



Health Effects of Hexazinone

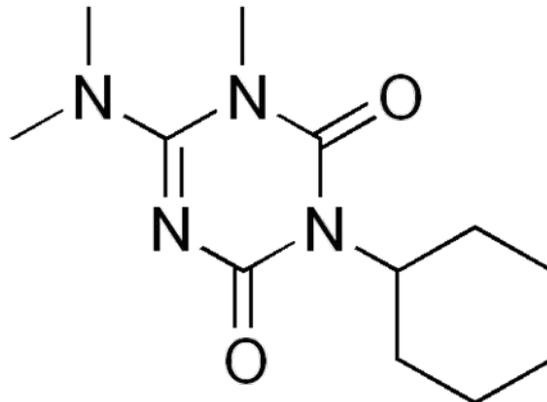
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Content

- Disposition: Absorption, Distribution, Metabolism and Excretion
- Toxicity Evaluation
- Identification of Critical Study
- Determination of Oral Reference Dose
- Derivation of Health Protective Drinking Water Concentration

Disposition

- At least 83% oral dose is absorbed
- Not accumulated in any tissues
- Most of the absorbed dose is excreted in 2 days
- Metabolized by N-demethylation and hydroxylation of the cyclohexane ring



Acute & Sub-chronic Oral Toxicity

Acute oral studies

- $LD_{50} \cong 1000$ mg/kg
- US EPA classification - Toxicity Class III (slightly toxic)

Sub-chronic oral studies in rat, dog, and mouse

- Loss of body weight or decreased weight gain
- Signs of liver toxicity
- LOAELs ranged from 38 – 120 mg/kg-day
- NOAELs ranged from 5 – 81 mg/kg-day

Reproductive & Developmental Effects

Two-generation reproductive study in rat (dietary)

- Decreased pup weight
- No obvious reproductive effects
- LOAEL = 117 mg/kg-day; NOAEL = 12 mg/kg-day

Developmental study in rat (gavage)

- Decreased fetal weight
- Increased incidence of kidney malformation
- LOAEL = 900 mg/kg-day; NOAEL = 400 mg/kg-day

Developmental study in rabbit (gavage)

- Decreased fetal weight
- LOAEL = 125 mg/kg-day; NOAEL = 50 mg/kg-day

Chronic & Carcinogenic Effects (2 years of exposure)

- Rat dietary study
 - Slight increase of thyroid adenoma in the high dose males. Increase was not statistically significant
 - NOAEL = 10 mg/kg-day (decreased body weight in both sexes)
- Mouse dietary study
 - Slight increase of hepatocellular neoplasia in the high dose females. Increase was not statistically significant
 - Increased incidence of focus/foci cellular alteration
 - NOAEL = 28 mg/kg-day (males) due to decrease body weight

Genotoxic Effects

- Mostly negative
- Positive in *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at concentrations that were cytotoxic, with or without activation
- Negative in more recent *in vitro* chromosomal aberration assay using human peripheral blood lymphocytes, with or without activation

Carcinogenic Effects

- Based on the cancer bioassay data and genotoxicity information evaluated, OEHHA determined that the evidence is insufficient to indicate hexazinone as an animal carcinogen
- US EPA has designated hexazinone as Category D, “not classifiable as to human carcinogenicity” and recommends the use RfD to characterize health risk

Endocrine Effects

- Positive E-Screen Assay
- Possibly as a secondary effect from thyroid adenomas in rats
- No evidence of organ or tissue effects related to endocrine systems from animal studies available
- Negative test from salmon smolts

Endocrine Effects

- Triazines such as atrazine, simazine, propazine, and their metabolites are determined by US EPA as members of the “common mechanism” group (CMG). They cause neuroendocrine and endocrine-related developmental, reproductive and carcinogenic effects.
- US EPA determined that because of the chemical structure of hexazinone, it is not in the CMG and is not expected to cause similar effects

Critical Study & Dose (Non-cancer)

Two-year rat dietary study:

- 36/sex/dose at 0, 0, 200, 1000, or 2500 ppm
- Male (0, 0, 10, 53, or 138 mg/kg-day); Female (0, 0, 12, 68, or 179 mg/kg-day)
- LOAEL = 1000 ppm (53 mg/kg-day), decreased body weight in both sexes
- NOAEL = 10 mg/kg-day

Oral Reference Dose (RfD)

Chronic oral RfD = 0.033 mg/kg-day, based on:

- NOAEL = 10 mg/kg-day
- Overall uncertainty factor (UF) = 300
- Default UF of 10 for inter-species extrapolation
- Default UF of 10 for intra-species variation
- Additional UF of 3 to account for rat, which may not be the most sensitive species and due to the quality of the study

Health-Protective Drinking Water Level

$$C = RfD \times RSC \times 1/(WC / BW)$$

Where:

- C = health-protective drinking water level, ppb
- RfD = 0.033 mg/kg-day
- RSC = relative source contribution, 0.2
- WC/BW = upper 95th percentile water consumption rate per body weight, 0.039 L/kg-day for adult*

$$C = (0.033 \text{ mg/kg-day})(0.2)(1/0.039) = 0.169 \text{ mg/L} \\ \text{(or 170 ppb)}$$

*derived from US EPA (2008) and Kahn and Stralka (2009)