible effect of medical surveillance measures.*J. Occup. Environ. Med. 59*:58–62 (2002).
40. **Tarlo, S.M., and G.M. Liss:** Diisocyanate-induced asthma: Diagnosis, prognosis and effects of medical surveillance measures. *Appl. Occup. Environ. Hyg. 17*:902–908 (2002).
41. **Chan-Yeung, M.:** Occupational asthma. *Chest 98(Suppl. 5)*:148S (1990).