1,4-Dioxane Exposure and Health Effects

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Outline

• What is 1,4-dioxane?
• Exposure to 1,4-dioxane
• Non-cancer health effects
• Carcinogenic effects
• Health-based screening levels
Public health evaluation

- Toxicity information (non cancer and cancer toxicity values)
- Exposure scenario (information on how people are exposed)
- Chemical-physical information on 1,4-dioxane

Above those, concerned about exposures – further evaluation needed
Below those, minimal to no exposure
What is 1,4-Dioxane?

- Chemical Abstract Services Number: 123-91-1
- Synthetic industrial chemical
- Very soluble in water

Where is it?

• Solvent for chemical processing

• Plastic, rubber, insecticides, herbicides

• Trace contaminant in cosmetics, detergents, and shampoos

• Contaminant in groundwater from past industrial activities

Occupational exposure to 1,4-Dioxane

- Inhalation
  - Documented exposures

- Dermal exposure
  - Documented exposure

- Ingestion
  - Least likely

Exposure Limits
NIOSH REL
Ca C 1 ppm (3.6 mg/m³) [30-minute] See Appendix A
OSHA PEL
TWA 100 ppm (360 mg/m³) [skin] See Appendix G

https://www.cdc.gov/niosh/npg/npgd0237.html
Non-occupational exposure to 1,4-Dioxane

- Exposure through contaminated environmental media
  - Ingestion
    - Primarily through drinking contaminated water
    - Unlikely to bioaccumulate in animals or plants
  - Dermal exposure is possible – small amount
  - Not likely to inhale 1,4-dioxane
    - Miscibility with the water
    - Considered a volatile organic chemical, but not very volatile
Absorption in people and/or experimental animals exposed to 1,4-Dioxane

• Oral exposure – Nearly all 1,4-dioxane is absorbed by the gastrointestinal tract (experimental animal data – rats)

• Inhalation exposure – rapid absorption of some 1,4-dioxane (human and experimental animals)

• Dermal exposure – absorption is possible, but not nearly as much as the other routes (human and experimental animals)
Elimination in people and/or experimental animals exposed to 1,4-Dioxane

- Primarily through urine
  - 1,4-dioxane and metabolite (β-hydroxyethoxy acetic acid [HEAA])
    - Metabolized through the cytochrome P450 enzymes
- Elimination half-life approximately an hour in humans and experimental animals exposed by inhalation
Evaluation of non-cancer health effects

- U.S. EPA Integrated Risk Information System
  - Reference Dose (RfD)
  - Reference Concentration (RfC)

- Agency for Toxic Substance and Disease Registry
  - Oral Minimal Risk Levels (acute, intermediate, chronic)
  - Inhalation Minimal Risk Levels (acute, intermediate, chronic)

These are non-cancer toxicity values developed to protect against the most sensitive health endpoint.

These values are used in calculation of health-based screening levels.
Available information on 1,4-dioxane exposure in humans
Health effects in humans exposed to 1,4-dioxane

• Two occupational studies

• Several short term inhalation studies with volunteers
Thiess et al. 1976 (human occupational study)

- 74 German workers (actively employed, formerly employed, retired, and deceased)
- Exposed for 3-41 years (0.06-7.2 ppm 1,4-dioxane in the air, higher levels prior to 1969)
- No liver or kidney disease
- No cancers in living participants, 2 cases of cancer in former workers (deceased at the time of the study)
- Small number of participants, small number of cases
Buffler et al. 1978 (human occupational study)

- 100 manufacturing plant workers and 65 processing area workers in Texas
- Grouped into low (<25 ppm), intermediate (50-75 ppm), and high (>75 ppm) 1,4-dioxane exposure
- Mean exposure duration <5 years; Latency period for evaluation <10 years
- No apparent excess mortality or deaths due to malignant neoplasms
- Small number of participants, small number of cases, authors recommended follow up studies for longer latency periods
Human inhalation studies (two examples)

• Five men exposed for 1 minute to 5500 ppm – eye irritation and a burning sensation in the nose and throat (Yant et al. 1930)

• Six male and six female volunteers (at rest) exposed to 1 or 20 ppm 1,4-dioxane for 2 hours - asked for self-reported symptoms and tested for pulmonary function, nasal swelling, and C-reactive protein and interleukin-6 in the plasma (Ernstgård et al. 2006)
Available information on 1,4-dioxane exposure in experimental animals
Non-cancer health effects

- Liver, kidney, and nasal toxicity
  - Different lesions by species and dose

- Liver degeneration, hepatocyte vacuolation and swelling, hepatic centrilobular necrosis and nuclear enlargement, increased cell foci, hepatocytomegaly

- Kidney swelling with hemorrhages and necrosis of the cortex, severe kidney damage – patchy cell degeneration of cortical tubules and intense vascular congestion and hemorrhages inter- & intra-tubular, nuclear enlargement of proximal tubule, degeneration and necrosis of tubular epithelium (higher doses)
Non-cancer health effects

• Nasal toxicity
  • Rhinitis and inflammation of the nasal cavity

• Developmental effects
  • Reduced body weight and ossification of the sternum in rats

• Short-term inhalation results in eye, nose, and throat irritation
  • Human exposure studies
Mode of action for non-cancer effects

- Not known

- Toxicity likely from the parent compound (1,4-dioxane) rather than any metabolites
Development of a non-cancer toxicity value

• Evaluate health effects from 1,4-dioxane exposure to identify a point of departure (POD)

• Divide the POD by uncertainty factors
  • Accounts for differences between experimental animals and humans, human variability, etc
Comparison of PODs for EPA RfD

Figure 5-4. Potential points of departure (POD) based on organ-specific toxicity endpoints with corresponding applied uncertainty factors and derived candidate RfDs following chronic oral exposure to 1,4-dioxane.
U.S. EPA Reference Dose

- Last update: 2010
- Chronic (for a lifetime of exposure)
- Liver and kidney toxicity (chronic oral male rats; Kociba et al. 1974)
- 10 for pharmacodynamic differences between rats and humans, 10 for human variability, 3 for database deficiencies (lack of a multi-generation reproductive toxicity study)

- Overall confidence in the RfD = medium
Comparison of PODs for EPA RfC

Figure 5-5. Potential points of departure (POD) for candidate endpoints with corresponding applied uncertainty factors and derived candidate RfCs following chronic inhalation exposure of F344 male rats to 1,4-dioxane.
U.S. EPA Reference Concentration

- Last update: 2013
- Chronic (for a lifetime of exposure)
- Atrophy and respiratory metaplasia of the olfactory epithelium (chronic inhalation male rats; Kasai et al. 2009)
- 3 for pharmacodynamic differences between rats and humans, 10 for human variability, 10 for use of a LOAEL, 3 for database deficiencies (lack of a multi-generation reproductive toxicity study)
- Overall confidence in the RfC = medium
ATSDR Oral Minimal Risk Levels

• Last update: 2012

• Acute (14 days or less of exposure)
  • Reduced maternal and fetal body weight and reduced sternum ossification in rats (Giavini et al. 1985)
  • 10 uncertainty factor for animal to human and 10 for human variability

• Intermediate (up to a year of exposure)
  • Liver toxicity in male rats (Kano et al. 2008)
  • 10 uncertainty factor for animal to human and 10 for human variability

• Chronic (over a year of exposure)
  • Liver toxicity in male rats (Kociba et al. 1974)
  • 10 uncertainty factor for animal to human and 10 for human variability
ATSDR Inhalation Minimal Risk Levels

- Last update: 2012
- **Acute (14 days or less of exposure)**
  - Eye and respiratory irritation and pulmonary function effects in 6 men and 6 women – no observed effects after 2 hours of exposure (NOAEL) (Ernstgård et al. 2006)
  - 10 uncertainty factor for human variability
- **Intermediate (up to a year of exposure)**
  - Toxicity to the olfactory epithelium male and female rats (Kasai et al. 2008)
  - 3 uncertainty factor animals to humans with dosimetric adjustment and 10 uncertainty factor for human variability
- **Chronic (over a year of exposure)**
  - Nasal lesions (Kasao et al. 2009)
  - 10 uncertainty factor for use of a LOAEL, 3 uncertainty factor animals to humans with dosimetric adjustment and 10 uncertainty factor for human variability
ATSDR Toxicity Values

• ATSDR inhalation MRLs
  • Acute = 2,000 parts per billion (ppb; 7,200 micrograms per cubic meter [µg/m³])
  • Intermediate = 200 ppb (720 µg/m³)
  • Chronic = 30 ppb (110 µg/m³)

• ATSDR oral MRLs
  • Acute = 5,000 micrograms per kilogram per day (µg/kg/day)
  • Intermediate = 500 µg/kg/day
  • Chronic = 100 µg/kg/day
Carcinogenicity of 1,4-dioxane

- International Association for Research on Cancer (IARC)
  - Possibly carcinogenic to humans (inadequate evidence in humans, sufficient evidence in experimental animals)

- EPA
  - “likely to be carcinogenic to humans” ((inadequate evidence in humans, sufficient evidence in experimental animals)

- National Toxicology Program
  - “Reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals”
Carcinogenic toxicity values

• U.S. EPA Oral Cancer Slope Factor
  • Incidence of hepatocellular adenomas and carcinomas in female mice exposed for 2 years (1,4-dioxane in drinking water; Kano et al. 2009)

• U.S. EPA Inhalation Unit Risk
  • Incidence of nasal, liver, kidney, peritoneal, mammary gland, and Zymbal tumors in male rats (inhalation of 1,4-dioxane for 6 hours/day, 5 days/week for 104 weeks; Kasai et al. 2009)
Mode of action for carcinogenic effects

• Not expected to be genotoxic, not expected to be an initiator

• May be a promoter

Fig. 2 – Chemical carcinogenesis stages and the occurrences involved in each one. (Oliveira et al., 2007)
EPA Toxicity Values

- Reference Dose = 30 µg/kg/day
- Reference Concentration = 30 µg/m³ (8.34 ppb)
- Oral Slope Factor = 0.1 per miligrams/kg-day
- Inhalation Unit Risk = 0.000005 per µg/m³
Children or other sensitive populations

- Children may have the same adverse health effects as adults exposed to 1,4-dioxane.
  - No information to indicate otherwise
  - Children can have reduced cytochrome P450 activity (less metabolism?)

- Individuals with compromised liver or kidney function may be at greater risk of adverse health effects from 1,4-dioxane exposure
  - Liver or kidney diseases
  - Medication that may affect liver or kidney function
EPA health-based screening levels for water

- Residential Tapwater – ingestion, dermal contact, and inhalation
  - Carcinogenic Screening Level = 0.46 µg/L (parts per billion [ppb]) for a theoretical extra one case of cancer out of 1,000,000 people exposed (4.6 ppb for a theoretical extra one case of cancer out of 100,000 people exposed)
    - Age-adjusted, for adults and children
  - Non carcinogenic Screening Level = 57 ppb for a hazard index of 1 (exposure is equivalent to the RfD)
    - Child only
MDEQ Residential Drinking Water Criterion

- 7.2 ppb
- Uses the EPA Cancer Slope Factor (more protective than one based non carcinogenic effects)
- Health-based screening level, Based on a carcinogenic risk of theoretical extra one case of cancer out of 100,000 people exposed
- Protective for 32 years of exposure, as a child and adult
- Only exposure is drinking water ingestion
Explanation of drinking water screening levels and criteria

**Understanding Risk: What's Behind the Numbers**

1,4-DIOXANE

**What is 1,4-Dioxane?**
1,4-Dioxane is a clear liquid chemical that easily dissolves in water. It is used primarily as a solvent for making other chemicals and as a laboratory reagent.

1,4-Dioxane is a trace contaminant of some chemicals used in cosmetics, detergents, and shampoos. However, now manufacturers remove as much 1,4-Dioxane from these chemicals as they can before they are made into consumer products.


**Definitions & Assumptions**

- **18,000 parts per billion (ppb)**
  - Agency for Toxic Substances and Disease Registry (ATSDR) Screening Level
  - Based on ATSDR Oral Intermediate Minimal Risk Level (MRL)
  - Protective for adults only
  - Protective for up to one year of exposure
  - Only considers drinking water ingestion pathway
  - Protects only for non-cancer health effects

- **5,000 ppb**
  - ATSDR Screening Level
  - Based on ATSDR Oral Intermediate MRL
  - Protective for children and adults
  - Protective for up to one year of exposure
  - Only considers drinking water ingestion pathway
  - Protects against non-cancer health effects

- **1,100 ppb**
  - ATSDR Screening Level
  - Based on EPA Integrated Risk Information System (IRIS) Reference Dose (2010)
  - Protective for adults
  - Protective for lifetime of exposure
Summary

• Non cancer health effects, primarily liver and/or kidney damage, have been observed in humans (occupational) and experimental animals exposed to 1,4-dioxane

• Carcinogenic effects, such as liver, kidney, and nasal tumors, have been observed in experimental animals exposed to 1,4-dioxane
  • Based on available information 1,4-dioxane exposure may increase people’s risk of developing various cancers

• Environmental media levels can be compared to health-based screening levels to evaluate human exposure to 1,4-dioxane
Public health evaluation

Health-based screening levels

Toxicity information (non cancer and cancer toxicity values)

Exposure scenario (information on how people are exposed)

Chemical-physical information on 1,4-dioxane

Above those, concerned about exposures – further evaluation needed

Below those, minimal to no exposure
Questions?

Thank you!

Jennifer Gray

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For more information

- MDHHS fact sheet on drinking water screening levels – hard copy or e-version (http://www.michigan.gov/documents/mdhhs/1-4_DIOXANE_RISK_VALUES_-FINAL_534905_7.pdf)

- U.S. EPA IRIS 1,4-Dioxane page https://www.atsdr.cdc.gov/ToxProfiles/tp187.pdf


- ATSDR Toxicological Profile for 1,4-Dioxane https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/o326tr.pdf