HEXAZINONE

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

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Water (OW), 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 percent of an individual's lifetime), and lifetime exposures based on data describing noncarcinogenic endpoints of toxicity. 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 lifelong exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linearized multistage model with 95 percent 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. 8001-35-2

Structural Formula

3-Cyclohexy 1-6- (dimethylamino) -1 methy1-1, 3,5-triazine-2,4 (1H, 3H) -dione

Synonyms

- Velpar; Hexazinone (Budavari et al., 1989; Sine et al., 1989; U.S. EPA, 1994a)

Uses

- Broad spectrum, pre- and post-emergence herbicide effective against woody and herbaceous weeds (Budavari et al., 1989).

- Used when plants are actively growing for control of many annual, biennial and perennial weeds and woody plants on noncropland areas; gives contact and residual control; rainfall is needed for soil activation; controls woody plants in reforestation areas; selective weed control in conifers, sugarcane, pineapple, rubber trees and alfalfa (Sine et al., 1989).

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

- Neilsen and Lee (1987) estimated that approximately 5,000 kg of hexazinone (active ingredient) was used per year for agricultural purposes (Goodrich et al., 1991).

Properties (Budavari et al., 1989; CHEMLAB, 1985; Kennedy, 1984; Sine et al., 1989; U.S. EPA, 1982)

Chemical Formula $C_{12}H_{20}N_4O_2$

Molecular Weight 252

Physical State (25ºC) White crystalline solid

Boiling Point

Melting Point 115 to 117ºC, or 113.5ºC, or 97 to 100.5ºC

Density

Vapor Pressure (25ºC) 2 x 10^{-7} mm Hg (extrapolated from 6.4 x 10^{-5} mm Hg at 86ºC)

Specific Gravity (25ºC) 1.25

Water Solubility (25ºC) 33,000 mg/L or 29,800 mg/L

Log Octanol/Water -4.40 (calculated)

Partition Coefficient Taste Threshold (Water)

Odor Threshold (Water) odorless

Occurrence

- Hexazinone has not been found in any surface water samples (9 samples taken at 2 locations) or groundwater samples analyzed (6 samples from 6 locations), STORET (1988).

- Hexazinone has been detected in ground water of five states including Maine (Yarborough et al., 1995, 1996), North Carolina, South Carolina (Vaught, 1995), Colorado (Austin, 1994). The Maximum concentration reported in ground water to date is 115 ppb in South Carolina. These detections resulted from probable nonpoint sources; additional detections in Hawaii resulted from point source mechanisms.

- Jennings and Gould (1995, draft) reported extensive use of hexazinone for blueberry farming in the State of Maine. Low levels of hexazinone were detected in ground water near blueberry sites. Water samples from 20 sites had detectable levels ranging from 0.093 to 5.97 ppb (jug/L) for fifteen of these sites, and 5 sites non-detectable levels. The Maine Cooperative Extension has been conducting ground water and surface water monitoring studies in blueberry-growing areas for the past several years. All 32 wells in these study areas contained hexazinone residues sometime during the study period. Concentratios in ground water from thesewells ranged up to 29.0 ppb In addition, four ponds and three streams contained hexazinone residues up to 9.2 ppb (Hess, 1966, yarborough et al., 1995, 1996). According to the Maine Pesticide Board, another 27 wells tested positive with relatively lower concentrations of hexazinone (McLaughlin, 1994a). In 1992,

hexazinone residues were also detected in two wells that supplied the drinking water of a school in Maine. Concentrations in these wells ranged from 3 to 10 ppb (McLauglin, 1994b).

Environmental Fate

- Hexazinone is generally resistant to hydrolysis and loss by volatilization, but is subject to both microbial degradation and photolysis. Its environmental half-life can vary between 2 weeks and 6 months, but frequently is less than 30 days (Neary et al., 1993).

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

- In an aerobic metabolism soil study, hexazinone was added to a Fallsington sandy loam and a Flanagan silt loam at 4 ppm. In these media, ^{14}C-Hexazinone and its residues had a half-life of about 25 weeks. Of the extractable ^{14}C residues, approximately one-half was present as parent compound and/or 3-cyclohexy1-1-methy1-6-methylamino-1,3,5-triazine-2,4-(1H,3H)-dione. Also present were 3-(4-hydroxycyclohexy 1) -6- (dimethylamino) -1-methy 1-1- (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 unchaged 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 groundwater (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 evaluated one month after application of hexazinone, including the 8- to 12-inch depth, when total rainfall equaled 8.43 inches. 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 thin layer chromatography (TLC) test for Fallsington sandy loam and Flanagan silt loam gave Rfvalues 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 in Delaware using a Keyport silt loam, 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).

- Neary et al. (1993) have concluded that most peak pesticide (including hexazinone) residue concentrations in groundwater are associated with storm run-off, principally during the first one to four storm events after application. However, these peak concentrations are not always associated with hydrograph peaks, and may not occur until weeks, months or even a year after application, and then may persist for only a month or more than a year. Soil types, water table depth, storm event duration and intensity, distance of residues from stream channels, routing and mechanism of transport were all apparent factors in the appearance and timing of base flow and run-off concentration peaks.

- Based on the octanol./water coefficient, hexazinone is not expected to accumulate in fish.

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. Similar results were observed in rats dosed with 1000 mg/kg without preconditioning.

- 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 only very low levels of ^{14}C-hexazinone (about 0.2% of the administered dose) were found in any body tissue 3-6 days after 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-hydroxycyclohexyl)-6-(dimethylamino)1-methy1-1,3,5-triazine-2,4- (1H,3H)-dione (metabolite A); 3-cyclohexyl-6-(methylamino)-1-methy1-1,3,5-triazine-2,4-(1H,3H)-dione (metabolite B); and 3-(4-hydroxycyclohexyl)-6-(methylamino)-1-methy1-1,3,5-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 database (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. Three additional cases of human incidents with hexazinone were reported since June 1992 to the "Incident Data System" of the Office of Pesticide Programs: one case involving a number of tree planters not wearing protective clothing, 30% developed skin irritation that desappeared 3-4 days later; and two other cases involving a backpack sprayer operator and a utility worker spraying this chemical, both sustained skin and eye irritation with rapid recovery from symptoms.

Animals

Short-term Exposure

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

- DuPont (1975d) 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 (DuPont, 1973a; 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, O or 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 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 DuPont (1976a), 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 occltisively for 24 hours to the shaved backs and trunks of male albino rabbits. No deaths were observed throughout a 14-day observation period. No other symptoms were reported.

- DuPont (1973b) 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 alanine aminotransferase (ALT, formerly glutamic pyruvic-transaminase or 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.

- DuPont (1977b) applied 6,000 mg/kg hexazinone as a 63% solution occlusively to the shaved backs and trunks of male albino rabbits. All rabbits showed moderate skin irritation which cleared 7 days after cessation of treatment. No treatment-related mortalities were reported after a 14-day observation period.

- DuPont (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, DuPont (1976b) repeated the DuPont (1972) study with guinea pigs and observed no irritation or sensitization.

- DuPont (1980a) reported that in albino rabbits, a single dose of hexazinone applied as a 27% (vehicle not specified) solution to one eye per animal and left 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 25-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, DuPont (1973c) 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 SAP 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-Effeet Level (LOAEL) of 5,000 ppm (125 mg/kg/day) were identified.

- In a 90-day feeding study (DuPont, 1973d), Crl-CD rats (10/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).

- Groups of purebred beagle dogs (5/sex/group) were fed ad libitum O, 200, 1,500 or 6,000 ppm of hexazinone in their diet for 12 months (DuPont, 1991a). Based on monitored food consumption, these doses corresponded to 0, 5.00, 41.24 and 161.48 mg/kg/day in males, and 0, 4.97, 37.57 and 166.99 mg/kg/day in females. Increased SAP, serum globulin and hepatocellular vacuolation, as well as decreased serum albumin were reported for males at the 41.24 mg/kg/day dose. Increased hepatocellular pigmentation and concentric membranous bodies, and decreased serum albumin were reported for females at the 41.24 mg/kg/day dose. Also at this dose, one male appeared emancieted and one female had pale kidneys. Additional effects were reported in the high-dose animals, including decreased body weight and food consumption that was perhaps due, at least in part, to poor palatability of the diet. The high dose caused also in these animals moderate macrocytic anemia as evidenced by decreased erythrocyte counts, hematocrits and hemoglobins in males, and by increased mean corpuscular volumes and mean corpuscular hemoglobins in both sexes. Clinical chemistry parameters affected at the high dose included increased blood urea nitrogen (BUN), creatinine (females), serum alanine aminotransferase, serum aspartate aminotransferase, SAP and globulin, and decreased glucose, cholesterol, total protein (females), calcium and inorganic phosphate. The lower cholesterol and phosphate were considered reflective of poor nutritional status in some high-dose animals, and the elevated BUN and creatinine of potential kidney damage. In addition to the histological and enzymatic indications of liver damage, relative liver weights were significantly increased at the high dose. No significant effects were observed at the low dose. The study thus establishes a chronic oral NOAEL of 200 ppm, or 5.0 mg/kg/day, of hexazinone in the diet. The LOAEL was determined to be 1,500 ppm, or 41.24 mg/kg/day for males and 37.57 mg/kg/day for females.

- Six-week old CD-1 mice (80/sex/group) were fed ad libitum either 0, 200, 2,500 or 10,000 ppm of hexazinone in the diet for 2 years (DuPont, 1981). These doses correspond to approximately 0, 30, 375 or 1,500 mg/kg/day using a conversion of 1 ppm in the diet equal to 0.15 mg/kg/day (Lehman, 1959). No treatment-related changes in mortality, hematological parameters or gross lesions were reported. Corneal opacity, sloughing and discoloration of the distal tip of the tail were noted as early as the fourth week of the study in some 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 organ weight changes included increases in the liver at 10,000 ppm (males and females) and 2,500 ppm (females), plus several judged by the authors not to be treatment-related: lung increases (absolute and relative) in males at 200 and 2,500 ppm, kidney decreases in males at all doses, testicular increases at 2,500 and 10,000 ppm, relative brain increases in males at 10,000 ppm and females at 2,500 ppm, and thymus, kidney and heart decreases in females at 10,000 ppm. Liver hypertrophy, hyperplastic nodules, cellular necrosis and inflammatory foci were reported in one or both sexes at the mid and/or high doses. The identified NOAEL and LOAEL for chronic oral exposure of mice to hexazinone were 200 ppm (30 mg/kg/day) and 2,500 ppm (375 mg/kg/day), respectively.

- DuPont (1977c) 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

- Two rat reproduction studies were performed by DuPont that provided supplementary or minimum data as judged by EPA (DuPont, 1979c; Kennedy and Kaplan, 1984). In the first, a one-generation reproduction study (Kennedy and Kaplan, 1984), Crl-CD rats (10/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 seperate, three-generation reproduction study that was part of a larger, long-term study, (DuPont, 1979c; Kennedy and Kaplan, 1984), Crl-CD rats (20/sex/dose) received hexazinone (95.8% 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 dietary assumptions for a rat). Following 90 days of feeding, 20 rats/sex/dose were selected to serve as the parental (F^o) 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 evaluated for the second and third generations. There were no significant differences between the control and treated groups with respect to the various calculated indices (fertility, gestation, viability and lactation), thus identifying a NOAEL of 2,500 ppm (125 mg/kg/day) for reproductive effects. 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, indicating a NOAEL of 1,000 ppm (50 mg/kg/day) and a LOAEL of 2,500 ppm (125 mg/kg/day) for developmental growth effects. Based upon all effects, the study supports an overall NOAEL of 1,000 ppm (50 mg/kg/day) and an overall LOAEL of 2,500 ppm (125 mg/kg/day).

- Groups of Sprague-Dawley rats (30/sex/group) were fed ad libitum diets containing 0, 200, 2,000 or 5,000 ppm of hexazinone during growth, mating, gestation and lactation in a 2-generation reproduction study (DuPont, 1991b). PI rats were dosed for 73 days prior to mating, and F1 rats for 105 days prior their first mating for the F2A litters (longer for the F2B litters). Maternal toxicity effects were noted at the mid and high doses. Based on reduced body weights and body-weight gains in PI and F1 females, the NOAEL and the LOAEL for systemic effects were determined to be 200 and 2,000 ppm, respectively (14.3 and 143 mg/kg/day based on body weight and dietary consumption data for P1 females during the premating period; corresponding doses for F1 females were somewhat higher). Male fertility, female fertility, gestation, viability and lactation indices were not affected by treatment. Increased absolute (P1) or relative (F1) testes weight at 5,000 ppm was not deemed toxicologically significant. The reproductive NOAEL was thus 5,000 ppm or, based upon body weight and dietary consumption data during the premating periods, 294 mg/kg/day (PI males), 399 mg/kg/day (FI males), 383 mg/kg/day (PI females), or 484 mg/kg/day (Fl females). Decreased Fl, F2A and F2B pup body weights were observed at 2,000 and 5,000 ppm, as was decreased F2B pup survival at 5,000 ppm. Based upon the decreased pup weights, the

developmental NOAEL and LOAEL were 200 and 2,000 ppm, respectively. Using body weight and dietary consumption data taken during the premating periods, the corresponding maternal doses were approximately 14.3 mg/kg/day (PI females) or 17.7 mg/kg/day (Fl females), and 143 mg/kg/day (PI females) or 180 mg/kg/day (Fl females). Therefore, this study supports an overall NOAEL of 200 ppm (14.3 mg/kg/day) and an overall LOAEL of 2,000 ppm (143 mg/kg/day), and was judged by EPA to be of guideline quality.

Development Effects

- In a developmental study in the rat that was conducted by DuPont (DuPont, 1974) and later published (Kennedy and Kaplan, 1984), 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 dietary 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 and were unaffected by treatment. Fetuses from the 0 and 5,000 ppm dose groups were evaluated for developmental effects (gross, soft tissue or skeletal abnormalities). Maternal weight gain during the exposure period was depressed modestly at 1,000 ppm and substantially at 5,000 ppm. At sacrifice, no adverse effects were observed for the dams. No malformations or adverse growth effects were noted in the fetuses. This study identified a NOAEL of 1,000 ppm (50 mg/kg/day) and a LOAEL of 5,000 ppm (250 mg/kg/day) for maternal effects based on substantially depressed maternal weight gain. A NOAEL of 5,000 ppm (250 mg/kg/day) was established for developmental effects in the fetus.

- Mated Sprague-Dawley rats were administered single oral daily doses of hexazinone by gavage during gestation days 7 through 16 (DuPont, 1987). The following dose levels were tested: 0, 40, 100, 400 and 900 mg/kg/day. Treatment-related effects, observed only in dams from the 400 mg/kg/day and 900 mg/kg/day groups, included alopecia, and stained chin and nose; decreased body weight gain and food consumption during and after dosing, until the termination of the study; and increased relative liver weight (liver weight/body weight ratio). Treatment-related developmental effects, observed only in the 400 mg/kg/day and 900 mg/kg/day groups, included decreased fetal body weights; and increased incidence of fetuses with no kidney papilla and with unossified sternebrae. Maternal and developmental toxic effects observed the 900 mg/kg/day group were, in most instances, statistically significant ($p < 0.05$) when compared with those observed in the control group. Maternal and developmental toxic effects observed in the 400 mg/kg/day group were minimal and only occasionally statistically significant ($p < 0.05$) when compared with those noted in the controls. Based on the above findings, maternal NOEL and LOEL were 100 mg/kg/day and 400 mg/kg/day, respectively. The developmental NOEL and LOEL were also 100 mg/kg/day and 400 mg/kg/day, respectively.

- Artificially inseminated New Zealand white rabbits (17/group) were exposed to 0, 20, 50 or 125 mg/kg/day hexazinone by gavage for gestation days 6-19 (DuPont, 1980). Significant changes in maternal toxic effects were observed only in the high-dose group and included increased incidence of depression and discharge from the eyes; decreased body weight gain; and increased resorptions. Treatment-related developmental effects were observed also only in the high-dose group and included decreased fetal body weight gain and delayed ossification of extremities. Based on these findings, the NOEL and LOEL for maternal toxicity were 50 mg/kg/day and 125 mg/kg/day, respectively. The NOEL and LOEL for developmental toxicity were also 50 mg/kg/day and 125 mg/kg/day, respectively.

Mutagenicity

- The ability of hexazinone to induce unscheduled DNA synthesis was assayed by DuPont (1983) in freshly isolated hepatocytes from 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.

- DuPont (1982b) 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). Concentrations above these yielded no analyzable metaphase cells due to cytotoxicity.

- In a study desigried to evaluate the clastogenic potential of hexazinone in rat bone marrow cells (DuPont, 1982c), Sprague-Dawley CD rats (12/sex/dose) were given a single dose of 0, 100, 300 or 1,000 mg/kg of 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 2,000)jg/plate. The compound was not found to be mutagenic, with or without s-9 activation (DuPont, 1977d).

- Hexazinone was tested in Chinese hamster ovary (CHO)/hypoxanthine-guanine-phosphoribosyltransferase assay (HGPRT), both withand without activation. The compound was not found negative in both tests (DuPont, 1992).

Carcinogenicity

- DuPont (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 (DuPont, 1977c; 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 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:

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

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, 1,000 or 10,000), in accordance with EPA or National Academy of Sciences/Office of Water (NAS/OW) guidelines.

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

One-day Health Advisory

No suitable information was found in the available literature for determining the One-day HA for hexazinone. The Ten-day HA of 2,000 hg/L, calculated below, is recommended for use as a conservative estimate for a 1-day exposure.

Ten-day Health Advisory

The developmental study in rabbits conducted by DuPont (1980c) has been selected to serve as the primary basis for the Ten-day HA because it examined an exposure of the appropriate duration, and because it established both a NOAEL and a LOAEL. In this study, artificially inseminated New Zealand white rabbits (17/group) were exposed to 0, 20, 50 or 125 mg/kg/day hexazinone by gavage during gestation days 6-19. Significant changes in maternal toxic effects were observed only in the high-dose group and included increased incidence of depression and discharge from the eyes, decreased body weight gain, and increased resorptions. Treatment-related developmental effects were also observed only in the high-dose group, and included decreased fetal body weight gain and delayed ossification of extremities. Based on these findings, the NOAEL and LOAEL for both maternal and developmental toxicity were 50 mg/kg/day and 125 mg/kg/day, respectively. These effect levels are generally supported by two rat teratology studies. In rats fed 0, 200, 1,000 or 5,000 ppm of hexazinone (approximately 0, 10, 50 or 250 mg/kg/day) from gestation days 6 through 15, no significant adverse maternal or fetal effects were observed, except that, during treatment maternal weight gain was substantially depressed at 5,000 ppm (Dupont, 1974). This study's NOAEL and LOAEL were thus 1,000 ppm (50 mg/kg/day) and 5,000 ppm (250 mg/kg/day), respectively. The second study, in which rats were fed 0, 40, 100, 400 or 900 mg/kg/day of hexazinone during gestation days 7 through 16, established both maternal and developmental NOAELs and LOAELs of 100 mg/kg/day and 400 mg/kg/day, respectively. In light of these three studies, the rabbit study (DuPont, 1980c) NOAEL of 50 mg/kg/day has been selected as the basis of the Ten-day HA. However, because rabbit appears tobe more sensisitive than the rat in these developmental studies. However, a 90-day dietary exposure study in the dog suggests that the rat and rabbit may not be the most sensitive test species for the effects of hexazinone (DuPont, 1973c). Therefore, an extra uncertainty factor of three has been incorporated into the derivation of the Ten-day HA to account for the lack of short-term toxicity data in the dog.

The Ten-day HA for the 10-kg child is calculated as follows:

Ten-day (50 mg/kg/day) (10 kg)

(300)(1 L/day) = 1.67

rounded to 2,000 ug/L

where:

50 mg/kg/day = NOAEL, based on absence of maternal systemic and pup developmental effects that were observed in rabbits after maternal exposure to hexazinone at higher doses

(125 mg/kg/day) via the diet for 10 days (gestation days 6 through 15).

10 kg = assumed weight of child.

300 = uncertainty factor; this uncertainty factor was chosen in accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal study is employed (a factor of 100 to account for interspecies extrapolation and variability in human sensitivity, and a factor of 3 to account for the lack of short-term toxicity data in the dog, which appears to be the most sensitive test species for hexazinone).

1 L/day = assumed water consumption by a 10-kg child.

Longer-term Health Advisory

The two-generation rat study by DuPont (1991b) has been selected to serve as the basis for the Longer-term HA because it was well conducted, provides both a NOAEL and LOAEL, and results in the most conservative (lowest) Longer-term HA. Groups of Sprague-Dawley rats (30/sex/group) were fed ad libitum diets containing 0, 200, 2,000 or 5,000 ppm of hexazinone during growth, mating, gestation and lactation in a 2-generation reproduction study . P1 rats were dosed for 73 days prior to mating, and F1 rats for 105 days prior their first mating for the F2A litters (longer for the F2B litters). Maternal toxicity effects were noted at the mid and high doses. Based on reduced body weights and body-weight gains in P1 and F1 females, the NOAEL and the LOAEL for systemic effects were determined to be 200 and 2,000 ppm, respectively (14.3 and 143 mg/kg/day, based on actual body weight and dietary consumption data for PI females during the premating period. The respective values calculated from data for Fl females were 17.7 and 180 mg/kg/day). Male fertility, female fertility, gestation, viability and lactation indices were not affected by treatment. Increased absolute (P1) or relative (F1) testes weight at 5,000 ppm was not deemed toxicologically significant. Based upon decreased pup weights observed at 2,000 and 5,000 ppm, the reproductive NOAEL and LOAEL were also determined to be 200 and 2,000 ppm (14.3 and 143 mg/kg/day), respectively. The 90-day feeding study in dogs conducted by DuPont (1973c) was also strongly considered as a basis for deriving the Longer-term, HA. Based on altered food consumption, body weight gain, liver weight, alkaline phosphatase activity and albumin/globulin ratios, this study established a NOAEL and LOAEL of 1,000 ppm (25 mg/kg/day) and 5,000 ppm (125 mg/kg/day), respectively. Because the true lowest-effect level cannot be adequately identified in either study and because 73 to 105+ days more closely approximates 10 percent of a rat's life than does 90 days for a dog (i.e., in terms of duration, there was a relatively more appropriate longer-term exposure for rats than for dogs), the rat reproduction study was selected as the basis for the Longer-term HA determination. The dog study provides good support for this level:

Longer-term HA =(14.3 mg/kg/day) (10 kg)/(100) (1 L/day) = $1.43^{mg/L}$

(Rounded to 1,000 ug/L)

where:

14.3 mg/kg/day = NOAEL, based on absence of reduced maternal weight gain and absence of reduced pup weight in rats exposed to hexazinone via the diet for 73 to 105+ days prior to mating and during gestation.

10 kg = assumed body weight of child.

100 = uncertainty factor; this uncertainty factor was chosen in, accordance with EPA or NAS/OW guidelines in which a NOAEL from an animal study is employed.

1 L/day = assumed water consumption by a 10-kg child.

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

Longer-term HA =(14.3 mg/kg/day) (70 kg)/(100) (2 L/day) 5.25 mg/L

(Rounded to 5,000 ug/L)

where:

14.3 mg/kg/day = NOAEL, based on absence of reduced maternal weight gain and absence of reduced pup weight in rats exposed to hexazinone via the diet for 73 to 105+ days prior to mating and during gestation.

70 kg = assumed weight of adult.

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

2 L/day = assumed water consumption by a 70-kg 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 is not available, a value of 20% is assumed. If the contaminant is classified as a known, probable or possible carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic end points of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

The one-year dog-feeding study by DuPont (1991a) has been selected to serve as the basis for the RfD because it was a well conducted study that established both a NOAEL and a LOAEL for relatively less severe effects, and because the dog may be more sensitive than rodent species to the toxic effects of hexazinone. In this study, groups of purebred beagle dogs (5/sex/group) were fed ad libitum 0, 200, 1,500 or 6,000 ppm of hexazinone in their diet for 12 months (DuPont, 1991a). Based on monitored food consumption, these doses corresponded to 0, 5.00, 41.24 and 161.48 mg/kg/day in males, and 0, 4.97, 37.57 and 166.99 mg/kg/day in females. Increased SAP, serum globulin and hepatocellular vacuolation, as well as decreased serum albumin were reported for males at the mid dose. Increased hepatocellular pigmentation and concentric membranous bodies, and decreased serum albumin were reported for females at the mid

dose. Also at this high dose level, one male appeared emanciated and one female had ale kidneys. Additional gross, histological, hematological and enzymatic effects were reported in the high-dose animals, while no significant effects were observed at the low dose. The study thus establishes a chronic oral NOAEL of 200 ppm, or 5.0 mg/kg/day, of hexazinone in the diet. The LOAEL was determined to be 1,500 ppm, or 41.24 mg/kg/day for males and 37.57 mg/kg/day for females.

Step 1: Determination of Reference Dose (RfD)

Based upon the DuPont (1991a) one-year dog-feeding study described above, and using a 100-fold uncertainty factor to account for intra- and inter-species variation, an RfD of 0.05 mg/kg/day can be established for hexazinone.

RfD* = 5 mg/kg/day/100 = 0.05 mg/kg/day

*This RfD was peer reviewed by both the Office of Pesticide Programs Peer Review Committee and the Office of Water Toxicology Review Panel. Further external peer review of the RfD was performed by two external reviewers. However, due to the Agency's revision of the IRIS operational procedures, the RfD calculated above for this chemical is not on IRIS.

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

DWEL = (0.05 mg/kg/day) (70 kg)/(2 L/day) = 1.75 mg/L

(Rounded to 2,000 ug/L)

where:

0.05 mg/kg/day = RfD

70 kg = assumed weight of adult.

2 L/day = assumed water consumption by 70-kg adult.

Step 3: Determination of the Lifetime HA

Lifetime HA = (1.75 mg/L) (20%) = 0.35 mg/L (rounded to 400 ug/L)

where:

1.75 mg/L = Lifetime HA at 100% contribution from ingestion of drinking water.

20% = assumed percentage of daily exposure contributed by ingestion of drinking water.

Evaluation of Carcinogenic Potential

- A reassessment of the available carcinogenicity studies in two rodent species, a two-year mouse study by DuPont (1981) and a two-year rat study by Kennedy and Kaplan (1984), did not provide evidence that hexazinone demonstrate either the presence or absence of a carcinogenic effect. Therefore, applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), hexazinone may be classified in Group D: not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of hexazinone.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The tolerances listed in 40 CFR §180.396 for the combined residues of hexazinone and its metabolites in or on plant and animal commodities range from 0.1 to 10 ppm (U.S. EPA, 1994a, 1987).

- Hexazinone meets the triggers for classification as a restricted-use chemical for groundwater concerns (U.S. EPA, 1996).

- Under the Worker Protection Standard (WPS), the interim restricted entry level for all registered uses of hexazinone is currently 24 hours (U.S. EPA, 1994a).

- There are no special toxicological concerns that warrant the establishment of active-ingredient-based personal protective equipment (PPE) requirements for hexazinone handlers. The PPE required for entry when concentrations of the chemical require restricted entry is: coveralls, chemical-resistant gloves, shoes plus socks, and protective eyewear (U.S. EPA, 1994a).

VII. ANALYTICAL METHODS

- Hexazinone can be analyzed by EPA Method 507. Determination of hexazinone using Method 507 -- sample is extracted with methylene chloride. The methylene chloride extract is dried and concentrated during a solvent exchange to methyl tert-butyl ether. The analytes in the extract are separated and identified by a capillary column gas chromatograph equipped with a nitrogen-phosphorus detector. Confirmation of the compounds may be obtained using a dissimilar column or by the use of GC-MS (U.S. EPA, 1991).

VIII. TREATMENT TECHNOLOGIES

- A pilot-scale treatability study for the removal of pesticides including hexazinone was conducted on production wastewaters at DuPont in Laporte, Texas. The plant consisted of a 100 L aeration basin, clarifier and sand filter, and the treatment process included the addition of powdered activated carbon to the activated sludge. Operating conditions reported were: hydraulic retention time of 2.1 days, solids retention time of 10 days, and carbon dose of 1,480 mg/L. A 96.2% removal was achieved for hexazinone with an influent concentration of approximately 658 μ/L (Meidl and Dietrich, 1989).

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

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This study was submitted to the USEPA Office of Pesticide Programs and is is subject to Sen 10 (Protection of Trade Secrets and Other Information) of the U.S. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Section 10 prohibits public disclosure of confidential business information.

CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Hexazinon

CASRN -- 51235-04-2

Last Revised -- 03/13/87

_I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

_I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased albumin; increased globulin, alkaline phosphatase and hepatocellular vacuolation in males; increased hepatocellular pigmentation and concentric membranous bodies in females; pale kidneys (1 female) and thinness (1 male)	NOAEL: 200 ppm (5.0 mg/kg/day)	100	1	5E-2 mg/kg/day
	LOAEL: 1,500 ppm (41.24 mg/kg/day, males) (37.57 mg/kg/day, females)			

1-year dog study (diet) DuPont, 1991a

*Conversion Factors: Doses determined from study.

_I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RFD)

DuPont. 1991a. E.I. du Pont de Nemours and Company. Chronic toxicology study with hexazinone in dogs. MRID No. 421623-01. HED/OPP Doc. No. 009575. Available from EPA. Write to FOI EPA, Washington, DC 20460.

Groups of purebred beagle dogs (5/sex/group) were fed ad libitum 0, 200, 1,500 or 6,000 ppm of hexazinone in their diet for 12 months (DuPont, 1991a). Based on monitored food consumption, these doses corresponded to 0, 5.00, 41.24 and 161.48 mg/kg/day in males, and 0, 4.97, 37.57 and 166.99 mg/kg/day in females. Increased serum alkaline phosphatase, serum globulin and hepatocellular vacuolation, as well as decreased serum albumin were reported for males at the mid dose. Increased hepatocellular pigmentation and concentric membranous bodies, and decreased serum albumin were reported for females at the mid dose. Thinness in 1 male and pale kidneys in 1 female were also observed at this dose. Additional effects were reported in the high-dose animals, including decreased body weight and food consumption that was perhaps

due at least in part to poor palatability, and moderate macrocytic anemia evidenced by decreased erythrocyte counts, hematocrits and hemoglobins in males, and by increased mean corpuscular volumes and mean corpuscular hemoglobins in both sexes. Clinical chemistry parameters affected at the high dose included increased BUN, creatinine (females), serum alanine aminotransferase, serum aspartate aminotransferase, serum alkaline phosphatase and globulin, and decreased glucose, cholesterol, total protein (females), calcium and inorganic phosphate. The lower cholesterol and phosphate were considered reflective of poor nutritional status in some high-dose animals, and the elevated BUN and creatinine of potential kidney damage. In addition to the histological and enzymatic indications of liver damage, relative liver weights were significantly increased at the high dose. No significant effects were observed at the low dose. The study thus establishes a chronic oral NOAEL of 200 ppm, or 5.0 mg/kg/day, of hexazinone in the

diet. The LOAEL was determined to be 1,500 ppm, or 41.24 mg/kg/day for males and 37.57 mg/kg/day for females. (Core grade: Guideline.) MRID No. 42162301.

2-year chronic feeding study in the rat: Groups (36/sex/group) of weanling Crl-CD rats (a Sprague-Dawley derivative strain) fed 0, 200, 1,000 or 2,500 ppm of hexazinone in the diet (1% corn oil) for 2 years (DuPont, 1977; published in 1984 by Kennedy and Kaplan). Based on the approximate conversion of 1 ppm in the diet = 0.05 mg/kg/day for older rats (Lehman, 1959), these doses correspond to about 0, 10, 50 and 125 mg/kg/day. There were no treatment-related clinical signs, histopathological findings or altered survival rates. High-dose males had decreased kidney and relative liver and spleen weights, while mid-dose males had increased relative lung weights. For females, elevated stomach and relative brain weights were reported at 2,500 ppm, while increased liver and spleen weights were observed only at 200 ppm. Slightly elevated leukocyte counts with a greater proportion of eosinophils were seen in males at 2,500 ppm. The urine of high-dose rats was more alkaline, and alkaline phosphatase activity was reduced in males at 1,000 and 2,500 ppm. Reduced body weight was reported at 2,500 ppm for males and females, and at 1,000 ppm for females. Based on these observations, a NOAEL of 200 ppm (10 mg/kg/day) and a LOAEL of 1,000 ppm (50 mg/kg/day) were determined for chronic oral exposure in the rat. (Core grade: Minimum.) MRID No. 00078045 and 00108638.

_I.A.3. ORAL RFD UNCERTAINTY FACTOR, MODIFYING FACTOR AND COMMENTS:

UF -- An uncertainty factor of 100 is proposed to account for inter- and intra-species variation, in accordance with EPA guidance for the use of a NOAEL from a chronic animal study.

MF -- None.

COMMENTS ON THE ORAL RFD

The toxicity data base on hexazinone is reasonably extensive, and is adequate to establish a chronic oral RfD with reasonable confidence. The principal cited study (DuPont, 1991a) was well conducted and monitored a variety of clinical signs, gross pathological, histopathological and clinical chemistry effects in the dog following a 12-month feeding exposure to hexazinone. A NOAEL of 200 ppm (5.0 mg/kg/day) and a LOAEL of 1,500 ppm (approximately 40 mg/kg/day for both sexes) were established by this study, primarily on the basis of critical effects observed in clinical chemistry parameters and liver histopathology. There was also some suggestion of kidney and body-weight effects at the LOAEL that were more apparent at the high dose, and which have been observed in other studies.

This study has been selected as the basis for deriving the chronic oral RfD because of its chronic duration, and because the dog appears more sensitive in general to the toxic effects of hexazinone than do rodent species. Although it would have been desirable for exposure to have lasted at least 2 years, it was by a pathway reasonably relevant to drinking water exposure. Because this study provides the lowest NOAEL and LOAEL values of any of the appropriate studies that were reviewed, because these levels are in general supported by a number of other relevant studies as summarized below, and because no human data suggests their inappropriateness, they provide an adequate basis for deriving a chronic oral RfD protective for humans against the known toxic effects of hexazinone.

_I. A. 4. ADDITIONAL STUDIES

1) Subchronic Feeding - dog: (DuPont, 1973a, authored by Sherman et al.).

In a 90-day feeding study, beagle dogs (four/sex/dose) were fed 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. (Core grade: Minimum.) MRID No. 00114484.

2) Subchronic Feeding - rat: (DuPont, 1973b, published in 1984 by Kennedy and Kaplan).

In a 90-day feeding study, Crl-CD rats (10/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. For both sexes, these findings identify a NOAEL of 1,000 ppm (50 mg/kg/day) and a LOAEL of 5,000 ppm (250 mg/kg/day). (Core grade: Minimum.) MRID No. 00104977.

3) 2-Year Feeding - mouse: (DuPont, 1981, authored by Goldenthal and Trumbull)

Six-week old CD-1 mice (80/sex/group) were fed ad libitum either 0, 200, 2,500 or 10,000 ppm of hexazinone in the diet for 2 years. These doses correspond to approximately 0, 30, 375 or 1,500 mg/kg/day using a conversion of 1 ppm in the diet = 0.15 mg/kg/day (Lehman, 1959). No treatment-related changes in mortality, hematological parameters or gross lesions were reported, although corneal opacity, sloughing and discoloration of the distal tip of the tail were noted as early as the fourth week of the study in some 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 organ weight changes included increases in the liver at 10,000 ppm (males and females) and 2,500 ppm (females), plus several judged by the authors not to be treatment-related: lung increases (absolute and relative) in males at 200 and 2,500 ppm, kidney decreases in males at all doses, testicular increases at 2,500 and 10,000 ppm, relative brain increases in males at 10,000 ppm and females at 2,500 ppm, and thymus, kidney and heart decreases in females at 10,000 ppm. Liver hypertrophy, hyperplastic nodules, cellular necrosis and inflammatory foci were reported in one or both sexes at the mid and/or high doses. The identified NOAEL and LOAEL for chronic oral exposure of mice to hexazinone were 200 ppm (30 mg/kg/day) and 2,500 ppm (375 mg/kg/day), respectively. (Core grade: Supplementary.) MRID No. 00079203, 41359301, 42509301.

4) 2-Generation Reproduction/Developmental toxicity - rat: (DuPont, 1991b).

Groups of Sprague-Dawley rats (30/sex/group) were fed ad libitum diets containing 0, 200, 2,000 or 5,000 ppm of hexazinone during growth, mating, gestation and lactation in a 2-generation reproduction study. Pl rats were dosed for 73 days prior to mating, and F1 rats for 105 days prior their first mating for the F2A litters (longer for the F2B litters). Maternal toxicity effects were noted at the mid and high doses. Based on reduced body weights and body-weight gains in P1 and F1 females, the NOAEL and the LOAEL for systemic effects were determined to be 200 and 2,000 ppm, respectively (14.3 and 143 mg/kg/day, based on actual body weight and dietary consumption data for P1 females during the premating period; the respective values calculated from data for F1 females were 17.7 and 180 mg/kg/day). Male fertility, female fertility, gestation, viability and lactation indices were not affected by treatment. Increased absolute (P1) or relative (F1) testes weight at 5,000 ppm was not deemed toxicologically significant. Based upon decreased pup weights observed at 2,000 and 5,000 ppm, the reproductive NOAEL and LOAEL were also determined to be 200 and 2,000 ppm (14.3 and 143 mg/kg/day), respectively. (Core grade: Guideline.) MRID No. 42066501.

5) Developmental toxicity - rat: (DuPont, 1974, published in 1984 by Kennedy and Kaplan).

Pregnant Crl-CD rats (at least 25/group) were fed dietary levels of 0, 200, 1,000 or 5,000 ppm of hexazinone during gestation days 6-15. No significant treatment-related differences were observed in number of implantation sites, live fetuses, resorptions/female, percentage females with partially resorbed litters, fetal size, major skeletal and internal abnormalities, or minor anomalies. The NOAEL for developmental effects in this rat study therefore 5,000 ppm (250 mg/kg/day). The study also supported a LOAEL of 5,000 ppm (250 mg/kg/day) for maternal effects, based upon substantially reduced maternal weight gain. (Core grade: Supplementary.) Accession No. 64258.

6) Developmental toxicity - rat: (DuPont, 1987)

Mated Sprague-Dawley rats were administered single oral daily doses of hexazinone by gavage during gestation days 7 through 16. The following dose levels were tested: 0, 40, 100, 400 and 900 mg/kg/day. Treatment-related effects, observed only in dams from the 400 mg/kg/day and 900 mg/kg/day groups, included alopecia, and stained chin and nose; decreased body weight gain and food consumption during and after dosing, until the termination of the study; and increased relative liver weight (liver weight/body weight ratio). Treatment-related developmental effects, observed only in the 400 mg/kg/day and 900 mg/kg/day groups, included decreased fetal body weights; and increased incidence of fetuses with no kidney papilla and with unossified sternebrae. Maternal and developmental toxic effects observed the 900 mg/kg/day group were, in most instances, statistically significant ($p < 0.05$) when compared with those observed in the control group. Maternal and developmental toxic effects observed in the 400 mg/kg/day group were minimal and only occasionally statistically significant ($p \leq 0.05$) when compared with those noted in the controls. Based on the above findings, maternal NOEL and LOEL were 100 mg/kg/day and 400 mg/kg/day, respectively. The developmental NOEL and LOEL were also 100 mg/kg/day and 400 mg/kg/day, respectively. (Core grade: Minimum.) MRID No. 40397501.

7) Developmental toxicity - rabbit: (DuPont, 1980, published in 1984 by Kennedy and Kaplan).

Artificially inseminated New Zealand white rabbits (17/group) were exposed to 0, 20, 50 or 125 mg/kg/day hexazinone by gavage for gestation days 6-19. Significant changes in maternal toxic effects were observed only in the high-dose group and included increased incidence of depression and discharge from the eyes; decreased body weight gain; and increased resorptions. Treatment-related developmental effects were observed also only in the high-dose group and included decreased fetal body weight gain and delayed ossification of extremities. Based on these findings, the NOEL and LOEL for maternal toxicity were 50 mg/kg/day and 125 mg/kg/day, respectively. The NOEL and LOEL for developmental toxicity were also 50 mg/kg/day and 125 mg/kg/day, respectively. (Core grade: Minimum.) MRID No. 00028863.

_I.A.5. CONFIDENCE IN THE ORAL RFD:

Study -- High

Data Base -- Medium

RfD -- Medium

The principal study appears well conducted and utilized a relatively sensitive species (the dog). Although a dog study lasting 2 or more years would have increased its relevance to long-term chronic or lifetime exposure in humans, the results are essentially corroborated qualitatively and quantitatively in the cited supporting studies. Reproductive or developmental effects do not appear to be of particular concern, and confidence in the cited and general data base is medium to high based on the endpoints tested and the consistency of results across species. Confidence could be further enhanced by examining functional-

developmental and immunological endpoints. Based on these considerations, overall confidence in the chronic oral RfD can also be considered medium to high.

_I.A. 6. EPA DOCUMENTATION AND REVIEW DATES OF THE ORAL RFD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- U.S. EPA, 1988, 1993.

Review Dates: 08/05/86 - 03/18/87

Verification Date:

_I.A.7. EPA CONTACTS (ORAL RFD)

Amal Mahfouz/OW/OST -- (202) 260-9568

_VI.A. ORAL RFD REFERENCES

OREF - DuPont. 1991a. E.I. du Pont de Nemours and Company. Chronic toxicology study with hexazinone in dogs. MRID No. 421623-01; HED/OPP Doc. No. 009575. Available from EPA. Write to FOI EPA, Washington, DC 20460.

OREF - DuPont. 1991b. E.I. du Pont de Nemours and Company. Reproductive and fertility effects with IN-A3674-207; multigeneration reproduction study in rats. MRID No. 420665-01; HED/OPP Doc. No. 009574. Available from EPA. Write to FOI EPA, Washington, DC 20460.

OREF - DuPont. 1987. E.I. du Pont de Nemours and Company. Developmental toxicity study in the rat. MRID No. 403975-01; HED/OPP Doc. No. 007205. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - DuPont. 1981. E.I. du Pont de Nemours and Company. Two-year feeding study in mice (study authored by Goldenthal, E.I. and R.R. Trumbull; study published in 1984 by Kennedy, Jr., G.L and A.M. Kaplan as: Chronic toxicity, reproductive, and teratogenic studies of hexazinone. Fund. Appl. Toxicol, 4:960-971). IRDC No. 125-026. MRID No. 0079203, 413593-01, 425093-01; HED/OPP Doc. No. 001355, 007205, 008659, 008658. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - DuPont. 1980. E.I. du Pont de Nemours and Company. Developmental toxicity study in the rabbit (study published in 1984 by Kennedy, Jr., G.L and A.M. Kaplan as: Chronic toxicity, reproductive, and teratogenic studies of hexazinone. Fund. Appl. Toxicol. 4:960-971). MRID No. 00028863; HED/OPP Doc. No. 002320, 007205.

OREF - DuPont. 1977. E.I. du Pont de Nemours and Company. Long-term feeding study in rats with hexazinone: Haskell Laboratory Report No. 353-77 (study authored by Kaplan, A.M., C.V. Frazier, L.L. Adams, et al.; study published in 1984 by Kennedy, Jr., G.L and A.M. Kaplan as: Chronic toxicity, reproductive, and teratogenic studies of hexazinone. Fund. Appl. Toxicol. 4:960-971). MRID No. 00078045, 00108686-38; HED/OPP Doc. No. 002331, 007205. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - DuPont. 1974. E.I. du Pont de Nemours and Company. Developmental toxicity study in the rat (study published in 1984 by Kennedy, Jr., G.L and A.M. Kaplan as: Chronic toxicity, reproductive, and teratogenic studies of hexazinone. Fund. Appl. Toxicol. 4:960-971). Accession No. 64258; HED/OPP Doc No. 002321, 007205. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - DuPont. 1973a. E.I. du Pont de Nemours and Company. Three month feeding study in dogs with sym-triazine-2,4(1H,3H)dione, 3-cyclohexyl-1-methyl(-6-dimethylamino) (INA-3674). Haskell Laboratory Report No. 408-73 (study authored by Sherman, H., N. Dale, L. Adams, et al.). MRID No. 00114484; HED/OPP Doc. No. 002320, 007205. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - DuPont. 1973b. E.I. du Pont de Nemours and Company. Three month feeding study in the rat (study published in 1984 by Kennedy, Jr., G.L and A.M. Kaplan as: Chronic toxicity, reproductive, and teratogenic studies of hexazinone. Fund. Appl. Toxicol. 4:960-971). MRID No. 00104977; HED/OPP Doc. No. 002321, 007205. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

OREF - Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs, and cosmetics. Assoc. Food Drug Officials. U.S., Q. Bull.

OREF - U.S. EPA. 1993. U.S. Environmental Protection Agency. RfD/Peer Review Report of Hexazinone. Washington, DC: U.S. EPA, RfD/Peer Review Committee, Health Effects Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances.

OREF - U.S. EPA. 1988. U.S. Environmental Protection Agency. Health advisory for hexazinone. Washington DC: U.S. EPA Health and Ecological Criteria Division, Office of Science and Technology, Office of Water.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF WATER
JAN 1 7 1996

MEMORANDUM

SUBJECT: Review of the Health Advisories for Toxaphene and Hexazinone

FROM: Tudor T. Davies, Director
Office of Science and Technology (4301)

TO: Daniel M. Barolo (OPP, 7501C)
William Sanders (OPPT, 7401)
Dorothy Patton (ORSI, 8104)
Stephen D. Luftig (OERR, 5201)
Michael H. Shapiro (OSW, 5301)
Margo T. Oge (ORIA, 6601J)

Attached for your review are the 1995 draft updated Drinking Water Health Advisories (HAs) and the draft revised Reference Doses (RfDs) for the 1985 Toxaphene HA and the 1988 Hexazinone HA. The Office of Water (OW) Health Advisory Program was initiated to provide information and guidance to individuals or agencies concerned with potential risk from drinking water contaminants for which no national regulations currently exist. Each HA contains information on the nature of adverse effects associated with the contaminants and the concentrations of the contaminants that would be anticipated to cause an adverse effect following various periods of exposure. In addition, the HA summarizes information on occurrence, environmental fate, available analytical methods and treatment techniques for the contaminant.

Toxaphene is a canceled chlorinated hydrocarbon insecticide known to contaminate water and accumulate in the environment. This contaminant is considered a potential human carcinogen and was regulated in 1991 using the best available technology approach to establish a Maximum Contaminat Level (MCL) at 0.003 mg/L. At the present time, the available new information on this chemical justifies the revision of the 1985 HA document to update the Shorter-term and Longer-term HA values. The 1985 RfD value of 0.1 mg/kg/day is also revised to 0.0004 mg/kg/day.

Hexazinone is also a water contaminant which is used as a broad spectrum pre- and post-emergence herbicide to effectively control woody and herbaceous weed. A HA for this chemical was issued in 1988 based on a 1986 RfD of 0.033 mg/kg/day. The Agency recently re-evaluated the data base for this chemical and updated the 1988 HA document using a revised RfD value of 0.05 mg/kg/day.

We would appreciate your review of the attached draft documents on Toxaphene and Hexazinone. Please submit all comments to Barbara Corcoran, the OST Health Advisory Program Manager (mail code 4304), or (202) 260-1332 by COB February 9, 1996.

Attachments