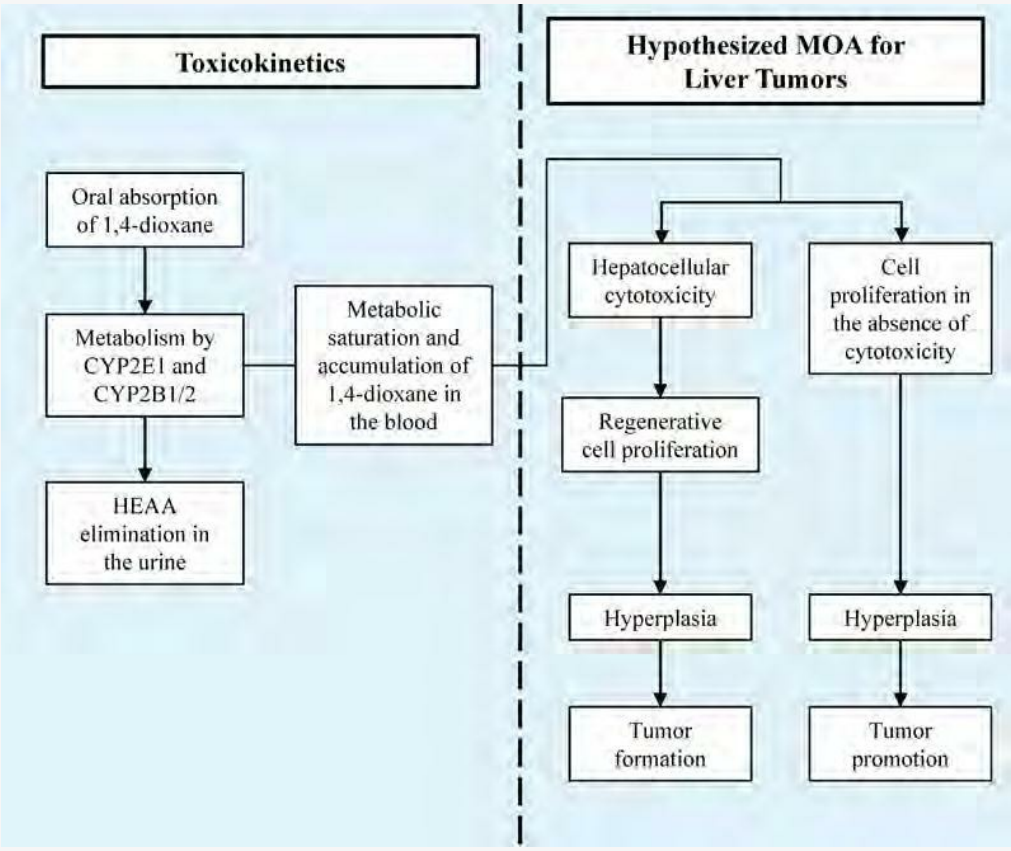
AOP ID and Title:

AOP 1: Uncharacterized liver damage leading to hepatocellular carcinoma
Short Title: Liver damage and hepatocellular carcinoma

Graphical Representation



Authors

Available for adoption

Status

Author status	OECD status	OECD project	SAAOP status
Not under active development			Archived

Abstract

1,4-Dioxane (also called dioxane) is a semi-volatile, colorless liquid with a faint sweet odor, produced in large amounts (1-10 million pounds in 1994, 1998, and 2002) in the United States.[1] For many years, it was primarily used as a stabilizer for 1,1,1-trichloroethane transport and storage, but that use is being phased out. It is also used as a solvent in the manufacture of household products such as detergents, soaps, lotions, shampoos, and cosmetics, in a variety of food manufacturing and food packaging processes, and is also used as a solvent in the manufacture of lacquers, paints, varnishes, waxes, resins, etc. 1,4-dioxane is water soluble and readily leaches into groundwater; thus,it has a high potential for entering the environment. Dioxane has affected groundwater supplies in many areas.

1,4-Dioxane has been classified by IARC as a Group 2N carcinogen, meaning that it is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals.[2] The United States Environmental Protection Agency classifies dioxane as a probable human carcinogen.[3] The compound has an LD50 of 5170 mg/kg.[4]

1,4-dioxane is absorbed rapidly following inhalation or oral exposure, with much less absorption occurring through skin contact. Toxicology data for exposure to 1,4-dioxane in humans is limited to a few inhalation exposure studies; no human data is available for oral or dermal exposures. The inhalation studies show that breathing 1,4-dioxane vapor for short periods of time causes irritation to the eyes, nose and throat, and that exposure to large amounts of 1,4-dioxane may cause kidney and liver damage. Accidental exposure of workers to high concentrations (unspecified) of 1,4-dioxane (via inhalation and dermal contact) have resulted in several deaths and the symptoms associated with

those deaths suggest adverse nervous system effects and kidney toxicity. Studies in humans found no conclusive evidence for a causal link between occupational exposure to dioxane and increased risk for cancer; however, only two studies were available and these were limited by small cohort size and a small number of reported cancer cases.[5,6]

All exposure routes have been studied and described in animals. The majority of these studies have been subchronic and chronic studies of exposure to 1,4-dioxane administered in drinking water where oral exposure induced squamous cell carcinomas in the nasal turbinates and hepatocellular carcinomas in rats of both sexes, and increased the incidence of hepatocellular carcinomas in mice of both sexes. Liver and kidney toxicity were the primary noncancer health effects of subchronic and chronic oral exposure to 1,4-dioxane in animals.

There are only two subchronic inhalation studies and two chronic inhalation studies in animals. Inhalation exposure induced hepatocellular carcinomas in rats of both sexes. Liver and nasal toxicity are the primary noncancer health effects associated with inhalation exposure.

An oral reference dose (RfD) has been established at 0.03 mg/kg-day, with an overall confidence of medium. The oral cancer slope factor (CSF) is 0.10 (mg/kg-day)-1. The inhalation reference concentration (RfC) is 0.03 mg/m3, also with an overall confidence of medium. The IUR is 5 x 10-6 (□g/m3 -1.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	294	N/A, Unknown	N/A, Unknown
2	KE	142	Hyperplasia, Hyperplasia	Hyperplasia, Hyperplasia
3	KE	57	Proliferation, Cell proliferation in the absence of cytotoxicity	Proliferation, Cell proliferation in the absence of cytotoxicity
4	AO	334	Promotion, Hepatocelluar carcinoma	Promotion, Hepatocelluar carcinoma

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
N/A, Unknown	adjacent	Proliferation, Cell proliferation in the absence of cytotoxicity	Moderate	
Proliferation, Cell proliferation in the absence of cytotoxicity	adjacent	Hyperplasia, Hyperplasia	Moderate	
Hyperplasia, Hyperplasia	adjacent	Promotion, Hepatocelluar carcinoma	High	

Overall Assessment of the AOP

Consider the following criteria (may include references to KE Relationship pages): 1. concordance of dose-response relationships; 2. temporal concordance among the key events and adverse effect; 3. strength, consistency, and specificity of association of adverse effect and initiating event; 4. biological plausibility, coherence, and consistency of the experimental evidence; 5. alternative mechanisms that logically present themselves and the extent to which they may distract from the postulated AOP. It should be noted that alternative mechanisms of action, if supported, require a separate AOP; 6. uncertainties, inconsistencies and data gaps.

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
rats	Rattus norvegicus	Moderate	NCBI

References

1. U.S. EPA (U.S. Environmental Protection Agency). (2002). Toxic Substances Control Act (TSCA) Inventory Update Database. Available online at http://www.epa.gov/iur/ (accessed February 22, 2010).

2. “Eleventh Report on Carcinogens” (http://ntp.niehs.nih.gov/ntp/roc/toc11.htm). United States Department of Health and Human Services’ National Toxicology Program. Retrieved 2 February 2006.

3. U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001F). Washington, DC: Risk Assessment Forum. http://www.epa.gov/cancerguidelines/

4. Surprenant, KS. (2002). Dioxane. In Ullmann's Encyclopedia of Industrial Chemistry (6th ed.). Weinheim, Germany: Wiley-VCH Verlag. http://dx.doi.org/10.1002/14356007.a08_545

5. Buffler, PA; Wood, SM; Suarez, L; Kilian, DJ. (1978). Mortality follow-up of workers exposed to 1,4-dioxane. J Occup Environ Med 20: 255-259.

6. Thiess, AM; Tress, E; Fleig, I. (1976). Arbeitsmedizinische Untersuchungsergebnisse von Dioxan-exponierten Mitarbeitern [Industrial-medical investigation results in the case of workers exposed to dioxane]. Arbeitsmedizin, Sozialmedizin, Umweltmedizin 11: 35-46.

Appendix 1

List of MIEs in this AOP

Event: 294: N/A, Unknown

Short Name: N/A, Unknown

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:33 - Kidney toxicity induced by activation of 5HT2C	KeyEvent
Aop:1 - Uncharacterized liver damage leading to hepatocellular carcinoma	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Molecular

Cell term

Cell term
eukaryotic cell

List of Key Events in the AOP

Event: 142: Hyperplasia, Hyperplasia

Short Name: Hyperplasia, Hyperplasia

Key Event Component

Process	Object	Action
hyperplasia		increased

AOPs Including This Key Event

AOP ID and Name	Event Type

AOP ID and Name	Event Type
Aop:1 - Uncharacterized liver damage leading to hepatocellular carcinoma	KeyEvent

Biological Context

Level of Biological Organization
Tissue

Organ term

Organ term
liver

Event: 57: Proliferation, Cell proliferation in the absence of cytotoxicity

Short Name: Proliferation, Cell proliferation in the absence of cytotoxicity

Key Event Component

Process	Object	Action
cell proliferation		increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:1 - Uncharacterized liver damage leading to hepatocellular carcinoma	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
eukaryotic cell

List of Adverse Outcomes in this AOP

Event: 334: Promotion, Hepatocelluar carcinoma

Short Name: Promotion, Hepatocelluar carcinoma

Key Event Component

Process	Object	Action
hepatocellular carcinoma		increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:1 - Uncharacterized liver damage leading to hepatocellular carcinoma	AdverseOutcome

Biological Context

Level of Biological Organization

Individual

Organ term

Organ term

liver

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 324: N/A, Unknown leads to Proliferation, Cell proliferation in the absence of cytotoxicity

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Uncharacterized liver damage leading to hepatocellular carcinoma	adjacent	Moderate	

Relationship: 69: Proliferation, Cell proliferation in the absence of cytotoxicity leads to Hyperplasia, Hyperplasia

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Uncharacterized liver damage leading to hepatocellular carcinoma	adjacent	Moderate	

Relationship: 158: Hyperplasia, Hyperplasia leads to Promotion, Hepatocelluar carcinoma

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Uncharacterized liver damage leading to hepatocellular carcinoma	adjacent	High	