Workers' Exposures to n-Propyl Bromide at an Optical Prism and Optical Assemblies Manufacturer

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Abstract

The National Institute for Occupational Safety and Health (NIOSH) conducted a field study at a prism and optical assembly manufacturing plant where n-propyl bromide (nPB) was used as a vapor degreasing solvent. Workers' breathing zone, and exhaled breath concentrations of nPB and isopropyl bromide (iPB) were measured on two consecutive days, as were urinary metabolite concentrations of bromide (Br) and propyl mercapturic acid (PMA).

n-Propyl bromide has been marketed to replace ozone depleting solvents 1,1,1-trichloroethane and freons®, as well as suspect carcinogens trichloroethylene and methylene chloride; chemicals commonly used in industry. Sparse data are currently available to evaluate *human* exposure to nPB. However, there is concern that nPB may be a hematological, reproductive, or neurological toxin, based on analogy to other Br-propanes, animal studies, and a few case studies.

Full-shift time weighted average (TWA) exposure to nPB collected in workers' breathing zone air samples ranged from 0.52 to 9.8 parts per million (ppm) and from 0.12 to 11 ppm, respectively, for day 1 and day 2. All of the workers were exposed to nPB at levels below the industrial guideline of 25 ppm published by the EPA in their proposed rulemaking to accept nPB under the Clean Air Act. However, five (out of 14) TWA nPB measurements exceeded or approached (> 75%) the American Conference of Governmental Industrial Hygienist (ACGIH) Threshold Limit Value® of 10 ppm. The average TWA exposure for all workers on both days combined was 4.9 ppm. Exhaled breath concentrations of nPB ranged from 0.035 to 0.59 ppm and 0.067 to 2.5 ppm, respectively, for pre- and post-shift samples. Isopropyl bromide (iPB), a low level contaminant in nPB solvents, was only detected in three air samples in very low quantities; iPB was not detected in any of the breath samples.

Average urinary bromide (Br) concentrations measured before the work week began and during both workdays, as measured by 24 hour composite samples, were approximately three times higher for all workers combined than for unexposed controls who were not employed by this company. Mill technicians had the highest workday urinary Br levels (range: 7.5 – 26 milligrams per liter; average = 15 mg/l). Bromide in urine can be influenced in general and working populations by non-occupational factors such as diet and medications, including over the counter medications. Propyl mercapturic acid (PMA) is a more specific metabolite for measuring exposure to nPB. The 24-hour average PMA concentrations determined for both workdays combined was fifty times higher than the average PMA concentration in controls. The mill technicians, who spent the most time using the degreaser or who were in closest proximity to the degreaser, had urinary PMA concentrations approximately 66 and 95 times higher than the average control concentrations for day 1 and day 2, respectively. Workers were observed to periodically contact nPB solvent with unprotected hands; dermal absorption, in addition to inhalation exposure, may contribute to the observed urinary metabolite concentrations.

Recommendations provided in this report include substitution of nPB solvents with a less toxic solvent, periodic exposure monitoring, local exhaust ventilation, degreaser modifications, implementation of a respiratory protection program, impermeable gloves to nPB, and routine medical examinations.

Site Survey Record
Industrywide Studies Branch
Division of Surveillance, Hazard Evaluations and Field Studies
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Centers for Disease Control and Prevention

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Introduction

The Industrywide Studies Branch of the National Institute for Occupational Safety and Health (NIOSH) conducted a field study at Precision Optical, a optical prism and assembly manufacturing plant in Costa Mesa, California on August 16-18, 2004. At this facility, n-propyl bromide (nPB) was used as a cleaning solvent to remove paint, wax and other protective coatings from polished glass articles during processing. In this research study, we measured workers' breathing zone concentrations to nPB and isopropyl bromide (iPB), an impurity, with standard air sampling methods in conjunction with new methods for measuring exhaled breath and urinary metabolites.

Based on the uncertainty regarding the toxicity of nPB, the Occupational Safety and Health Administration (OSHA) and NIOSH requested the National Toxicology Program (NTP) to evaluate the toxicity of this chemical (OSHA, 1999; NTP, 2004). The absence of nPB exposure assessment information has prompted NIOSH to conduct a multi-industry occupational exposure study to evaluate workers' industrial exposures to nPB. One objective is to evaluate a variety of industries listed by the Environmental Protection Agency (EPA) for review of nPB approval under the Clean Air Act. This study is an exposure assessment study, not a health study; as such it did not provide medical determinations. This site report describes the monitoring performed at one of these facilities which will be compiled into the larger NIOSH-IWSB study regarding occupational exposure to nPB in multiple industries.

Background

The toxicity of nPB, also named 1-bromopropane (CAS no. 106-94-5), is not fully understood as there is limited information in the published literature. The Environmental Protection Agency (EPA, 1999; 2003) is evaluating nPB as an alternative to ozone-depleting solvents for vapor-degreasing and liquid cleaning of metal, precision, and electronic components as well as for use as a solvent in aerosol products and adhesives. n-Propyl bromide has been marketed to replace 1,1,1-trichloroethane, freons®, and suspect carcinogens trichloroethylene and methylene chloride, chemicals that were commonly used in industry. Very little data are currently available to evaluate *human* exposure to nPB. However, based on analogy to other brominated-propanes, animal toxicity studies, and a limited number of case studies, there is concern that nPB may be a hematological (blood), reproductive, or neurological toxin. (Refer to Attachment I for more detailed information regarding the toxicity of nPB and iPB.)

Process Description

Precision optical manufactures laser quality prisms and optical assemblies primarily for the defense, aerospace, biomedical and lithography industries. These components include a large variety of prisms, corner cubes, alignment cubes, laser optical windows and beam splitters. The manufacturing process starts with rough cutting quartz and other glass raw materials to obtain the

basic shape. The glass is then mounted on plaster blocks and wax, pitch, paint and other protective coatings are applied on some surfaces. The blocked part is subsequently ground in mills to remove one to five thousandths of an inch. Following grinding, the glass is polished to get the final finish and coatings may be applied for some product lines.

A nPB-based solvent containing over 94% nPB (Solvon PB®, PolySystems USA, Inc.) is used as the vapor degreasing solvent primarily by two departments. One vapor degreaser is shared by approximately a half dozen workers in the Milling department. A second degreaser is located in the Blocking department but was out for repairs during this survey. The actual number of technicians who need to use the degreaser on a given day depends on the product line and work production schedule. The production schedule for this company is dictated by customer orders. As such, the vapor degreaser is not continuously operated, rather parts are cleaned in batches on an "as-needed" basis to remove plaster, wax, pitch, paint and other protective coating prior to, and after grinding and polishing.

A medium capacity (14 gallon), open-top vapor degreaser is located in the Mill room. This degreaser utilized a 3" refrigerated cooling coils around the top of the perimeter (18" x 28") of the vapor chamber with 10" of freeboard height, and a similar cooling coil around the center of the chamber. The cooling coil condenses nPB vapor into liquid droplets on the cool surface of parts to remove surface contamination. Excess solvent drips back into the solvent sump and is recycled as the parts ascend from the vapor to condensing zones. A secondary function of the cooling coil is to control solvent vapor emissions by "capping" the heated vapor zone with a refrigerated air space, typically six to twelve inches in height. A hand actuated spray wand and nozzle was also used with this degreaser to supplement the vapor cleaning.

The room that contains the vapor degreaser also contains mills, grinders, and saws. Local exhaust ventilation was not provided for the vapor degreaser but the room was serviced with general dilution ventilation and doors were frequently left open. The only personal protective equipment employees were observed to use were safety glasses and safety shoes. Respirators and chemical resistant gloves were not used when using the vapor degreaser.

Evaluation Criteria

At present, occupational exposure limits (OELs) for nPB are not available from either OSHA (2006) or NIOSH (1992), and suggested manufacturers' guidelines are inconsistent, ranging from 5 to 100 parts per million (ppm) (Great Lakes Chemicals, 2005; Enviro-Tech International, 2005). The EPA initially reviewed industry-sponsored animal studies and suggested that 50 to 100 ppm should provide adequate protection, but cautioned that this was a preliminary decision since it was based on limited data with considerable uncertainty (EPA, 2000). This proposal was largely based on hepatic toxicity observed in rats, not on reproductive, hematopoietic, or neurologic effects. After reviewing industry studies (Clintrials Biorecherches1997a, 1997b; WIL Research Laboratories, 2000) and published literature, Rozman and Doull (2002) concluded that neurotoxicity is the most sensitive end point and an OEL for nPB in the range of 60 to 90 ppm should provide an adequate margin of safety.

On June 03, 2003, the EPA published a proposed rulemaking to accept nPB as a replacement solvent for ozone depleting substances for general metals, precision, and electronics cleaning, aerosol products, and adhesives (EPA, 2003). In this proposed rule, the EPA recommends an industrial exposure guideline for nPB of 25 ppm over an 8-hr work shift. The proposed rulemaking is currently being re-assessed by the EPA. Albemarle Co. (2003), one of the domestic suppliers of nPB solvents, also recommends an exposure guideline for nPB equal to 25 ppm as an 8-hour time weighted average (TWA) concentration. In 2005, ACGIH published a recommended Threshold Limit Value® (TLV) for nPB as a 10 ppm, 8-hr TWA based on suspected neurological toxicity (ACGIH, 2006). As one can see from these exposure guidelines, the OELs for nPB recommended by different organizations vary by an order of magnitude.

Following a case study of reproductive and hematological health effects in workers exposed to iPB in an electronics plant (Kim et al., 1996; Park et al., 1997), the Republic of South Korea and Japan promulgated an OEL for iPB of 1 ppm, measured as an 8-hour TWA. No other OELs are presently published for iPB. Occupational exposure criteria for two of the urinary metabolites of nPB which were analyzed at these facilities (e.g., bromide and propyl mercapturic acid) are currently unavailable.

Methods

In this research study, nPB exposures were determined with standard air sampling methods in conjunction with new methods for exhaled breath and urinary metabolites. Employees voluntarily participating in the study were informed of the study requirements and provided their written consent in accordance with Human Subjects Review Board protocol.

At this facility, workers' exposures to nPB and isopropyl bromide (iPB) were measured over two consecutive workdays using three types of monitoring: 1) air sampling in their personal breathing zones; 2) exhaled breath; and 3) urinary metabolites. Seven workers voluntarily consented to participate, each of whom worked with nPB or was expected to be in the vicinity of vapor degreasers using nPB. These workers included five technicians (three mill operators, an edger, and a blocker) as well as two maintenance workers. The workers wore light-weight air sampling pumps on 2 consecutive days; provided exhaled breath samples before and after their work shifts; and provided all of their urine collected over a 48-hour period, both while at and away from work. The air and breath samples were analyzed for nPB as well as iPB, a low level contaminant in nPB solvents. The urine samples were analyzed for bromide (Br) ion and propyl mercapturic acid (PMA), also called N-acetyl-S-(n-propyl)-L-cysteine.

Personal breathing zone and exhaled breath samples were collected with Anasorb carbon molecular sieve (CMS) sorbent tubes. The sorbent tubes were desorbed with 1 milliliter (ml) of carbon disulfide, and analyzed for nPB and iPB by gas chromatography with flame ionization detection (GC-FID) via NIOSH method 1025 (NIOSH, 2003a). The limit of detection (LOD) for this method is 0.5 μg which equates to a minimum detectable concentration (MDC) of 0.0083 ppm in air using the maximum recommended air sampling volume of 12 liters and a MDC of 0.033 ppm in an exhaled breath volume of 3 liters. Qualitative evaluation of skin contact

potential was conducted by visual observation of job tasks since effective quantitative skin exposure measurement methods do not exist for compounds, such as nPB, which are volatile and readily penetrate intact skin. The workers were interviewed to determine the amount of time that they used the degreaser which ranged from not using it at all to a couple of hours.

To obtain data on nPB metabolites excreted by humans, all of the workers' urine voids over a 48-hour period were collected, including the amount excreted while away from work. The specimens were collected as composite samples over sequential time intervals: 1) at work, 2) after work but before bedtime, and 3) upon awakening. Each sampling survey was intended to occur over a 48-hour period that started at the beginning of the work week (Monday, pre-shift), following a weekend of no exposure and end before the work shift on Wednesday. For comparison, single "spot" control samples were collected from twenty-one unexposed office workers who were not employed by this company.

Urine specimens were collected in nitric acid rinsed Nalgene® bottles [high density polyethylene (HDPE)] and immediately chilled in 10 quart coolers with gel ice which were individually supplied to each participant. Upon the end of the collection period, three-25 ml sample aliquots were dispensed into nitric acid rinsed HDPE bottles and immediately frozen on carbonic acid (dry-ice). The total urine volume for this collection period was also measured with a graduated cyclinder. In addition to Br and PMA, the specimens were also analyzed for creatinine (cr).

Bromine

Bromide (Br) ion was measured with inductively coupled plasma/mass spectrometry (ICP/MS; Varion Ultra-mass 700) using yttrium as an internal standard (Allain et al., 1990; Ichihara et al., 2004; Kawai et al., 2001). The LOD for bromine was 90 micrograms per liter (μg/l). One ml of each sample was diluted to 10 ml with 1% nitric acid prior to analysis. Analytical standards and quality control samples were prepared using Uri-sub, a synthetic urine solution. This was necessary because background concentrations of Br may be present in pooled urine from the general population.

Propyl mercapturic acid

The urine specimens were analyzed for PMA, one of the major mercapturic acid metabolites of nPB (Grenby and Young, 1960; Jones and Walsh, 1979). Four ml aliquots of the urine specimens were loaded onto a solid phase extraction cartridge, rinsed with three ml of a methanol-acidified water mixture (pH = 3); PMA was then extracted in four ml of acetone, dried under nitrogen, and reconstituted in one ml of methanol. Analysis was performed using high performance liquid chromatography (HPLC) with electrospray ionization-tandem mass spectrometry (ESI-MS/MS) for improved sensitivity and specificity (e.g., confirmation of chemical identity).

Creatinine

Creatinine was analyzed using Sigma diagnostics test kit, procedure #555. Room temperature urine specimens were diluted by a factor of 20 (or 40 if very concentrated) and mixed with six ml of alkaline picrate. After 10-15 minutes, color analysis of the creatinine-picrate complex was performed with a spectrophotometer (Milton Roy Spectronic 20 D). A 0.2 ml aliquot of acid reagent was then added and the specimen was re-analyzed after five minutes; positive results from the second analysis were subtracted from the first measurements as it is due to interfering compounds.

Creatinine is a protein by-product excreted in urine due to the metabolism of creatine from muscle exertion. It is often used to adjust urine data due to different levels of physical activity, hydration, and urine concentrations between different individuals or time periods. The urine data in this report, however, are only presented as unadjusted concentrations, either mg/l or µg/l for Br and PMA, respectively. Once the data are compiled from multiple sites in this study, the urine data will be adjusted ("normalized") for creatinine (mg Br/gm creatinine or µg PMA/gm creatinine) for publication in scientific journals.

Results

Table 1 presents the time weighted average (TWA) air sampling results collected in workers' breathing zones over 2 full work shifts. Full-shift exposure to nPB ranged from 0.52 to 9.8 parts per million (ppm) and from 0.12 to 11 ppm, for the first and second monitoring days, respectively. Daily averages for all workers combined were 5.1 ppm on day 1, and 4.6 ppm on day 2. All of the workers were exposed to nPB at levels below the industrial guideline of 25 ppm published by the EPA in their proposed rulemaking to accept nPB under the Clean Air Act and recommended by several solvent distributors. However, five (out of 14) TWA measurements exceeded or approached (> 75%) the American Conference of Governmental Industrial Hygienist (ACGIH) Threshold Limit Value (TLV®) of 10 ppm, measured over an 8-hour workshift. Iso-propyl bromide was not detected in any of the air samples with a minimum detectable concentration above 0.0083 ppm (for a 12 liter sample); well below 1 ppm, the only published occupational exposure limit for iPB. Interviews of the workers were conducted to determine the amount of time they used the degreaser which ranged from not using it at all to a couple of hours. Workers who used the degreaser most often or were in closest proximity to it had the highest exposure levels.

Table 2 provides a summary of the exhaled breath concentrations for nPB. The nPB concentrations measured in the pre-shift breath samples ranged from 0.059 to 0.59 ppm, and from 0.067 to 2.5 in the post-shift samples. The average pre-shift breath concentrations of nPB were less than the respective post-shift average for both monitoring days (i.e., average pre-shift and post-shift concentration pairs were 0.12 and 0.9 for day 1, and 0.26 and 0.51 for day 2). Iso-propyl bromide was not detected in any of the breath samples with a minimum detectable concentration above 0.033 ppm for a 3 liter sample. There are no criteria to compare breath concentrations because this is a new experimental method.

The average Br concentration from urine samples collected before the work-week began was 13 milligrams per liter (mg/l) for all seven workers (Table 3). Moreover, the 24-hour average concentrations of urinary Br ranged from 1.3 to 26 mg/l, and the daily averages were 13 and 12 mg/l. For comparison, the average Br concentration was 4.0 mg/l in spot samples from control subjects who were not employed by this company. Hence, workers average urinary Br levels were about three times greater than the control average.

Bromide in urine can be influenced by non-occupational factors such as diet and medications, including over the counter medications. Propyl mercapturic acid (PMA) is a more specific metabolite for measuring exposure to nPB. The data for PMA are provided in Table 4. The PMA concentrations before the work week for workers ranged from 63 to 902 microgram per liter (μg/l), and the average was over five times higher than the average calculated from control specimens. Furthermore, the average 24-hour concentrations of PMA from all workers over both workdays were about forty to fifty times higher than the control average. More specifically, average 24 hour PMA concentrations for mill technicians and the blocker were approximately 54 and 78 times greater the control subjects' average, for day 1 and day 2, respectively.

The potential for solvent splashing and dermal contact exists with vapor degreasing processes, especially when the shape of the parts or racks could carry solvent out of the degreaser vapor zone. Chemical resistant gloves were not observed to be used in these departments and some assemblers contacted nPB solvent and recently cleaned parts with unprotected skin.

Statistical analyses were not conducted for the data collected at this single site since only seven workers participated in the monitoring. Statistical analyses will be performed after all of the data collected at separate sites are pooled into larger data bases.

Conclusions

- All of the workers' full-shift TWA exposures to nPB were below the industrial guideline of 25 ppm proposed by the EPA and several solvent distributors, however, several TWAs exceeded or approached (> 75%) the ACGIH TLV® of 10 ppm.

- Given the observed production rate, the general ventilation provided for the vapor degreaser and door openings were marginally controlling nPB air emissions below 10 ppm. Increased work load for degreaser users may cause workers' nPB exposure to exceed the ACGIH TLV more frequently.

- Workers' exposures to iPB were not detected with a minimal detected concentration well below 1 ppm, the only occupational exposure limit available (published by South Korea).

- The pre- and post-shift breath monitoring showed measurable levels of nPB but not iPB, and the post-shift averages were greater than the pre-shift averages on both work days.

The technicians with the full-shift-TWAs to nPB that approached the TLV also had the highest post shift nPB breath concentrations.

- Average "pre-week" concentrations of the urinary Br were three times higher for workers than for control subjects; workers' average 24-hour Br concentrations during work days were similar to the pre-week average.

- Average 24-hour concentrations of the urinary PMA measured in worker specimens during work days were over forty to fifty times higher than the average PMA concentration measured in control specimens.

- Unprotected dermal contact with nPB solvents and recently degreased parts may contribute to the workers' exposures. nPB is appreciably absorbed through workers' intact skin, which contributes to their overall absorbed dose.

- The conclusions drawn are based on the data from the grouped population of workers. These data demonstrate that workers using degreasers are exposed to and are excreting nPB metabolites. However, the health significance of an individual's urine metabolite level is uncertain.

Recommendations

Human health effects from exposure to nPB are not fully understood as there are only a few reports in the published literature. The occupational exposure criteria of 25 ppm suggested by the EPA and some solvent manufacturers are largely based on limited data observed in animal toxicity studies. The ACGIH TLV of 10 ppm for nPB is based on suspected neurological toxicity. As additional scientific information becomes available, the OEL currently proposed may, in fact, be lowered. Therefore, NIOSH scientists believe it is prudent to reduce occupational exposure of nPB to the lowest feasible levels.

To reduce the risk of hazardous exposures in the work environment, industrial hygiene principles incorporate the following hierarchy of exposure control, in decreasing order of preference and effectiveness:

a) Eliminate a toxic substance by substituting it with a less toxic one or by process changes,
b) Install engineering controls to remove or reduce the airborne contaminants, preferably at the point of emission using: local exhaust ventilation; isolation of contaminant emissions away from worker positions; or by process changes,
c) Use administrative controls to reduce individual exposures by altering or rotating job tasks and work schedules, thereby reducing high exposure durations, and
d) Use personal protective equipment (PPE), such as respiratory protection, gloves, aprons, etc., to reduce the absorbed dose from potential exposure. Although PPE is frequently used because it is a cheaper and easier method of control, it is the least desirable because it is not always effective. NIOSH policy is that PPE should only be

used when engineering controls are infeasible; during the interim period when engineering controls are being installed or repaired; or when engineering controls are not effective in reducing exposure below hazardous levels.

More specific recommendations to minimize workers' exposures to nPB at this facility are provided below:

1. Eliminate nPB based solvents if feasible by using a less toxic substitute. It is advisable to consult with technical experts and solvent distributors to evaluate if there are any suitable alternative solvents that are less toxic which perform in accordance with engineering specifications. If alternative solvents are not feasible, use nPB solvents that have the lowest iPB contamination as is possible. Based on the non-detectable iPB results, it appears that nPB solvents used at your facilities do not contain excessive iPB contamination. The ASTM (2001) standard for iPB contamination in nPB solvents is 0.10%. In the EPA proposed rulemaking (2003) to accept nPB solvents, a use restriction includes using nPB solvents with an iPB contamination not exceeding 0.05%, before blending into products. It is advisable to confirm that the nPB solvents used at your facility meet, and continue to meet, this criterion.

2. Employee exposures to nPB should be periodically re-evaluated. If monitoring results exceed relevant criteria, install engineering controls (i.e., local exhaust ventilation) for the degreaser and provide an adequate make-up air ventilation system to reduce airborne nPB concentrations. The ventilation system should include a slotted plenum ventilation hood adjacent to the back of the degreaser so that it removes solvent vapor away from workers' breathing zones. Furthermore, the work bench where parts are allowed to dry should also be provided with similar local exhaust ventilation. Design specifications are available in the ACGIH Industrial Ventilation Manual, 25th edition (2006) or similar industrial ventilation textbook. In addition, a routine maintenance schedule for ventilation systems is necessary to ensure effective performance of the equipment.

3. Workers' exposure levels to nPB could be reduced further with modifications to the degreaser. These include the use of a motorized hoist set at a pre-determined speed to prevent workers from lifting parts baskets too quickly through the vapor zone. This will reduce liquid and vapor solvent carry-out and, and reduce the amount of time workers must lean over the degreaser opening. Expanding the number of loops and height of the top condensing coil may also reduce solvent carry-out because it would provide a larger zone to cap the solvent vapors. The degreaser cover should also remain closed when not in use.

4. n-Propyl bromide readily penetrates intact skin and common glove materials. The observed work practices coupled with high nPB metabolites (urinary Br and PMA) suggests that dermal contact and absorption of nPB is substantial for some workers using the vapor degreasers. When skin contact potential with nPB or

parts recently removed from the degreaser is high, appropriate gloves, arm sleeves, aprons or other PPE should be used as appropriate. Solvent manufacturers recommend use of multiple layer laminates for protection against nPB. These include, but are not limited to, Viton™, 4H (PE/EVAL)™, and Silver Shield™. Other more common glove/PPE materials [e.g., latex, nitrile, neoprene, butyl rubber, poly vinyl chloride (PVC), etc.] do not adequately prevent nPB from penetrating the PPE material for more than a few minutes to a few hours. This may include time after the glove is contaminated even though it is no longer worn by a worker.

5. Respiratory protection should be provided for those workers who desire to use it when operating the vapor degreaser or if the controls are not effective in reducing exposures sufficiently. Only NIOSH approved air purifying respirators with organic vapor cartridges or NIOSH approved air supplied respirators should be used. The use of respiratory protection requires the implementation of a comprehensive respiratory protection program in accordance with OSHA regulations (29 CFR 1910.134) and NIOSH recommended procedures (NIOSH, 1987). A minimal acceptable program must be managed by a competent person and include: written procedures; proper selection; user training; routine cleaning and inspection; proper storage; surveillance of work conditions and worker exposures; program audits; medical determination of user fitness; and use of approved respirators.

6. Company management must maintain an awareness of the latest scientific information regarding occupational exposure guidelines for nPB as well as relevant health, safety, and environmental standards from regulatory agencies.

7. Employees potentially exposed to nPB should be provided with routine medical examinations. Reports of health effects should be referred to a health care provider who specializes in occupational or environmental medicine.

Table 1.
Summary of workers' TWA[a] air sample concentrations of n-propyl bromide and isopropyl bromide for the milling and maintenance workers.

Precision Optical
Costa Mesa, CA

National Institute for Occupational Safety and Health
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Chemical	Measure	TWA Air Concentration *(ppm)*[b] (n = 7)	
		Day 1	Day 2
nPB[c]	Average	5.1	4.6
	Range	0.52 - 9.8	0.12 – 11
iPB[d]	Average	—	0.026[e]
	Range	ND[f]	0.024 – 0.028

Footnotes:

a) TWA = time weighted average. It is used when multiple samples are collected over the work shift to calculate the average exposure concentration "pro-rated" for time.

Example:

TWA = [(time 1 x conc. 1) + (time 2 x conc. 2)… + ($time_i$ x $conc._i$)] ÷ total time for both sample 1 and 2 plus all additional samples (i)

b) Units are in parts per million by volume; the amount of bromopropane per 1 million parts of air.

c) nPB = n-propyl bromide (also called 1-bromopropane).

d) iPB = isopropyl bromide (also called 2-bromopropane).

e) Average was calculated only with detectable results (n = 3).

f) ND = non-detectable.

Table 2.
Summary of workers' breath concentrations of n-propyl bromide[a] for milling and maintenance workers.

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Date	Measure	nPB Breath concentration *(ppm)*[b] (n = 7)	
		Pre-shift	Post-Shift
Day 1	Average	0.12[c]	0.90
	Range	0.059 – 0.19	0.10 – 2.5
Day 2	Average	0.26	0.51
	Range	0.059 - 0.59	0.067 – 1.7
Day 3	Average	0.10[d]	n.a.[e]
	Range	0.035 – 0.34	n.a.

Footnotes:
a) iPB was not detected in any of the breath samples.
b) Units are in parts per million by volume; the amount of bromopropane in 1 million parts of breath.
c) Average was calculated only with detectable results (n = 6).
d) Average was calculated only with detectable results (n = 5).
e) Not applicable. Only a "before work" breath sample (e.g. 16-hour post shift) was collected on day 3.

Table 3.
Summary of workers' bromide concentrations in urine for milling and maintenance workers.

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Chemical	Job	Day 1, Before Work[a]	
		Range	Average
Bromide (*mg/liter*)[b]	Workers (n = 7)	2.9 – 22	13
	Controls[c]	0.98 – 16	4.0

Chemical	Job	Day 1, 24-Hr. Concentration[d]		Day 2, 24-Hr. Concentration	
		Range	Average	Range	Average
Bromide (*mg/liter*)	Workers (n = 7)	3.7 – 23	13	1.3 – 26	12

Footnotes:
a) Sample was collected before or near the start of the work shift, after the weekend away from work.
b) Units are in milligrams of bromide per liter of urine.
c) Control samples were collected from 21office workers unexposed to nPB, not employed by this company.
d) 24-Hour concentrations were calculated from 3 combined samples of all urine specimens collected at work; after work before bedtime; and upon awakening.

Table 4.
Summary of workers' propyl mercapturic acid concentrations in urine for milling and maintenance workers.

Precision Optical
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Chemical	Job	Day 1, Before Work	
		Range	Average
PMA[a] (μg/liter)[b]	Workers (n = 7)	63 – 902	321
	Controls[c]	ND[d] – 207	59.7

Chemical	Job	Day 1, 24-Hr. Concentration[e]		Day 2, 24-Hr. Concentration	
		Range	Average	Range	Average
PMA (μg/liter)	Workers (n = 7)	289 – 5920	2520	129 – 10300	3460

Footnotes:

a) PMA = propyl mercapturic acid.

b) Units are in micrograms of propyl mercapturic acid per liter of urine. (One microgram is one thousand times less than a milligram.)

c) Control samples were collected from 21office workers unexposed to nPB, not employed by this company.

d) ND = non-detectable.

e) 24-Hour concentrations were calculated from 3 combined samples of all urine specimens collected at work;after work before bedtime; and upon awakening.

Attachment I

Toxicity of n-propyl bromide and isopropyl bromide

The molecular structure of bromopropanes is a simple three carbon alkane chain containing a single bromine substitution. There are two bromopropane isomers: n-propyl bromide [(nPB) also called 1-bromopropane; CAS No. 106-94-5] and isopropyl bromide [(iPB) also called 2-bromopropane; CAS No.75-26-3]. Prior to the last several years, nPB was primarily used to manufacture pharmaceuticals, pesticides, and other chemicals typically in well controlled closed processes. An international agreement between a number of industrial nations restricts the manufacture and use of ozone depleting substances including some compounds which were widely used throughout general industry: 1,1,1-trichloroethane and chlorofluorocarbons (freons®). In an effort to develop alternatives to replace these ozone depleting solvents, nPB products have been marketed, or are being considered, for metal cleaning/degreasing, automotive degreasing, electronics cleaning, precision cleaning (e.g., plastics, optics, and medical equipment), aerosol products, adhesive solvents, paint and coating solvents, textile dry cleaning, printing inks, and asphalt blending (EPA, 2003; Dead Sea Bromine, 1999; Petroferm, 2000). Products containing potential carcinogens trichloroethylene and methylene chloride are also candidates for alternative solvents, especially since the OSHA methylene chloride standard imposes more stringent occupational exposure and medical surveillance criteria with increased compliance costs. Currently, the principal application for nPB, in terms of quantities used, is for a vapor degreasing and liquid cleaning agent as well as spray adhesive solvent (EPA, 2003). However, the need to find suitable alternative solvents could expand nPB market applications, substantially increasing the quantities manufactured.

The first reports of health effects for bromopropanes occurred in 1996 in a Korean electronics plant where iPB was used as a cleaning solvent for electronic switches (Kim et al., 1996; Park et al., 1997). An epidemiology case study of 33 workers revealed that approximately two-thirds were experiencing reproductive disorders affecting both genders (e.g., low sperm concentrations, low motility or deformed sperm in men; and amenorrhea and elevated follicle stimulating hormone in women) (Kim et al., 1996). Further, seven workers had pancytopenia (e.g., reduced blood cell counts). An exposure-health effect association was obscured in this study since breathing zone monitoring was not performed, and the significance of reported dermal contact and brief short-term exposure to very high air concentrations is unclear. Ichihara et al. (1997; 1999) conducted a similar study at a chemical plant manufacturing iPB in China. Although severe reproductive disorders were not observed, reduced sperm concentrations and motility as well as decreased hemoglobin and hematocrit were suspected by the authors to be related to iPB exposure.

Subsequent to these occupational investigations, a series of rat studies were conducted in Japan with iPB to evaluate male reproductive and female reproductive or hematopoietic toxicity. In a review of the literature, Takeuchi et al. (1997) concluded that iPB impairs: *(i)* the testes, especially spermatogonia, *(ii)* ovarian function by disturbing the estrous cycle, damaging

primordial follicles and oocytes, *(iii)* bone marrow causing pancytopenia. Neurologic effects in rats exposed to iPB were also discovered by Yu et al. (1999; 2001).

There has been incentive to use nPB in lieu of iPB because of the perception that nPB has lower toxicity. There are several reports in the published literature regarding epidemiological and toxicological studies of nPB which are contrary to this supposition. In a 2001 report, Yu et al. (2001) demonstrated peripheral and possibly central neurotoxicity in rats but did not show reproductive or hematologic effects. Several additional reports have concluded that nPB produces dose dependant estrous cycle irregularities (Yamada et al., 2003; Takeuchi et al., 2001); spermiation destruction (Takeuchi et al., 2001; Ichihara et al., 2000a); reproductive and developmental toxicity (NTP, 2002; 2004; Ichihara et al., 2005); increased liver enzymes (Lee et al., 2005); and peripheral and central neurotoxicity (Yu et al., 2001; Ichihara et al., 2000b) in rats at similar dose levels that produced these effects by iPB. Ichihara et al. (2000b) concluded that nPB appeared to be a more potent neurotoxin than iPB. This conclusion is supported by several rat studies which have shown ataxic gait and hyper-excitability of the central nervous system, particularly at higher doses (Fueta et al., 2000, 2002a, 2002b, 2004; Honma et al., 2003; Wang et al., 2003).

Garner et al. (2006) published a metabolism study which investigated the disposition and excretion of nPB following intravenous, inhalation and dermal administration using mice and rats of both genders, metabolic inhibitors, and genetically altered animals. The authors concluded that metabolism and excretion were independent of route of administration. Elimination of nPB was very rapid with a half life under one hour, mostly via exhalation. Urinary excretion occurred by two principal mechanisms: dehalogenation by cytochrome P-450 and conjugation with glutathione. Minor metabolites were also observed indicating several other pathways for elimination.

Two case studies in the US have been published which describe decreased peripheral nerve functioning for three foam cushion workers using spray adhesives containing over 50% nPB (Ichihara, et al. 2002) and a worker who performed metal stripping using a degreasing solvent with approximately 95% nPB (Sclar, 1999). Presenting symptoms included numbness, weakness of lower extremities, staggering, and parasthesia or dysesthesia. The authors concluded that nPB likely caused the peripheral and central nervous system defects in these workers.

NIOSH has conducted Health Hazard Evaluations (HHEs) at two foam cushion fabricators and an aircraft seat cushion manufacturer where nPB was used as a spray adhesive solvent (NIOSH, 2003b; 2002a; 2002b). Full-shift nPB exposures at these plants identified numerous excursions exceeding 100 ppm, one recommended exposure guideline by some solvent distributers. For comparison, the 2003 proposed EPA industrial exposure guideline is 25 ppm, and the ACGIH TLV® published in 2005 is 10 ppm, measured as an eight-hour time-weighted average (TWA). At the aircraft seat cushion plant, full-shift nPB exposures ranged from 60 to 381 ppm, and 67 of 69 measurements exceeded 100 ppm (NIOSH, 2002a). Analysis of complete blood counts obtained from 43 (61%) of the aircraft cushion workers did not establish nor exonerate abnormalities associated with nPB exposure. A reproductive health questionnaire was also administered but the results were also inconclusive.

Toraason et al. (2006) conducted genotoxic studies to assess DNA damage, in vitro, and from 64 workers employed at two of the above HHE foam fabricating plants NIOSH investigated using PB-based adhesives. The authors concluded that limited evidence existed at these facilities to show exposure to nPB was associated with increased DNA damage.

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