California Department of Health Services
Occupational Health Branch

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

PATRICE SUTTON, M.P.H.
JULIA QUINT, PH.D.
JANICE PRUDHOMME, D.O., M.P.H.
JENNIFER FLATTERY, M.P.H.
ROBERT HARRISON, M.D., M.P.H.
BARBARA MATERNA, PH.D., C.I.H.

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 always 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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