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HEXAZINONE

DRAFT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

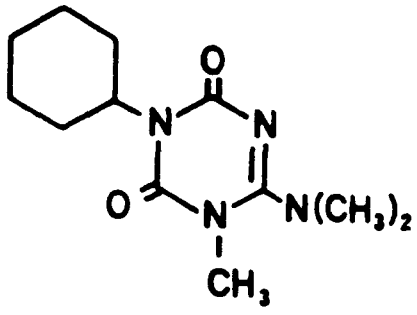
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No.: 51235-04-2

Structural Formula:



3-Cyclohexyl-6-(dimethylamino)-1 methyl-1,3,5-triazine-2,4(1H,3H)-dione;

Synonyms

- Velpar; Hexazinone.

Use

- Contact and residual herbicide (Meister, 1983).
- Usage areas include plantations of coniferous trees, railroad right-of-ways, utilities, pipelines, petroleum tanks, drainage ditches, and sugar and alfalfa (Kennedy, 1984).

Properties (Kennedy, 1984; CHEMLAB, 1985)

Chemical Formula	$C_{11}H_{20}O_2N_3$
Molecular Weight	226 (calculated)
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	115-117°C
Density	--
Vapor Pressure (86°C)	6.4×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (25°C)	33,000 mg/L
Log Octanol/Water Partition Coefficient	-4.40 (calculated)
Taste Threshold	--
Odor Threshold	odorless
Conversion Factor	--

Occurrence

- Hexazinone has been found in none of the surface water samples or ground water samples analyzed from 13 samples taken at 6 locations (STORET, 1987).

Environmental Fate

- Hexazinone did not hydrolyze in water within the pH range of 5.7 to 9 during a period of 8 weeks (Rhodes, 1975a).

- In a soil aerobic metabolism study, hexazinone was added to a Fallsington sandy loam and a Flanagan silt loam at 4 ppm. ^{14}C-Hexazinone residues had a half-life of about 25 weeks. Of the extractable ^{14}C residues, half was present as parent compound and/or 3-cyclohexyl-1-methyl-6-methylamino-1,3,5-triazine-2,4-(1H,3H)-dione. Also present were 3-(4-hydroxycyclohexyl)-6-(dimethylamino)-1-methyl-1-(1H,3H)-dione and the triazine trione (Rhodes, 1975b).

- A soil column leaching study used ^{14}C-hexazinone, half of which was aged for 30 days and applied to Flanagan silt loam and Fallsington sandy loam. Leaching with a total of 20 inches of water showed that unaged hexazinone leached in the soils; however, leaching rates were slower for the aged samples, indicating that the degradation products may have less potential for contaminating ground water (Rhodes, 1975b).

- A field soil leaching study indicated that ^{14}C-hexazinone residues were leached into the lower sampling depths with increasing rainfall. A Keyport silt loam (2.75% organic matter; pH 6.5) and a Flanagan silt loam (4.02% organic matter; pH 5.0) were used. For the Keyport silt loam, ^{14}C residues were found at all depths measured, including the 8- to 12-inch depth, when total rainfall equaled 8.43 inches, 1 month after application of hexazinone. For the Flanagan silt loam, ^{14}C residues were found at all depths sampled, including the 12- to 15-inch depth, 1 month after application, when a total of 7.04 inches of rain had fallen (Rhodes, 1975c).

- A soil TLC test for Fallsington sandy loam and Flanagan silt loam gave R_f values for hexazinone of 0.85 and 0.68, respectively. This places hexazinone in Class 4, indicating it is very mobile in these soils (Rhodes, 1975c).

- In a terrestrial field dissipation study using a Keyport silt loam in Delaware, hexazinone had a half-life of less than 1 month. In a field study in Illinois (Flanagan silt loam), hexazinone had a half-life of more than 1 month (62% of the parent compound remained at 1 month) (Rhodes, 1975b). In a separate study with Keyport silt loam, some leaching of the parent compound to a depth of 12 to 18 inches was observed (Holt, 1979).

III. PHARMACOKINETICS

Absorption

- Rapisarda (1982) reported that a dose of 14 mg/kg ^{14}C-labeled hexazinone (>99% pure) was about 80% absorbed in 3 to 6 days (77% recovery in urine, 20% in feces) when administered by gastric

intubation to male and female Charles River CD rats with or without 3 weeks of dietary preconditioning with unlabeled hexazinone.

- Rhodes et al. (1978) administered 2,500 ppm (125 mg/kg) hexazinone in the diet to male rats for 17 days. This was followed by a single dose of 18.3 mg/300 g (61 mg/kg) ^{14}C-labeled hexazinone. The hexazinone was rapidly absorbed within 72 hours, with 61% detected in the urine and 32% in the feces. Trace amounts were found in the gastrointestinal (GI) tract (0.6%, tissues not specified) and expired air (0.08%).

Distribution

- Orally administered hexazinone has not been demonstrated to accumulate preferentially in any tissue (Rhodes et al., 1978; Holt et al., 1979; Rapisarda, 1982).

- Studies in rats by Rapisarda (1982) and Rhodes et al. (1978) showed that no detectable levels of ^{14}C-hexazinone were found in any body tissues when the animals were administered >14 mg/kg hexazinone by gastric intubation with or without dietary preconditioning.

- In a study with dairy cows by Holt et al. (1979) hexazinone was given in the diet at 0, 1, 5 or 25 ppm for 30 days. Assuming that 1 ppm in the diet of a cow equals 0.015 mg/kg (Lehman, 1959), these levels correspond to 0, 0.015, 0.075 or 0.37 mg/kg/day. The investigators reported no detectable residues in milk, fat, liver, kidney or lean muscle.

Metabolism

- Major urinary metabolites of hexazinone in rats identified by Rhodes et al. (1978) were 3-(4-hydrocyclohexyl)-6-(dimethylamino)1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione (metabolite A); 3-cyclohexyl-6-(methylamino)-1-methyl-1,3,5-triazine-2,4-(1H, 3H)-dione (metabolite B); and 3-(4-hydrocyclohexyl)-6-(methylamino)-1-methyl-1,3,5-triazine-2,4-(1H,3H)-dione (metabolite C). The percentages of these metabolites detected in the urine were 46.8, 11.5 and 39.3%, respectively. The major fecal metabolites detected by Rhodes et al. (1978) were A (26.3%) and C (55.2%). Less than 1% unchanged hexazinone was detected in the urine or the feces. Similar results were reported by Rapisarda (1982).

Excretion

- Rapisarda (1982) and Rhodes et al. (1978) reported that excretion of ^{14}C-hexazinone and/or its metabolites occurs mostly in the urine (61 to 77%) and in the feces (20 to 32%).

IV. HEALTH EFFECTS

Humans

- The Pesticide Incident Monitoring System data base (U.S. EPA, 1981) indicated that 3 of 43,729 incident reports involved hexazinone. Only one report cited exposure to hexazinone alone, without other compounds involved. A 26-year-old woman inhaled hexazinone dust (concentration not specified). Vomiting occurred within 24 hours. No other effects were reported and no treatment was administered. The other two reports did not involve human exposure.

Animals

Short-term Exposure

- Reported oral LD_{50} values for technical-grade hexazinone in rats range from 1,690 to >7,500 mg/kg (Matarese, 1977; Dashiell and Hinckle, 1980; Kennedy, 1984).

- Henry (1975) and Kennedy (1984) reported the oral LD_{50} value of technical-grade hexazinone in beagle dogs to be >3,400 mg/kg.

- Reported oral LD_{50} values for hexazinone in guinea pigs range from 800 to 860 mg/kg (Dale, 1973; Kennedy, 1984).

- Kennedy (1984) studied the response of male rats to repeated oral doses of hexazinone (89 or 98% active ingredient). Groups of six rats were intubated with hexazinone, 300 mg/kg, as a 5% suspension in corn oil. Animals were dosed 5 days/week for 2 weeks (10 total doses). Clinical signs and body weights were monitored daily. At 4 hours to 14 days after exposure to the last dose, microscopic evaluation of lung, trachea, liver, kidney, heart, testes, thymus, spleen, thyroid, GI tract, brain, and bone marrow was conducted. No gross or histological changes were noted in animals exposed to either active ingredient percentage of hexazinone.

- In an 8-week range-finding study (Kennedy and Kaplan, 1984), Charles River CD-1 mice (10/sex/dose) received hexazinone (>98% pure) in the diet for 8 consecutive weeks at concentrations of 0, 250, 500, 1,250, 2,500 or 10,000 ppm. Assuming 1 ppm in the diet of mice equals 0.15 mg/kg (Lehman, 1959), these dietary concentrations correspond to doses of about 0, 37.5, 75.0, 187.5, 375.0 or 1,500 mg/kg/day. No differences were observed in general behavior and appearance, mortality, body weights, food consumption or calculated food efficiency between control and exposed groups. No gross pathologic lesions were detected at necropsy. The only dose-related effects observed were increases in both absolute and relative liver weights in mice fed 10,000 ppm. A No-Observed-Adverse-Effect-Level (NOAEL) of 2,500 ppm (375.0 mg/kg/day) was identified by the authors.

Dermal/Ocular Effects

- In an acute dermal toxicity test performed by McAlack (1976), up to 7,500 mg/kg of a 24% aqueous solution of hexazinone (reported to be 1,875 mg/kg of active ingredient) was applied occlusively for 24 hours to the shaved backs and trunks of male albino rabbits. No deaths were observed throughout a 14-day observation period.

- Morrow (1973) reported an acute dermal toxicity test in which 60 mL of a 24% aqueous solution of hexazinone (reported as 5,278 mg/kg) was applied occlusively to the shaved trunks of male albino rabbits for 24 hours. No mortalities were observed through an unspecified observation period. One animal exhibited a mild, transient skin irritation.

- In a 10-day study conducted by Kennedy (1984), semiocclusive dermal application of hexazinone for 6 hours/day for 10 days to male rabbits at 70 or 680 mg/kg/day resulted in no signs of skin irritation or toxicity. A trend toward elevated serum alkaline phosphatase (SAP) and serum glutamic pyruvic-transaminase (SGPT) activities was observed, but no hepatic damage was seen by microscopic evaluation. In a second 10-day study using 35, 150 or 770 mg/kg/day, the highest dose again resulted in elevated SAP and SGPT activities, but they returned to normal after 53 days of recovery. Histopathological evaluations were not performed in the second study.

- Edwards (1977) applied 6,000 mg/kg hexazinone as a 63% solution occlusively to the shaved backs and trunks of male albino rabbits. No treatment-related mortalities were reported after a 14-day observation period.

- Morrow (1972) reported the results of dermal irritation tests in which a single dose of 25 or 50% hexazinone was applied to the shaved, intact shoulder skin of each of 10 male guinea pigs. To test for sensitization, four sacral intradermal injections of 0.1 mL of a 15% solution were first given over a 3-week period. After a 2-week rest period, the guinea pigs were challenged with 25 or 50% hexazinone applied to the shaved, intact shoulder skin. The test material was found to be nonirritating and nonsensitizing at 48 hours post-application.

- Using a 10% solution, Goodman (1976) repeated the Morrow study with guinea pigs and observed no irritation or sensitization.

- Dashiell and Henry (1980) reported that in albino rabbits, a single dose of hexazinone applied as 27% (vehicle not specified) solution to one eye per animal and unwashed was a severe ocular irritant. When applied at 27% (vehicle not specified) and washed or at 4% (aqueous solution) unwashed, mild to moderate corneal cloudiness, iritis and/or conjunctivitis resulted. By 21 days post-treatment with the higher dose, two of the three rabbit eyes had returned to normal; a small area of mild corneal cloudiness persisted through the 35-day observation period in one of the three eyes. Eyes treated with lower doses were normal within 3 days.

Long-term Exposure

- In a 90-day feeding study, Sherman et al. (1973) fed beagle dogs (four/sex/dose) hexazinone (97.5% active ingredient) in the diet at levels of 0, 200, 1,000 or 5,000 ppm. Assuming 1 ppm in the diet of a dog equals 0.025 mg/kg/day (Lehman, 1959), these levels correspond to about 0, 5, 25 or 125 mg/kg/day. At the highest dose level tested, decreased food consumption, weight loss, elevated alkaline phosphatase activity, lowered albumin/globulin ratios and slightly elevated liver weights were noted. No gross or microscopic lesions were observed at necropsy. Based on the results of this study a NOAEL of 1,000 ppm (25 mg/kg/day) and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 5,000 ppm (125 mg/kg/day) were identified.

- In a 90-day feeding study (Kennedy and Kaplan, 1984), Crl-CD rats (16/sex/dose) received hexazinone (>98% pure) at dietary levels of 0, 200, 1,000 or 5,000 ppm. Assuming 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), these levels correspond to about 0, 10, 50 or 250 mg/kg/day. Hematological and biochemical tests and urinalyses were conducted on subgroups of animals after 1, 2 or 3 months of feeding. Following 94 to 96 days of feeding, the rats were sacrificed and necropsied. The only statistically significant effect reported was a decrease in body weight in both males and females receiving 5,000 ppm. No differences in food consumption were reported. Results of histopathological examinations from the control and high-dose groups were unremarkable. The authors identified a NOAEL of 1,000 ppm (50 mg/kg/day).

- In a 1-year feeding study (Kaplan et al., 1975) weanling Charles River CD rats (36/sex/dose) received hexazinone (94 to 96% pure) at dietary levels of 0, 200, 1,000 or 2,500 ppm (which, according to the authors, corresponds to 0, 11, 60 or 160 mg/kg/day for males and 0, 14, 74 or 191 mg/kg/day for females). Results of this study indicated a decrease in weight gain by both sexes at 2,500 ppm and by females at 1,000 ppm. The authors indicated that various unspecified clinical, hematological and biochemical parameters revealed no evidence of adverse effects. No significant gross or histopathological changes attributable to hexazinone were noted. From the information presented in the study, a NOAEL of 200 ppm (11 mg/kg/day for males and 14 mg/kg/day for females) can be identified.

- In a 2-year study, Goldenthal and Trumball (1981) fed hexazinone (95 to 98% pure) to Charles River CD-1 mice (80/sex/dose) at dietary levels of 0, 200, 2,500 or 10,000 ppm. Assuming that 1 ppm in the diet of a mouse equals 0.15 mg/kg/day (Lehman, 1959), these levels correspond to 0, 30, 375 or 1,500 mg/kg/day. Corneal opacity sloughing and discoloration of the distal tip of the tail were noted as early as the fourth week of the study in mice receiving 2,500 or 10,000 ppm. A statistically significant decrease in body weight was observed in male mice receiving 10,000 ppm and in female mice receiving 2,500 or 10,000 ppm. Statistically significant increases in liver weight were noted in male mice receiving 10,000 ppm; male and female mice in the 10,000-ppm dose group also displayed statistically significant increases

in relative liver weight. Sporadic occurrence of statistically significant changes in hematological effects were considered by the authors to be unrelated to hexazinone treatment. Histologically, a number of liver changes were observed among mice fed 2,500 or 10,000 ppm. The most characteristic finding was hypertrophy of centrilobular parenchymal cells. Other histological changes included an increased incidence of hyperplastic liver nodules and an increased incidence and severity of liver cell necrosis. Mice fed 200 ppm showed no compound-related histopathological changes. A NOAEL of 200 ppm (30 mg/kg/day) was identified by the authors.

- Kennedy and Kaplan (1984) presented the results of a 2-year feeding study in which Crl-CD rats (36/sex/dose) received hexazinone (94 to 96% pure) at dietary levels of 0 (two groups), 200, 1,000 or 2,500 ppm (approximately 0, 10, 50 or 125 mg/kg/day assuming that 1 ppm in the diet of a rat equals 0.05 mg/kg/day)(Lehman, 1959). After 2 years of continuous feeding, all rats in all groups were sacrificed and examined. Males fed 2,500 ppm and females fed either 1,000 or 2,500 ppm had significantly lower body weights than controls ($p < 0.05$). Male rats fed 2,500 ppm had slightly elevated leukocyte counts with a greater proportion of eosinophils. Male rats fed either 1,000 or 2,500 ppm displayed decreased alkaline phosphatase activity. Statistically significant effects on organ weights included elevated relative lung weights in males fed 1,000 ppm; lower kidney and lower relative liver and heart weights in males fed 2,500 ppm; increased liver and spleen weights in females fed 200 ppm; and elevated stomach and relative brain weights in females fed 2,500 ppm. At necropsy, gross pathologic findings were similar among all groups. Changes attributed to hexazinone were not apparent in any of the tissues evaluated microscopically. The authors identified 200 ppm (10 mg/kg/day) as the NOAEL. However, the increased liver and spleen weights observed in females would indicate that 200 ppm might be more appropriately identified as a LOAEL.

Reproductive Effects

- In a one-generation reproduction study (Kennedy and Kaplan, 1984), Crl-CD rats (16/sex/dose) received hexazinone (>98% pure) for approximately 90 days at dietary levels of 0, 200, 1,000 or 5,000 ppm. Assuming that 1 ppm in the diet of rats equals 0.05 mg/kg/day (Lehman, 1959), this corresponds to approximately 0, 10, 50 and 250 mg/kg/day. Following the 90-day feeding period, six rats/sex/dose were selected to serve as the parental generation. The authors concluded that the rats had normal fertility. The young were delivered in normal numbers, and survival during the lactation period was unaffected. In the 5,000 ppm group, weights of pups at weaning (21 days) were significantly ($p < 0.01$) lower than controls or other test groups. The results of this study identify a NOAEL of 1,000 ppm (50 mg/kg/day) (no decrease in weanling weight).

- In a three-generation reproduction study (DuPont, 1979), Crl-CD rats (36/sex/dose) received hexazinone (98% pure) at dietary levels of 0, 200, 1,000 or 2,500 ppm for 90 days (approximately 0, 10, 50 or 125

mg/kg/day, assuming the above assumptions for a rat). Following 90 days of feeding, 20 rats/sex/dose were selected to serve as the parental (F_0) generation. Reproductive parameters tested included the number of matings, number of pregnancies and number of pups per litter. Pups were weighed at weaning, and one male and female were selected from each litter to serve as parental rats for the second generation. Similar procedures were used to produce a third generation; the same reproductive parameters were collected for the second and third generations. The authors stated that there were no significant differences between the control and treated groups with respect to the various calculated indices (fertility, gestation, viability and lactation). However, body weights at weaning of pups in the 2,500 ppm dose group were significantly ($p < 0.05$) lower than those of controls for the F_2 and F_3 litters. The results of this study identify a NOAEL of 1,000 ppm (50 mg/kg/day).

Developmental Effects

- Kennedy and Kaplan (1984) presented the results of a study in which Charles River Crl-CD rats (25 to 27/dose) received hexazinone (97.5% pure) at dietary concentrations of 0, 200, 1,000 or 5,000 ppm (approximately 0, 10, 50 or 250 mg/kg/day following the previously stated assumptions for the rat) on days 6 through 15 of gestation. Rats were observed daily for clinical signs and were weighed on gestation days 6, 16 and 21. On day 21, all rats were sacrificed and ovaries and uterine horns were weighed and examined. The number and location of live fetuses, dead fetuses and resorption sites were noted. Fetuses from the 0 and 5,000 ppm dose groups were evaluated for developmental effects (gross, soft tissue or skeletal abnormalities). At sacrifice, no adverse effects were observed for the dams. No malformations were noted in the fetuses. However, pup weights in the high-dose group were significantly lower than in the controls. This study identified a NOAEL of 1,000 ppm (50 mg/kg/day).

- Kennedy and Kaplan (1984) presented the results of a study in which New Zealand white rabbits (17/dose) received hexazinone suspended in a 0.5% aqueous methyl cellulose vehicle by oral intubation on days 6 through 19 of gestation at levels of 0, 20, 50 or 125 mg/kg/day. Rabbits were observed daily and body weights were recorded throughout gestation. On day 29 of gestation, all rabbits were sacrificed, uteri were excised and weighed, and the number of live, dead and resorbed fetuses was recorded. Each fetus was examined externally and internally for gross, soft tissue and skeletal abnormalities. No clinical signs of maternal or fetal toxicity were observed. Pregnancy rates among all groups compared favorably. The numbers of corpora lutea and implantations per group were not significantly different. Resorptions and fetal viability, weight and length were also similar among all groups. Based on the information presented in this study, a minimum NOAEL of 125 mg/kg/day for maternal toxicity, fetal toxicity, and teratogenicity can be identified.

Mutagenicity

- The ability of hexazinone to induce unscheduled DNA synthesis was assayed by Ford (1983) in freshly isolated hepatocytes from the livers of 8-week-old male Charles River/Sprague-Dawley rats. Hexazinone was tested at half-log concentrations from 1 x 10^{-5} to 10.0 mM and at 30.0 mM. No unscheduled DNA synthesis was observed.

- Valachos et al. (1982) conducted an in vitro assay for chromosomal aberrations in Chinese hamster ovary cells. Hexazinone was found to be clastogenic without S-9 activation at concentrations of 15.85 mM (4.0 mg/mL) or 19.82 mM (5.0 mg/mL); no significant increases in clastogenic activity were seen at 1.58, 3.94 and 7.93 mM (0.4, 1.0 and 2.0 mg/mL). With S-9 activation, significant increases in aberrations were noted only at a concentration of 15.85 mM (4.0 mg/mL).

- In a study designed to evaluate the clastogenic potential of hexazinone in rat bone marrow cells (Farrow et al., 1982), Sprague-Dawley CD rats (12/sex/dose) were given a single dose of 0, 100, 300 or 1,000 mg/kg of the hexazinone by gavage (vehicle not reported). No statistically significant increases in the frequency of chromosomal aberrations were observed at any of the dose levels tested. The authors concluded that, under the conditions of this study, hexazinone was not clastogenic.

- Hexazinone was tested for mutagenicity in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 at concentrations up to 7,000 ug/plate. The compound was not found to be mutagenic, with or without S-9 activation (DuPont, 1979).

Carcinogenicity

- Goldenthal and Trumball (1981) fed hexazinone (98% pure) for 2 years to mice (80/sex/dose) in the diet at 0, 200, 2,500, or 10,000 ppm (0, 30, 375 or 1,500 mg/kg/day, based on Lehman [1959]). A number of liver changes were observed histologically at the 2,500- and 10,000-ppm level. These included hypertrophy of the centrilobular parenchymal cells, increased incidence of hyperplastic liver nodules and liver cell necrosis. The authors concluded that hexazinone was not carcinogenic to mice.

- No carcinogenic effects were observed in Crl-CD rats (36/sex/dose) given hexazinone (94 to 96% pure) in the diet at 0, 200, 1,000, or 2,500 ppm (0, 10, 50, or 125 mg/kg/day) for 2 years (Kennedy and Kaplan, 1984). The authors concluded that none of the tumors were attributable to hexazinone.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA for hexazinone. It is, therefore, recommended that the Longer-term HA value of 2.5 mg/L (2,500 ug/L, calculated below) for a 10-kg child be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study reported by Kennedy and Kaplan (1984) in which pregnant rabbits (17/dose) received hexazinone by oral intubation at levels of 0, 20, 50 or 125 mg/kg/day on days 6 through 19 of gestation was considered to serve as the basis for deriving the Ten-day HA for a 10-kg child. Since no signs of maternal or fetal toxicity were observed in this study, a NOAEL of 125 mg/kg/day (the highest dose tested) was identified. The NOAEL from this study is greater than that identified in a 90-day rat feeding study (50 mg/kg; Kennedy and Kaplan, 1984). The LOAEL from the one-generation rat reproduction study was 250 mg/kg based on decreased weanling weight. Effects at doses between 50 and 250 mg/kg have not been reported for the rat. However, in a 90-day dog study, a LOAEL of 125 mg/kg was identified (Sherman et al., 1973). Therefore, the rabbit study was not selected to derive a Ten-day value. It is, therefore, recommended that the Longer-term HA value of 2.5 mg/L (2,500 ug/L) for the 10-kg child be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The 90-day feeding study in dogs (Sherman et al., 1973) has been selected to serve as the basis for determination of the Longer-term HA for hexazinone. In this study, dogs received hexazinone in the diet at levels of 0, 200, 1,000 or 5,000 ppm (0, 5, 25, or 125 mg/kg/day) for 90 days. Decreased food consumption and body weight gain, elevated alkaline phosphatase activity, lowered albumin/globulin ratios and elevated liver weights were observed at the highest dose. A NOAEL of 1,000 ppm (25 mg/kg/day) and a LOAEL of 5,000 ppm (125 mg/kg/day) were identified. This NOAEL is generally supported by a 90-day

rat feeding study that reported a NOAEL of 50 mg/kg/day (Kennedy and Kaplan, 1984). Effects in dogs exposed to hexazinone at 50 mg/kg/day have not been reported.

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 2.5 \text{ mg/L } (2{,}500 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of hepatic effects or weight loss in dogs exposed to hexazinone via the diet for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 8.75 \text{ mg/L } (8{,}750 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of hepatic effects or weight loss in dogs exposed to hexazinone via the diet for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at

which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A 2-year rat feeding/oncogenicity study (Kennedy and Kaplan, 1984) was selected as the basis for determination of the Lifetime HA for hexazinone. Crl-CD rats (36/sex/dose) received 0, 200, 1,000, or 2,500 ppm hexazinone (0, 10, 50, or 125 mg/kg/day) for 2 years. Body weight gain in males and females in the 2,500-ppm group, and females in the 1,000-ppm group, was significantly lower than that in controls. No clinical, hematological or urinary evidence of toxicity was reported. Based on decreased body weight gain, a NOAEL of 200 ppm (10 mg/kg/day) and LOAEL of 1,000 ppm (50 mg/kg/day) were identified.

Using a NOAEL of 10 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10\ mg/kg/day)}{(100)\ (3)} = 0.03\ mg/kg/day$$

where:

10 mg/kg/day = NOAEL, based on absence of body weight effects in rats exposed to hexazinone via the diet for 2 years.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

3 = modifying factor; to account for data gaps (chronic dog-feeding study) in the total data base for hexazinone.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.03\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 1.05\ mg/day\ (1{,}050\ ug/L)$$

where:

0.03 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of Lifetime Health Advisory

Lifetime HA = (1.05 mg/L) (20%) = 0.21 mg/L (210 ug/L)

where:

1.05 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity in rats or mice has been observed.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of hexazinone.
- The criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), place hexazinone in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances range from 0.5 to 5.0 ppm for the combined residues of hexazinone and its metabolites in or on the raw agricultural commodities pineapple, pineapple fodder and forage (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of hexazinone is by a gas chromatographic method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1985b). This method requires a solvent extraction of approximately 1 liter of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by gas chromatography, and measurement is made with a thermionic bead detector. The method detection limit for hexazinone is 0.72 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies used to remove hexazinone from contaminated water.

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