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Workplace assessment of exposure to 2-ethoxyethanol

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In recent years, certain monoalkyl glycol ethers have become implicated as potential reproductive toxins. One of the more suspect members of the family showing teratogenic effects in pregnant female rodents, as well as testicular toxicity in male rodents, has been 2-ethoxyethanol. Researchers from the National Institute for Occupational Safety and Health (NIOSH) have searched for several years to locate a population of occupationally exposed workers for study to determine whether adverse reproductive health effects occur. A population of roughly 100 exposed workers was identified on the West coast of the United States where exposure was adequately high to justify an evaluation of their reproductive health status.

This paper presents industrial hygiene and biomonitoring data which were collected in conjunction with a reproductive epidemiology study. The levels measured in this survey ranged from nondetectable to 23.8 ppm (for an 8-hour time-weighted average), and a biomonitoring effort was undertaken to determine if metabolites of the chemical could be detected in the urine of exposed workers or if the parent compound could be detected in their blood. One of the suspected major metabolites of 2-ethoxyethanol is 2-ethoxyacetic acid, and detection of this metabolite in urine would confirm exposure and biological uptake of the chemical with greater validity than breathing zone sampling alone. No evidence of 2-ethoxyethanol was detected in any of the blood samples; however, exposed workers were found to have measurable levels of the metabolite in urine (up to 163 mg/g creatinine), while unexposed control subjects showed nondetectable urine levels of this compound. The study demonstrated that urinary monitoring is a promising method for assessing exposure to 2-ethoxyethanol, particularly when skin absorption is suspected. **Clapp, D. E.; Smallwood, A. W.; Mosely, C.; DeBord, K. E.:** Workplace assessment of exposure to 2-ethoxyethanol. *Appl. Ind. Hyg. 2*:183–187; 1987.

Introduction

The chemical compound, 2-ethoxyethanol (2EE), is one member of a family of ethylene glycol ethers. Based on the National Occupational Hazard Survey (NOHS) conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1972 and 1974, it is estimated that as many as 400,000 workers are potentially exposed to 2EE.[1] Both 2EE and 2-methoxyethanol (2ME) have been identified as potent reproductive toxins leading to testicular atrophy and sterility in male animals, as well as embryonic death, teratogenesis, and growth retardation in growing fetuses.[2] Importantly, animals demonstrating these effects were exposed at levels below the prevailing Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs).

A colorless liquid at room temperature, 2EE is highly miscible with water and with many organic solvents. The compound is highly reactive in the presence of strong oxidizers. It has a low vapor pressure of 4 mm of mercury at 20°C (vs. 75 mm for benzene at 20°C). In the coatings industry, 2EE is rated as a slow evaporator with an evaporation rate of 0.3 relative to the standard, n-butyl acetate (evaporation rate = 1.0). Fast evaporators have relative rates above 2.5.[3] This slow evaporation rate and low vapor pressure suggest that the potential for exposure to airborne concentrations of 2EE is less than for more volatile solvents; however, the American Conference of Governmental Industrial Hygienists (ACGIH) has appended the "skin" notation with its published threshold limit value (TLV) for 2EE indicating a likelihood of absorption of the compound through the skin.[4]

Due to the positive animal reproductive toxicity of 2EE, NIOSH researchers initiated a search for workers exposed to 2EE in several industrial settings to determine any adverse reproductive effects which may have occurred due to occupational exposures to this compound. The search for a study location was complicated by the need for a large group of male workers with substantial 2EE exposure, but without confounding exposures to other substances with potentially adverse reproductive effects.

In the spring of 1984, a plant was located with an adequate number of exposed male workers and where 2EE exposures were sufficiently high to justify a reproductive health study. Data obtained from the company indicated that airborne concentrations ranging up to 20 ppm were common in certain areas of the plant throughout the workweek and that these exposure levels had existed for at least four years. Due to the nature of the process, the worker exposures were approximately equal across all work classifications in 2EE

exposure areas.

This paper presents the results of the industrial hygiene assessment of exposures to 2EE at this facility. Two surveys were conducted: one in April 1984 and a second in June 1984. The first survey was intended to determine if exposures were sufficiently high to justify the proposed reproductive health study. Based upon the results of the first industrial hygiene survey, a reproductive health study was conducted in June 1984. During the intervening period, the use of 2EE was eliminated in two of three facilities at this plant. To evaluate reduced exposures, a second industrial hygiene survey was scheduled concurrently with the reproductive study. During both of these surveys, a major industrial hygiene objective was the evaluation of biomonitoring as a viable strategy for assessing 2EE exposure. To pursue this objective, concurrent air samples and biological specimens were collected. The biological specimens were collected to determine if the parent compound (2EE) could be found in blood or the metabolite (ethoxyacetic acid [EAA]) could be found in urine.

Process description

The company surveyed in this study was engaged in casting precision metal parts including castings for pumps, compressors, turbochargers, and devices for surgical bone repair and replacement. These parts are cast using a process sometimes called the "lost wax process."

The process begins with the preparation of a wax replica of the part which is to be cast in metal. The wax replicas serve as patterns for preparing a ceramic shell for casting the metal part. The shells are prepared by immersing the wax replicas in a ceramic slurry which contains approximately ten percent 2EE by volume. By dipping the replica repeatedly in the ceramic slurry, followed by a sand shower, a thick shell is built up on the outer surface of the wax. Between dips, shells are suspended from an overhead conveyor system or stored on open racks to dry. Numerous fans are used to keep the room air in constant motion. The room air is conditioned for temperature and humidity control and recirculated by a large air handling system.

After the desired thickness of ceramic shell is achieved, the wax is removed from the shell in a steam autoclave. The shells are heated prior to pouring the molten metal. When the molds cool and solidify, they are moved to a cleaning operation where the ceramic material is removed from the newly formed metal part (an exact replica of the wax pattern related earlier). Cast parts are cleaned and repaired as necessary following several inspections.

Exposure standards and criteria

OSHA has promulgated a full-shift, eight-hour, time-weighted average (TWA) PEL for occupational exposure to 2EE of 200 ppm, which has remained unchanged since the PELs were established.[5] The OSHA PEL is based primarily on reports of blood, kidney, liver, and central nervous system toxicity caused by 2ME and 2EE in animals and on case reports of human exposure to 2ME. ACGIH recommends a TLV of 5 ppm based primarily on testicular effects observed in recent animal studies.[4] Both the OSHA PEL and the ACGIH TLV bear the "skin" notation indicating the potential for absorption of toxic amounts of 2EE through the intact skin. Based upon the potential for adverse reproductive and embryonic effects, NIOSH recommends that exposures be reduced to the lowest extent possible.[2]

Exposure assessment methods

Air samples

Both personal and area air samples were collected on these surveys. Accuhaler™ (Model 808) pumps manufactured by the MDA Company were used for full-shift personal samples. These pumps were operated at a flow rate of 50 cc/min in accordance with NIOSH Method 1403.[6] The full-shift breathing zone (BZ) samples were collected by attaching the sample media (sorbent tubes containing 150 mg of activated charcoal) to the worker's collar or lapel. The pump and tube were connected by a convenient length of Tygon tubing for comfortable positioning of the pump on the worker's belt after looping the tubing across the worker's back. No short-term personal samples were collected since the nature of the process did not reveal any probable sudden releases of 2EE or other sources of peak exposure.

To insure greater likelihood of detecting 2EE in various areas of the plant, full-shift TWA area air samples were collected using charcoal tubes at higher flow rates to obtain a larger amount of 2EE on the sample media. For these higher volume samples, DuPont P 200™ constant flow pumps were used at a flow rate of 200 cc/min. All samples were analyzed by gas chromatography according to NIOSH Method 1403.[6]

Biological samples

As stated earlier, an objective of these surveys was to investigate biological monitoring as a viable strategy for assessing 2EE exposures. Since animal studies have shown that 2EE exposure leads to detectable levels of 2EE in blood and EAA in urine, both blood and urine sampling were attempted on these surveys. On the first survey, 5 ml blood samples were collected one time at the end of a workshift using Vacutainers® containing EDTA anticoagulant. Blood samples were chilled (not frozen) and hand carried to the laboratory for analysis. NIOSH researchers have developed methods for analyzing both blood (for 2EE) and urine (for EAA).[7]

For the first survey, urine samples were collected from five workers (3 exposed, 2 controls) on a timed basis during a 24-hour sampling period after four workdays of exposure. Urine was collected in 200 ml Nalgene® bottles which participating workers marked at the time of each void. The volume of each void was determined and a portion of the urine was transferred to 20 ml scintillation vials and frozen on dry ice for shipment to the laboratory for analysis. All samples were analyzed as described in Smallwood *et al.*[7]

On the second survey, blood samples were not collected since the results of the earlier collections were nondetectable (ND). Also, on the second survey only spot urine samples (not timed) were collected

TABLE I
Results: Full-shift time-weighted average area samples for 2-ethoxyethanol (ppm)

	April 1984 survey			June 1984 survey		
	GM	GSD	N	GM	GSD	N
Investment room, Bldg. A	16.9	(1.1)	(3)	3.0	(6.8)	(3)
Investment room, Bldg. B	10.7	(1.3)	(3)	14.9	(1.1)	(4)
Investment room, Bldg. C		NA		2.4	(5.5)	(5)
2EE mixing/storage rooms	5.9	(1.6)	(6)		NA	

NA = not applicable, no samples collected.
GM = geometric mean, GSD = geometric standard deviation, N = number samples.
LOD = limit of detection, (0.01 mg).

TABLE II
Results: Full-shift time-weighted average personal samples for 2-ethoxyethanol (ppm)

	April 1984 Survey			June 1984 Survey		
	GM	GSD	N	GM	GSD	N
Building A						
Hand dipper	14.5	(1.2)	(5)		NA	
Manual Shell Processor	3.0	(4.7)	(2)		NA	
Building B						
Grabber Operator	6.5	(1.1)	(2)	8.1	(3.2)	(7)
Auto Shell Processor		NA		4.5	(3.2)	(8)
Investment Supervisor	6.0	(1.1)	(2)	5.0	(1.0)	(1)

NA = not applicable, no samples collected.
GM = geometric mean, GSD = geometric standard deviation, N = number samples.
LOD = limit of detection (0.01 mg).

to permit the participation of a larger number of workers over a longer time interval.

Results

Area air samples

On both the April and June 1984 surveys, the full-shift, TWA area samples were collected at high flowrates to insure detectable levels of 2EE. The results (Table I) clearly indicate that detectable exposures did exist in the range indicated by company historical records. The highest levels, approaching 20 ppm, were found in the investment rooms where open tanks of slurry were located. In the April survey, concentrations of 2EE in the investment rooms appeared to be slightly higher in Building A than in Building B. Also in the April survey, investment room concentrations at both buildings were generally higher than chemical storage and mixing areas.

Comparing the results of the April and June surveys confirms the elimination of 2EE from slurry mixes at Buildings A and C. The 2EE airborne concentrations were still detectable, but substantially lower, indicating that traces of 2EE remained in the process stream. At Building B, where 2EE was not eliminated, the airborne concentrations remained at comparable levels.

Personal air samples

The personal exposure data (Table II) demonstrates exposures of the same order of magnitude as the area air samples (Table I), ranging up to 24 ppm. Hand dippers appeared to have the highest exposures of all the jobs sampled, ranging from 12 to 19 ppm. These workers spent the entire shift manually dipping small molds into open slurry tanks, then inserting wet molds into a sand shower to build up the shell covering the wax replicas. Hand dipping and manual shell processing was done only in Building A, where small parts were processed. At Building B large parts were handled with forklift trucks (auto shell processors), and dipping was performed by robot (grabber) dipping machines (operated by a worker at each robot). Grabber operator exposures were under 10 ppm in both April and June surveys. Their overall lower exposures (compared with the hand dippers) were undoubtedly due to the location of their work stations and their less intimate contact with the slurry.

In the April 1984 survey, personal exposures at Building B averaged under 6 ppm while those at Building A averaged over 11 ppm. The higher exposures are seen in both area and personal samples. This difference was judged most likely due to construction differences between the buildings, as well as process differences (hand dipping vs. robot operation). Building A was newer and more airtight with a closed ventilation system. The investment department at Building A was physically isolated from the remainder of the building. At Building B, outside doors were typically left open to encourage cross ventilation, and all departments were interconnected.

Exposures for grabber operators and auto shell processors (Bldg. B) remained in a comparable range during the June 1984 survey reflecting the continued use of 2EE during the period. Personal samples were not collected for hand dippers and manual shell processors (Bldg. A) since use of 2EE was discontinued after the April 1984 survey. A single supervisor at Building B volunteered for personal sampling, and his results are similar to other workers in this building, reflecting his practice of spending most of his work day in the production area.

Biological samples

Seventeen blood samples were collected from individual workers in the April 1984 survey. Nine exposed workers and four controls participated by providing at least one blood sample. Four exposed workers provided two samples each for replicate samples. In the animal studies used to develop the method, 2EE was applied directly to the skin. None of the workers who submitted blood samples reported any routine, recognized 2EE skin contact, and exposure was thought to occur by inadvertent skin contact, inhalation, or by airborne vapor condensing on the skin.

The analysis of the blood samples revealed no detectable levels of 2EE. As a part of the analysis, the laboratory prepared spiked blood samples for a recovery study. The results of five spiked samples (spiked at 25 μg 2EE/g blood) averaged 100 percent recovery, suggesting that the method was in control at that level. The limit of quantitation (LOQ) of the method was 10 μg/g blood. Blood sampling was not repeated on the June 1984 survey. More detail on the comparable efficacy of blood versus urine monitoring is given in Smallwood *et al.*[7]

As opposed to the blood sample results, urine monitoring did reveal positive evidence of 2EE absorption (Table III). In the April survey, timed individual urine voids

TABLE III
Results: urine monitoring— individual voids (mg EAA/g creatinine)

Job Code	1	2	3	4	5	6	Average
Hand dipper Bldg. A	ND	26	37	40	46	55	40.8
Hand dipper Bldg. A	21	21	40	38	31		30.2
Supervisor Bldg. B	18	27	28	35	32		28.0
Control Bldg. A	ND	ND	ND	ND	ND		
Control Bldg. A	ND	ND	ND	ND			

ND = none detected.
LOD = limit of detection (10 mg/L, before creatinine adjustment).

were collected from three exposed workers and two controls as voided throughout a 24-hour sampling period. The number of voids varied from worker to worker. The control subjects whose results are shown in Table III were employed outside of the investment department, in areas where 2EE was not used.

The urine monitoring results for the exposed workers clearly indicate 2EE absorption. For all the voids collected from the exposed workers, the concentrations are well above the limit of quantitation (10 μg/L before creatinine adjustment). The hand dippers' results are higher than the supervisor's, reflecting the supervisor's reduced potential for exposure. The controls (who had no apparent 2EE exposure) had nondetectable EAA concentrations in their urine samples.

In the June survey, additional urine samples were collected from cooperating workers in Building B (the only building where 2EE was still in use) with the intent of studying variation over an extended period. These samples were spot samples collected over a seven-day week. Although some workers agreed to give one sample, seven workers agreed to provide multiple samples throughout the week. The logistics of worker cooperation, sample collection, and handling prevented more frequent sampling or sampling from more individuals. The goal of the extended sampling was to determine if trends in the concentration of EAA in urine occurred either during a work shift or over a workweek. Also, to explore excretion rates, some samples were collected after workers were away from exposure for a day or more.

In the seven cooperating workers providing multiple samples, it is possible to make comparisons during shifts and over the workweek (Table IV). Results for the investment room supervisor generally were low and showed little variability over the shift—consistent with his job assignment which did not require working in close proximity with 2EE sources. The three samples he submitted on day 6 showed a slight decrease after one day away from work (day 5 was an off day for him). Grabber operators and shell processors, who work closely with 2EE sources for their entire work shift, showed higher urine concentrations. Generally, these concentrations increased during a given work shift. Samples from grabber operator 1 evidenced increased EAA concentrations through the shift (values of 70, 101, and 106) on those days he submitted multiple samples (day 2 and day 3). The worker with the highest urine concentrations (grabber operator 2) was observed cleaning slurry containers the night before the urine samples were submitted. Shell processor 1, who had a relatively high concentration on day 2, submitted a sample with a non-detectable concentration after two days away from work (day 7).

TABLE IV
Exposure results: individual urine monitoring mg EEA/g creatinine—June 1984 survey, Building B

	Day of Collection						
Person/Job	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Supervisor	29		30			16*	
	40				Off	20*	
					Work	16*	
Grab. Opr. 1		70	97		68	59	108
		101	102				
		106					
Grab. Opr. 2			121		52	59	79
			163				
Grab. Opr. 3				74	55	45	
Shell Proc. 1		79			Off	Off	ND**
					Work	Work	
Shell Proc. 2			78	87			
Shell Proc. 3							61
							60

Notes: multiple values shown on a single day for a single worker are sequential voids during a work shift.
*after one day off work.
**after two days off work.

In the June survey, ten individual urine voids were collected from control subjects with no known exposure to 2EE. Without exception, all urine samples collected from these subjects (not shown in Table IV) were nondetectable. This result is similar to the findings in the April survey for workers with no 2EE exposure. A few urine samples were collected from workers in Buildings A and C (where 2EE use was suspended), and most of these samples contained no detectable concentrations of EAA. For the few urine samples from workers in Buildings A and C with detectable amounts of EAA in urine, the concentrations were all below 8 mg EAA/g creatinine (which approximated the limit of detection of the analytical instrumentation). While company officials stated that 2EE had been eliminated from these buildings, these urine results suggest that some residual 2EE evidently remained in the process stream.

Discussion and conclusions

The results of this study revealed that biological monitoring can be a viable method for assessing 2EE exposure. While animal studies suggested the likelihood of the presence of 2EE in blood and a metabolite (EAA) in urine, this is the first study to actually monitor blood and urine in human workers exposed to 2EE. Although the blood samples were negative, the urine monitoring revealed quantifiable EAA concentrations in exposed workers, and these results were roughly proportional to the relative potential for exposure (e.g., dippers vs. supervisors). Furthermore, urine samples collected from nonexposed workers (controls) consistently contained no detectable EAA concentrations. These results indicate the viability of urine monitoring as a method for assessing exposure to 2EE. Biological monitoring should be especially useful for 2EE exposures since skin absorption is a major route of entry for the chemical into the body; also, since 2EE is readily absorbed through the skin, these results suggest the desirability of developing a biological exposure index (BEI) for this substance.

Although all of the exposures measured were well below the prevailing OSHA PEL of 200 ppm, the concentrations ranged up to four times the current ACGIH TLV of 5 ppm. These exposures are high enough to warrant concern, particularly since persistent concentrations of EAA were detected in exposed workers' urine. These data, and subjective observations, justified a follow-up reproductive study to determine if any evidence of impairment of reproductive function has occurred due to 2EE exposure. The results of this reproductive study are reported elsewhere.[8]

Recommendations

Reduction or elimination of exposures to glycol ethers is warranted in view of potential adverse reproductive effects. Where possible, 2EE should be eliminated from the production process. In cases where 2EE cannot be readily eliminated, exposures

can be reduced through conventional control practices including engineering controls (equipment redesign, ventilation, etc.), personal protective equipment, and work practices. The establishment of a biological exposure index is needed for 2EE as well as other members of the glycol ether family with similar properties and hazards.

Special vigilance is required for worker exposures to glycol ethers due to the ready absorption of these substances through the skin. Workers who may come in direct contact with 2EE should wear butyl rubber gloves and work clothing which covers as much exposed skin as possible (long-sleeved shirts). Properly fitted respirators are recommended where potential exists for inhalation exposure.

A continuous industrial hygiene exposure assessment program is essential to quantify glycol ether exposures. Exposure data is required to develop meaningful and effective strategies for reducing exposures. Since air sampling is inadequate for estimating absorbed dose through the skin, biological monitoring should be considered. The analysis for glycol ether metabolites in urine is a relatively straightforward chemical analysis and collection; shipping of samples is simple. If glycol ether metabolites are detected in urine samples (even in the absence of airborne concentrations), follow-up action is clearly needed.

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