# Health Effects of n-Propyl Bromide

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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/$m^3$ (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

## Cancer

- 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.

## Liver

- ClinTrials, 1997a. 28-Day Inhalation Study
- ClinTrials, 1997b. 13-Week Inhalation Study
- NTP, 2003. 13-Week Inhalation Study
- WIL Research Laboratories. 2001.

## Metabolism

- Ishidao et al., 2002.
- RTI, 2005./ Garner et al., 2006.

## Nervous System

- ClinTrials, 1997a. 28-Day Inhalation Study
- ClinTrials, 1997b. 13-Week Inhalation Study
- Fueta et al., 2002, 2004.
- Honma et al., 2003.
- Ichihara et al. 1999, 2000b.
- Sohn et al., 2002.
- Wang et al., 2003.
- WIL Research Laboratories. 2001.
- Yu et al., 2001.

## Reproductive System & Development

- Furuhashi et al., 2006.
- Huntingdon Life Sciences, 2001. Developmental Study
- Ichihara et al. 1997, 1998, 1999, 2000a
- Sekiguchi et al., 2002.
- Wang et al.,1999.
- WIL Research Laboratories. 2001. Multi-generation Reproductive Study
- Yamada et al., 2003.

# 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:

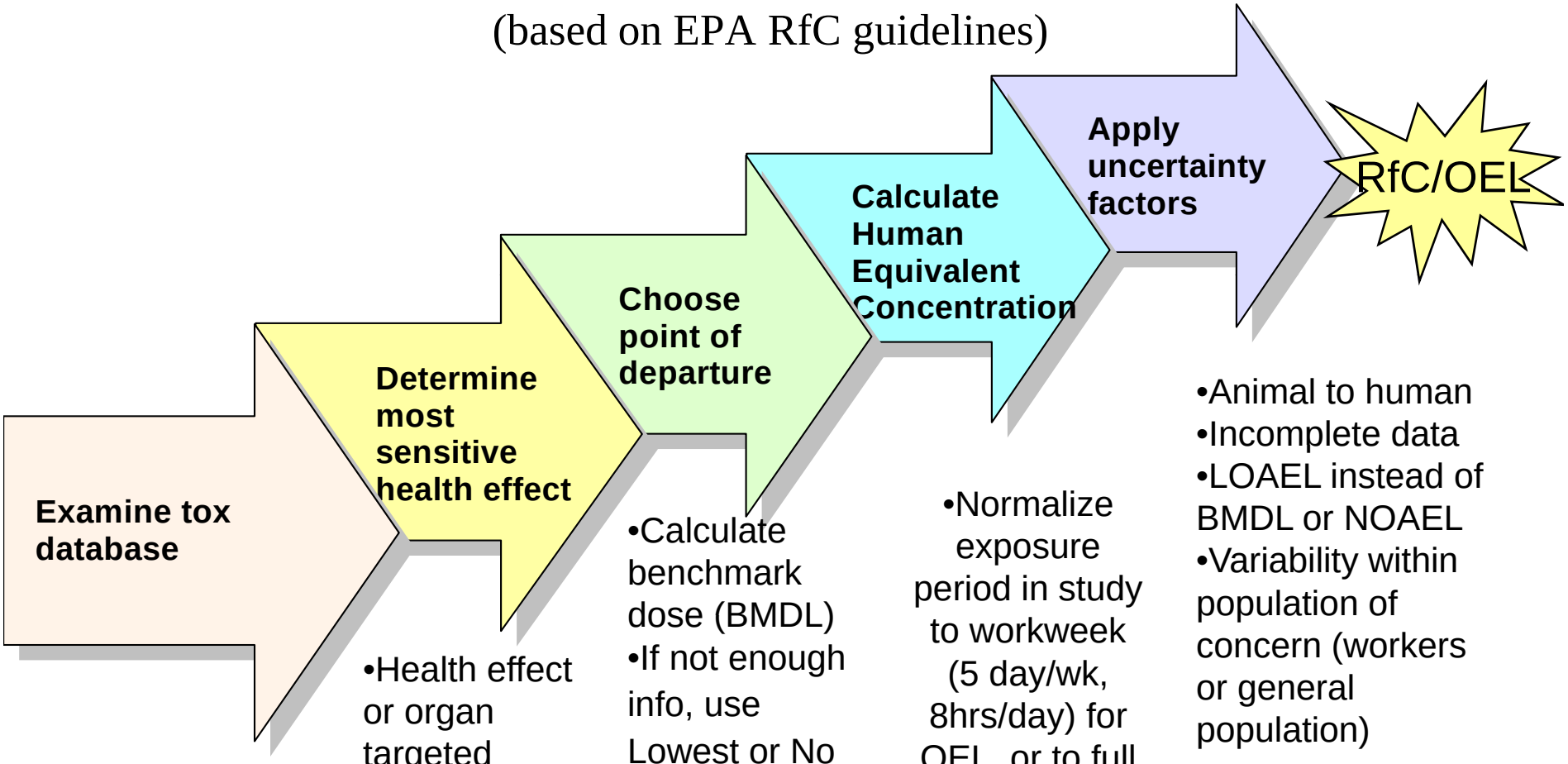
    92-127, 60-261, 18-254 ppm
  - Avg concentrations of 108, 116, 133 ppm--8 hr TWA
- Workers suffered severe neurological symptoms
  - Pain in legs, numbness, difficulty walking
  - Anxiety, apathy, insomnia, memory and concentration difficulties
  - Symptoms persisting for months, years
- Raises concerns about use of nPB where exposure levels > 90 ppm; gloves, proper ventilation needed

# Center for Evaluation of Risk to Human Reproduction - Review of nPB

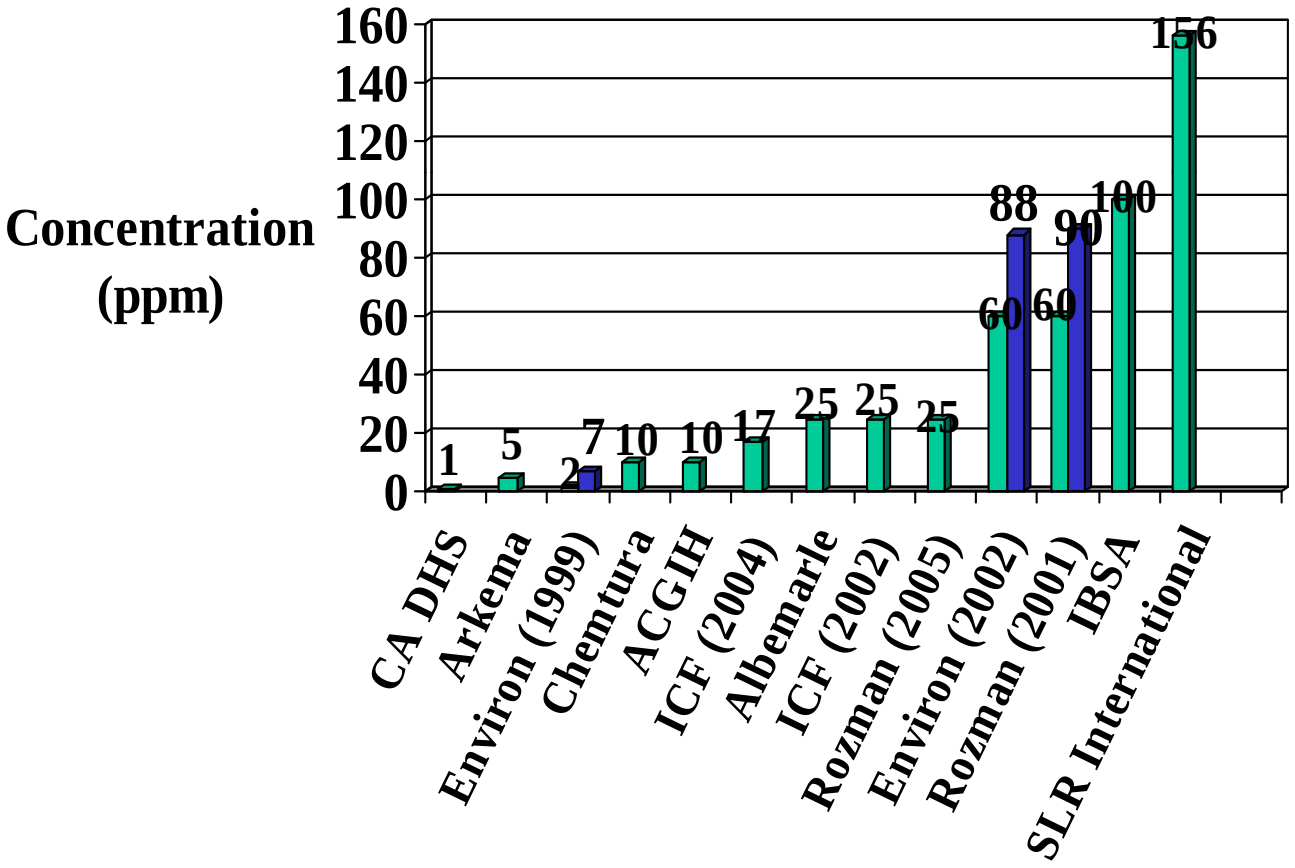
- CERHR expert panel report published March 2002
  - Reviews available toxicity studies and identified no observed adverse effect concentrations (NOAECs) and lowest observed adverse effect concentrations (LOAECs)
  - Identifies whether studies are useful for risk assessment
  - Does not recommend an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



# No Consensus on Occupational Exposure Limit for nPB



# Information for Some Solvents

| Solvent | Exposure limit (source) | VOC? | Listed HW? | HAP? |
|---|---|---|---|---|
| Perchloro-ethylene | 25 ppm (ACGIH)<br>100 ppm (OSHA) | No | Yes | Yes |
| n-Propyl Bromide | 10 ppm (ACGIH)<br>5-100 ppm (mfr) | Yes | No | No |
| Decamethyl-cyclopenta-siloxane (D5) | 10 ppm (mfr) | Yes | No | No |
| Trichloro-ethylene | 50 ppm (ACGIH)<br>100 ppm (OSHA) | Yes | Yes | Yes |

# 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
  - Elseviere Science Direct www.sciencedirect.com/
- Contact Margaret Sheppard
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