Health Effects of n-Propyl Bromide

Margaret Sheppard
US EPA Stratospheric Protection Division
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Agenda

• Acute health effects of n-propyl bromide (nPB)
• Long-term health effects of nPB
• Case studies on workplace exposure
• Workplace exposure guidelines
• Information sources
Acute Health Effects of nPB

- Lethal inhaled concentration for 50% of test animals (LC50) after 4 hrs = 35,000 mg/m³ (7000 ppm)
- Lethal gavage dose for 50% of animals (LD50) > 2000 mg/kg
- No skin reactions or toxicity seen for dermal dose of 2000 mg/kg
- **Conclusion:** short-term toxicity not a great concern for nPB

*Sources:* Elf Atochem 1997, 1993, 1995a
Long-term Health Effects of nPB

Health effects of greatest concern:
- Liver and blood formation
- Nervous system
- Reproductive system

Major animal studies performed:
- 28-day subacute (ClinTrials, 1997a)
- 90-day subchronic (ClinTrials, 1997b)
- Reproductive (WIL, 2001)
- Developmental (Huntingdon Life Sciences, 2001)
- 2-year cancer study being finalized in 2008 (NTP)
Conclusions from Animal Test Data

• Liver effects: Centrilobular vacuolation found at relatively low levels
  – Data comparing rat and human liver cells in vitro shows comparable effects

• Carcinogenicity: Cytotoxicity occurs at higher levels, no clear evidence of mutagenicity

• Neurotoxic effects: Decreased hind limb grip strength, vacuolation of brain cells
  – Neurotoxic effects seen in short studies, not longer

• Reproductive effects: Sperm motility, male gland weights, ovarian cycling, pups born
  – Highly sensitive effects
# Animal Studies on Health Effects of nPB

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Liver</th>
<th>Nervous System</th>
<th>Reproductive System &amp; Development</th>
</tr>
</thead>
</table>
| • Barber et al., 1981.  
• Elf Atochem S.A. 1994. Ames Test  
• Elf Atochem, 1995. Micronucleus Test  
• NTP, 2003. Micronucleus Test  
• NTP, 2004. Ames Test  
• Saito-Suzuki et al., 1982.  
• SLR International, 2001a.  
• Toraason et al., 2006. | • ClinTrials, 1997a. 28-Day Inhalation Study  
• ClinTrials, 1997b. 13-Week Inhalation Study  
• NTP, 2003. 13-Week Inhalation Study  
• WIL Research Laboratories. 2001.  | • ClinTrials, 1997a. 28-Day Inhalation Study  
• ClinTrials, 1997b. 13-Week Inhalation Study  
• Honma et al., 2003.  
• Sekiguchi et al., 2002.  
• Wang et al., 1999.  
• WIL Research Laboratories. 2001.  
• Yu et al., 2001. | • Furuhashi et al., 2006.  
• Huntingdon Life Sciences, 2001. Developmental Study  
• Sekiguchi et al., 2002.  
• Wang et al., 1999.  
• WIL Research Laboratories. 2001. Multi-generation Reproductive Study  
• Yamada et al., 2003. |
| **Metabolism** | | | |
| • Ishidao et al., 2002.  
• RTI, 2005./Garner et al., 2006. | | | |
| | | | |
Observed Effects of nPB on Humans

- Peripheral, central nervous system toxicity
  - Several case reports of severe effects
  - Dermal exposure & inhalation both contribute
- Case reports ambiguous about reproductive, carcinogenic effects
  - nPB may have had an impact on women’s menstrual cycle at higher concentrations (> 100 ppm)
  - Limited evidence that nPB may damage DNA
- Concentrations causing effects are not certain

Sources: Beck and Caravati, 2003; CERHR, 2002a; Ichihara et al., 2002a, 2004a, 2004b; Majersik et al., 2004, 2005, 2007; Miller, 2005; Nemhauser et al., 2005; NIOSH, 2003; Raymond & Ford, 2005; Sclar, 1999; Toraason et al., 2006
Case Studies of nPB Worker Overexposure

• Workers overexposed to nPB-based adhesives
  – nPB concentration ranges:
    92-127, 60-261, 18-254 ppm
  – Avg concentrations of 108, 116, 133 ppm--8 hr TWA

• Workers suffered severe neurological symptoms
  – Pain in legs, numbness, difficulty walking
  – Anxiety, apathy, insomnia, memory and concentration difficulties
  – Symptoms persisting for months, years

• Raises concerns about use of nPB where exposure levels > 90 ppm; gloves, proper ventilation needed
Center for Evaluation of Risk to Human Reproduction - Review of nPB

- CERHR expert panel report published March 2002
  - Reviews available toxicity studies and identified no observed adverse effect concentrations (NOAECs) and lowest observed adverse effect concentrations (LOAECs)
  - Identifies whether studies are useful for risk assessment
  - Does not recommend an exposure limit

- Conclusions
  - “There is sufficient evidence to conclude that inhaled [nPB] causes reproductive toxicity in male and female rats. The NOAEC for these effects was 100 ppm. These results are assumed relevant for human hazard assessment.”
  - “Available human data are insufficient to draw conclusions on the potential for reproductive or developmental toxicity.”
  - “A well-conducted study of men and women occupationally exposed to [nPB] is urgently needed.”
Exposure Limit Derivation Methodology
(based on EPA RfC guidelines)

1. **Examine tox database**
   - Health effect or organ targeted
   - Concentration or dose

2. **Determine most sensitive health effect**
   - Calculate benchmark dose (BMDL)
   - If not enough info, use Lowest or No Observed Adverse Effect Level

3. **Choose point of departure**
   - Normalize exposure period in study to workweek (5 day/wk, 8hrs/day) for OEL, or to full week (7 day/wk, 24 hr/day) for RfC

4. **Calculate Human Equivalent Concentration**
   - Animal to human
   - Incomplete data
   - LOAEL instead of BMDL or NOAEL
   - Variability within population of concern (workers or general population)

5. **Apply uncertainty factors**
   - RfC/OEL
No Consensus on Occupational Exposure Limit for nPB
# Information for Some Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Exposure limit (source)</th>
<th>VOC?</th>
<th>Listed</th>
<th>HW?</th>
<th>HAP?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perchloroethylene</td>
<td>25 ppm (ACGIH)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>100 ppm (OSHA)</td>
<td></td>
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<tr>
<td>n-Propyl Bromide</td>
<td>10 ppm (ACGIH)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td></td>
<td>5-100 ppm (mfr)</td>
<td></td>
<td></td>
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<tr>
<td>Decamethyl-cyclopentasiloxane (D5)</td>
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<tr>
<td>Trichloroethylene</td>
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<tr>
<td></td>
<td>100 ppm (OSHA)</td>
<td></td>
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For More Information

• Center for Evaluation of Risks to Human Reproduction
  – cerhr.niehs.nih.gov/chemicals/bromopropanes/1-bromopropane/1-bromopropane.html

• National Toxicology Program
  – ntp.niehs.nih.gov/index.cfm?objectid=BD3C2054-123F-7908-7BB6085C71ABD211

• Description of references in EPA Federal Register notices
  – www.epa.gov/ozone/snap/regulations.html#rule12

• Many background documents available online
  – Docket for EPA rulemaking on nPB: go to www.regulations.gov, look for docket EPA-HQ-OAR-2002-0064
  – Elsevier Science Direct www.sciencedirect.com/

• Contact Margaret Sheppard
  – Tel. 202-343-9163 email: sheppard.margaret@epa.gov