Workers' Exposures to n-Propyl Bromide at a Helicopter Transmission Factory

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Introduction

The Industrywide Studies Branch of the National Institute for Occupational Safety and Health (NIOSH) conducted a field study at a helicopter transmission manufacturing plant in Texas on February 9-10, 2004. At this facility, n-propyl bromide (nPB) was used as a vapor degreasing solvent to remove oils and dirt from transmission parts prior to the plating operation necessary to affix a protective surface treatment. In this research study, we measured workers' breathing zone concentrations to n-propyl bromide (nPB) and isopropyl bromide (iPB) with standard air sampling methods in conjunction with new methods for measuring exhaled breath and urinary metabolites.

Background

The toxicity of nPB, also named 1-bromopropane, is poorly 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. Unfortunately, very little data are currently available to evaluate *human* exposure to nPB. There is concern, however, that nPB may be a hematological (blood), reproductive, or neurological toxin, based on analogy to other brominated-propanes, animal toxicity studies, and a limited number of case studies. (Refer to the attachment for more detailed information regarding the toxicity of nPB and iPB.)

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 this occupational exposure study to evaluate industrial exposures to nPB by measuring workers' personal breathing zone, exhaled breath, and urinary metabolite concentrations.

Process Description

This company is a subsidiary of a multi-industry corporation which manufactures helicopters, light and mid-size business jets, fastening systems, tools, pumps, transmissions, fuel tanks, as well as light weight industrial vehicles. Transmissions were manufactured at this plant for a variety of commercial helicopters including those designed for emergency medical transport, homeland security, law enforcement, corporate and utility markets.

The facility is a large industrial machine shop with affiliated manufacturing processes. Raw stock of steel and magnesium alloys are lathed, milled, machined, ground, and formed into casings, gears, rods, bushings, etc. and hardened with an emulsion oil heat treatment. Some parts may require additional processing such as abrasive blasting, precision grinding, finishing, and/or surface treatments (e.g., plating, anodizing). Quality control inspections and testing occurs throughout the processes. The casings are painted with a chromated primer and the transmissions are assembled and tested, and shipped to helicopter assembly plants.

n-Propyl bromide (Nu Tri Clean, Selig Industries) is used as a vapor degreasing solvent in the Plating department to remove oil and dirt from transmission parts prior to and between surface treatments. Surface treatments are applied by immersing parts into chemical solutions which include copper, nickel, cadmium, cadmium-chromate and black oxide plating; chemical film; and aluminum and titanium anodizing. Cadmium and black oxide plating require the most nPB degreasing. Perchloroethylene and Stoddard solvent are also used as degreasing solvents in this department. A series of open-topped tanks are arranged in series to clean the parts and apply a particular surface coating. A number of acid, alkaline, and chemical solutions are used as well as water rinses, some of which are heated to 200-260°F. These include hydrofluoric acid, hydrochloric acid, sulfuric acid, chromic acid, phosphoric acid, sodium and potassium hydroxide, permanganate, and cyanide solutions.

For many of the chemical tanks, local exhaust ventilation was installed with back and side slot plenums, but not for the nPB and perchloroethylene degreasers or water tanks. Vapor degreasers utilize a refrigerated cooling coil around the top of the interior of the vapor chamber, which condenses nPB (or perchloroethylene) vapor into liquid droplets on the surface of parts to remove oils and dirt. Excess solvent drips back into the solvent sump and is recycled as the parts slowly 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 eight inches in depth. The nPB degreaser also had a roll-top cover that was closed when the degreaser was not in use, and a mechanical hoist that removed the parts rack at a programmed speed to minimize excessive vapor from being carried out of the unit.

During the first shift, the chemical process department was operated by five hourly employees, all of whom participated in the monitoring survey; a department supervisor did not participate in the study. A lead operator oversaw the work flow, monitored the processes, and provided on-the-job training for new employees. Although employees had specific assignments and process lines, they may be required to service other lines as needed, or for lunch and relief breaks. Overall, the nPB degreaser was reported to be used for approximately one and a half to two hours per shift; it was used slightly less than that on both monitoring days. Personal protective equipment used by employees included nitrile or latex gloves, safety glasses, and safety shoes. Hearing protection, organic vapor or acid mist half-face piece respirators, PVC aprons, and face shields were also available, if needed.

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 equivocal, ranging from 10 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 newly adopted change to recommend a 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 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, we measured nPB inhalation exposures with standard air sampling methods in conjunction with new methods for measuring 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.) A total of 5 workers were included from this plant, each of whom worked in the chemical plating department (5F). The workers also wore a light-weight air sampling device on 2 consecutive days, provided pre- and post-shift exhaled breath samples, and all of their urine specimens over a 48-hour period. The air and breath samples were analyzed for nPB and iPB, a low level contaminant in nPB solvents. The urine samples were analyzed for bromide ion and another metabolite of nPB [propyl mercapturic acid (PMA) also called N-acetyl-S-(n-propyl)-L-cysteine].

Personal breathing zone exposures 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 by gas chromatography with flame ionization detection (GC-FID) via NIOSH method 1025 (NIOSH, 2003a). The limit of detection (LOD) for this method is 1 μg which equates to a minimum detectable concentration (MDC) of 0.016 ppm of nPB in air using the maximum recommended air sampling volume of 12 liters and a MDC of

0.07 ppm of nPB 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, that are volatile and readily penetrate the skin.

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 wake-up. Each sampling survey occurred over a 48-hour period and started at the beginning of the work week (Monday, pre-shift) following a weekend of no exposure and ended 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 that were individually supplied to each participant. Upon the end of the collection period, a 25 ml sample aliquot was 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. The specimens were analyzed for bromine, propyl mercapturic acid, and creatinine.

Bromine

Bromine (Br) was measured using 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 bromine may be present in pooled urine from the general population.

Propyl mercapturic acid

The urine specimens were analyzed for propyl mercapturic acid (PMA), the major mercapturic acid metabolite of nPB, also called N-acetyl-S-(n-propyl)-L-cysteine (Grenby and Young, 1960; Jones and Walsh, 1979). A four-ml aliquot of the urine specimens were loaded onto a solid phase extraction cartridge, rinsed with three-ml of a methanol and 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 and urine concentrations between different individuals. 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 air sampling results collected in workers' breathing zones over 2 full work shifts. The TWA concentrations for the platers ranged from 0.077 to 7.49 ppm with daily averages of 1.55 and 2.20 ppm. All of the platers' TWA exposures were less than 25 ppm, the industrial exposure guideline proposed by the EPA and Albemarle Corp., a manufacturer of nPB solvents as well as the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value® (TLV) of 10 ppm. Much lower concentrations of iPB were detected with a concentration ranging from 0.017 to 0.097 ppm. The highest iso-propyl bromide (iPB) concentration detected was well below the only occupational exposure limit (OEL) available, which is 1 ppm 8-hour time weighted average, promulgated by South Korea. The plater who used the vapor degreaser most often had the highest breathing zone exposures.

Table 2 provides a summary of the breath concentrations for nPB. The nPB concentrations measured in the post-shift samples ranged from 0.12 to 0.28 ppm. Only one sample had detectable levels of nPB in the pre-shift samples. Iso-propyl bromide was not detected in any of the breath samples.

In Table 3, the average Br concentration from urine samples collected before the work-week began was 10.6 milligrams per liter (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. Moreover, the 24-hour average concentrations of urinary Br for the platers was approximately twice as high as those for the control subjects. The data for another urinary metabolite, propyl mercapturic acid (PMA), are provided in Table 4, which show the same trends as the average before work week concentrations for platers were nearly twice as high as that of control subjects. Furthermore, the average 24-hour concentration of PMA from workers was substantially higher than controls, especially for the most heavily exposed worker. Twenty-four hour concentrations of PMA averaged for each day were over 30 times as high as the average PMA concentration measured from control specimens.

Statistical analyses were not conducted for the data collected at this site since only five 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 exposures were below the industrial guideline of 25 ppm proposed by the EPA as well as the ACGIH TLV® of 10 ppm. However, the plater who used the vapor degreaser most frequently was exposed to moderate levels of nPB that approached the TLV®.
- In conjunction with high ceilings and open floor plan, the ventilation provided in the plating department is relatively effective in controlling nPB emissions from the vapor degreasing operation, given the observed production rate.
- Workers' exposures to iPB were not detected except in low concentration well below 1 ppm, the occupational exposure limit published by South Korea.
- The post-shift breath monitoring showed measureable levels of nPB but not iPB.
- With the exception of one sample, breath concentrations of nPB were not detected in pre-shift samples.
- Dermal contact with recently degreased parts may contribute to the workers' exposures. nPB is appreciably absorbed through workers' intact skin, which contributes to their overall absorbed dose.
- Average 24-hour concentrations of the urinary Br were approximately twice as high for platers than for control subjects.
- Average 24-hour concentrations of the urinary PMA measured in worker specimens were at least 30 times as high as PMA concentrations measured in control specimens.
- The conclusions drawn are based on the data from the grouped population of workers. These data demonstrate that workers in the plating department are exposed to and are metabolizing nPB. However, the health significance of an individual's urine metabolite level is uncertain.

Recommendations

Human health effects from exposure to nPB are poorly 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. 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):

- i) Eliminate a toxic substance by substituting it with a less toxic one or by process changes,
- ii) Install engineering controls to: remove or reduce the airborne contaminants, preferably at the point of emission using local exhaust ventilation; isolate contaminant emissions away from worker positions; or by process changes,
- iii) Use of administrative controls to reduce individual exposures by altering or rotating job tasks and work schedules, thereby reducing high exposure durations, and
- iv) Use of 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. Perchloroethylene is also used in some vapor degreasing tasks at this facility. However, perchloroethylene should not be considered as a less toxic alternative since NIOSH considers perchloroethylene as a potential occupational carcinogen. 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.

2. Employee exposures to nPB should be periodically re-evaluated. If monitoring results exceed relevant criteria, install engineering controls consisting of local exhaust for the degreaser and provide make-up air ventilations systems to reduce airborne nPB concentrations. Design specifications are also available in the ACGIH Industrial Ventilation Manual, 25th edition (2006). In addition, a routine maintenance schedule must be implemented to ensure effective performance of the equipment.

3. Respiratory protection should be provided for those workers who desire to use it when operating the vapor degreser 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 includes: 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.

4. n-Propyl bromide readily penetrates intact skin and common glove materials. 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. 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, butyl rubber, PVC, etc.) do not adequately prevent nPB from penetrating the PPE material for more than 30 minutes to a few hours. However, these gloves may still be required in the plating department for protection against other chemicals used in this area. It is advisable to consult with technical experts and safety supply vendors to select an array of gloves needed in this department. Periodic training of employees is important to prevent them from using the wrong gloves for different applications.

5. If alternative solvents are not feasible, use nPB solvents with the lowest iPB contamination possible. 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.

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.

Data Tables

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention
U.S. Public Health Service
U.S. Department of Health and Human Services

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

Chemical	Measure	TWA (n = 5)	
		Day 1	**Day 2**
nPB[b] *(ppm)*[c]	Average	1.55	2.20
	Range	0.077 – 3.23	0.084 – 7.49
iPB[d] *(ppm)*	Average	0.073	0.022
	Range	0.042 – 0.097	0.017 – 0.031

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

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

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

Table 2.
Summary of workers' breath concentrations of n-propyl bromide[e] for the plating department.

Date	Measure *(ppm)*[f]	TWA (n = 5)	
		Pre-shift	Post-Shift
Day 1	Average	–	0.17
	Range	ND[g]	0.12 – 0.22
Day 2	Average	–	0.18
	Range	ND	0.13 – 0.28
Day 3	Average	–	n.a.[h]
	Range	0.062[i]	n.a.

Footnotes:

e) iPB was not detected in any of the breath samples.
f) Units are in parts per million by volume; the amount of bromopropane in 1 million parts of breath.
g) ND = non-detectable.
h) Not applicable. Only a "before work" breath sample (e.g. 16-hour post shift) was collected on day 3.
i) nPB was detected in only one breath sample.

Table 3.
Summary of workers' bromine concentrations in urine for the plating department.

Chemical	Job	Day 1, Before Work[j]	
		Range	Average
Bromine (*mg/liter*)[k]	Platers (n = 5)	6.0 - 19.0	10.6
	Controls[l]	0.98 - 16.0	4.0

Chemical	Job	Day 1, 24-Hr. Concentration[m]		Day 2, 24-Hr. Concentration	
		Range	Average	Range	Average
Bromine (*mg/liter*)	Platers (n = 5)	4.7 – 12.5	8.5	2.9 – 13.0	7.9

Footnotes:

j) Sample was collected before or near the start of the work shift, after the weekend away from work.

k) Units are in milligrams of bromine per liter of urine.

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

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

Table 4.
Summary of workers' propyl mercapturic acid concentrations in urine for the plating department.

Chemical	Job	Day 1, Before Work	
		Range	Average
PMA[n] (*µg/liter*)[o]	Platers (n = 5)	29 - 178	104
	Controls	ND[p] – 207.5	59.7

Chemical	Job	Day 1, 24-Hr. Concentration		Day 2, 24-Hr. Concentration	
		Range	Average	Range	Average
PMA (*µg/liter*)	Platers (n = 5)	28 – 7551	2134	143 - 9878	2819

Footnotes:

n) PMA = propyl mercapturic acid.

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

p) ND = non-detectable.

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 nPB-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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