August, 1988

CYANAZINE

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.

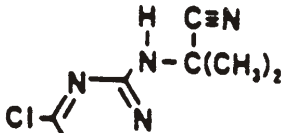
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 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. 2172546-2

Structural Formula



2-[[4-Chloro-6-(ethylamino)-1,3,5-triazin-2-yl]amino]-2-methylpropanenitrile

Synonyms

- Cyanazine (common name), Bladex, Fortrol, Payze, SD1518, VL19804, DW3418 and WL19805 (Meister, 1983).

Uses

○ Cyanazine is used as a pre- and postemergence herbicide for the control of annual grasses and broad leaf weeds (U.S. EPA, 1984a).

Properties(U.S. EPA, 1984a; Meister, 19831 CHEMLAB, 1985)

Chemical Formula	$C_9H_{13}ClN_6$
Molecular Weight	240.7
Physical State (25ºC)	White crystalline solid
Boiling Point	--
Melting Point	167.5 to 169ºC
Density	0.35 (fluffed) to 0.45 (packed) g/cc
Vapor Pressure (20ºC)	1.6 x $10^{-9}$to 7.5 x 10^{-9}mm Hg
Water Solubility (25ºC)	171 mg/L
Log Octanol/Water Partition Coefficient	2.24
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

○ Cyanazine has been found in 1,708 of 5,297 surface water samples analyzed and in 21 of 1,821 ground water samples (STORET, 1988). Samples were collected at 392 surface water locations and 1,314 ground water locations. The 85th percentile of all non-zero samples was 4.11 ug/L in surface water and 0.20 ug/L in ground water sources. The maximum concentration found in surface water was 1,300 ug/L and in ground water it was 3,500 ug/L. Cyanazine was found in surface water in 7 States and in ground water in 5 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

○ Cyanazine was identified in drinking water in New Orleans, Louisiana, in concentrations ranging from 0.01 to 0.35 ug/L.

○ Cyanazine was monitored in a newly-built reservoir on the Des Moines River in Iowa during September 1977 through November 1978. Agricultural runoff (from corn and soybeans) was a major source of pollution in the river: levels of 71 to 457 ng/L were detected during the active months of May through August; levels of 2 to 151 ng/L were detected during September through December; and zero levels were found from January through April (U.S. EPA, 1984a; NAS, 1977).

○ Cyanazine has been found in surface water in Ohio river basins (Datta, 1984).

○ Cyanazine has also been found in ground water in Iowa and Pennsylvania; typical positives found were 0.1 to 1.0 ppb (Cohen et al., 1986).

Environmental Fate

○ 14C-Cyanazine, at 5 to 10 ppm, degraded with a half-life of 2 to 4 weeks in an air-dried sandy clay loam soil, 7 to 10 weeks in a sandy loam soil, 10 to 14 weeks in a clay soil, and 9 weeks in a fresh sandy

clay soil incubated in the dark at 22ºC and field capacity (Osgerby et al., 1968). Three degradation. products, the amide and two acids, were identified in all four soils; a fourth degradate, the amine, was found only in the air-dried sandy clay loam soil.

○ Freundlich K values were 0.72 for a sandy loam soil (2.0% organic matter), 2.0 for a sandy clay soil (5.4% organic matter), 1.25 for a sandy clay loam soil (6.8% organic matter) and 6.8 for a clay soil (16% organic matter) treated with unaged ^{14}C-cyanazine (Osgerby et al., 1968). No linear correlation was found between organic matter content and adsorption.

○ 14C-Cyanazine readily moved through columns of sandy clay loam (52% of applied compound) and loamy sand (18% of applied) soil leached with 78 cm of water over a 13-day period; unaged ^{14}C-cyanazine was intermediately mobile on sandy clay loam and of low mobility on loamy sand soil thin-layer chromatography (TLC) plates (R_f 0.36 and 0.20, respectively) (McMinn and Standen, 1981). Aerobically and anaerobically aged ^{14}C-cyanazine residues, primarily the amide degradate (SD 20258), were intermediately mobile to mobile on sandy clay loam soil TLC plates.

○ Aged ^{14}C-cyanazine residues readily leached through columns containing sand (47.8% of applied compound), loamy sand (69.7% of applied compound and sandy loam (26.9% of applied compound) soils eluted with 20 cm of water (Eadsforth, 1984). The amide degradation product (SD 20258) was predominant in the leachate from the sandy soil (45% of radioactivity in leachate); the acid degradate (SD 20196) was predominant in leachate from the loamy sand (84%) and sandy loam (47%) soils. Unaltered cyanazine and SD 31222 were also identified in leachate from all three soils (≤6% of recovered residues).

III. PHARMACOKINETICS

Absorption

○ Studies by Shell Chemical Company (1969) and Hutson et al. (1970) indicated that cyanazine is rapidly absorbed from the gastrointestinal tract when administered orally at low dosage levels to three different animal species: rat, dog and cow. Measurements of urinary, fecal and biliary excretion indicated that 80 to 88% of 2,4,6-^{14}C-labeled cyanazine was eliminated within 4 days from the rat and dog, and within 21 days from the cow. The initial dosages were 1 to 4 mg/kg for the rat, 0.8 mg/animal for the dog and 5 ppm in the total ration of the cow. The dosages were administered by gavage in the rat studies and in gelatin capsules in the dog study.

Distribution

○ In rats treated with a single oral dose of 4 mg/kg cyanazine, samples of the carcass, skin and gut reflected 2.02, 0.62 and 2.73% residual radioactivity, respectively, 4 days after exposure (Shell, 1969).

○ In cows, samples of brain, liver, kidney, muscle and fat reflected concentrations of 0.55, 0.27, 0.24, 0.14 to 0.06 and less than 0.06 ppm cyanazine, respectively, after 21 days of continuous exposure to feed that contained 5 ppm cyanazine; however, when a lower dosage (0.2 ppm) was used in the feed, the detectable residues in each of these tissues were less than 0.05 ppm (Shell, 1969).

Metabolism

○ Based on the analyses of metabolites in urine, the major metabolic pathways of cyanazine in the rat and cow involved: (1) conversion of the cyano group to an amide to form 2-chloro-4-ethyl amino-6-(1-amido-1-methylethylamino)-s-thiazine; (2) N-deethylation to form 2-chloro-4- amino-6-(1-cyano 1-methyl -ethylamino)-s-triazine; (3) conversion of the cyano group of deethylate cyanazine to form the amide of deethylated cyanazine, 2-chloro-4-amino-6(1-amino-1-methyl ethylamino)-s-triazine; (4) dechlorination via glutathione, partial hydrolysis of glutathione conjugate and N-acetylation to form mercapturic acid, N-

acetyl-S-[4-amino-6-(1-cyano-1-methylethylamino) L-cysteine; and (5) dechlorination via hydrolysis (occurs only in the cow) to form 2-hydroxy-4-ethylamino-6-(1-carboxy-1-methylethylamino) -s-triazine and 2-hydroxy -4-amino-6-(1,carboxy-l-methylamino)-s-triazine, respectively (Shell, 1969).

○ Studies by Shell Chemical Company (1969) and Hutson et al. (1970) in rats with ring-labeled and side-chain-labeled cyanazine (cyano-^{14}C isopropyl $^{-14}$C and ethylamino-^{14}C) indicated that only the ethylamino -14C side chain underwent extensive degradation, since 478 of the initial radioactivity was detected in the exhaled carbon dioxide. Thus, N-deethylation was found to be a major route of degradation of cyanazine.

○ Crayford and Hutson (1972) identified 5 metabolites in urine of rats, an additional 2 (total 7) in feces and 4 metabolites in bile.

○ Crayford et al. (1970) studied the metabolism of two major plant metabolites, DW4385 and DW4394, in rats. These two compounds were identified in the rat metabolism studies by Crayford and Hutson (1972) as 2-hydroxy -4-ethylamino-6-(1-carboxy-1-methyl amino)-s-triazine (DW4385) and as 2-hydroxy-4-amino-6-(1-carboxy-1-methylethylamino)-s-triazine) (DW4394). Approximately 918 of compound DW4385 and 848 of compound DW4394 were recovered unchanged from urine and feces.

Excretion

○ Orally administered low doses of cyanazine (described above) were rapidly excreted in the urine and feces of rats and dogs (Shell, 1969; Hutson et al., 1970; Crayford and Hutson, 1972).

○ In rats treated with 1 to 4 mg/kg cyanazine by gavage, a total of 888 of cyanazine was eliminated in 4 days. Elimination via urine was almost equal to elimination via feces; about 5.378 of the administered cyanazine remained in the body; and approximately 218 of the 1 mg/kg dose appeared in the bile within the first 20 hours (Shell, 1969).

○ Hutson et al. (1970) reported that 338 of an oral dose of cyanazine was excreted in the urine of rats within 24 hours.

○ A study in rats with ^{14}C-labeled 4-ethyl-amino cyanazine indicated that 478 of the radioactivity was eliminated in carbon dioxide (Shell, 1969).

○ In dogs administered 0.8 mg of cyanazine in gelatin capsules, 51.67 and 36.298 of the dose were eliminated in the urine and feces, respectively, over a 4-day period (Shell, 1969).

○ In cows exposed to treated feed (5 ppm cyanazine) for 21 consecutive days, the amount of daily excretion of radioactivity in urine and feces was constant throughout the study period. The total cyanazine equivalents in urine and feces were 53.7 and 26.88 of the dose, respectively. The concentration in milk was reported as 0.022 ppm (Shell, 1969).

IV. HEALTH EFFECTS

Humans

○ No information was found in the available literature on the health effects of cyanazine in humans.

Animals

Short-term Exposure

○ Acute oral LD_{50} values reported for rats range from 149 to 835 mg/kg (SRI, 1967b; NIOSH, 1987; Young and Adamik, 1979b; Meister, 1983). In these studies, the percentage of active ingredient (a.i.) in the tested product(s) was not clearly identified. However, studies by Walker et al. (1974) with technical cyanazine (97% a.i.) in three different animal species reflected LD_{50}s of 182, 380 and 141 mg/kg for the rat, mouse and rabbit, respectively.

○ The acute dermal LD_{50} in rabbits treated with technical cyanazine (purity unspecified) was >2,000 mg/kg (SRI, 1967a; Young and Adamik, 1979c); in rats, the LD_{50} was >1,200 mg/kg (97% a.i.) (Walker et al., 1974).

○ The acute inhalation LC_{50} for cyanazine dust (% a.i. not specified) in rats was >2.28 mg/L/hr (Bishop, 1976) (thus cyanazine would be classified in toxicity category III).

○ In a study by Walker et al. (1968), groups of 10 female CFE rats, 5 months old, were treated by gavage with single oral doses of 1, 5 or 25 mg/kg of a wettable powder formulation (75% a.i.); the control group received water. No diuretic effects were produced in the rats receiving the formulation; however, serum protein and potassium concentrations increased at the high dose, and serum osmolality increased at 5 mg/kg, the Lowest-Observed-Adverse-Effect Level (LOAEL). The 146-Observed-Adverse-Effect Level (NOAEL) in this study appeared to be 1 mg/kg; however, this study did not provide enough information to determine the presence or absence of more significant effects at this dosage level.

○ A 4-week oral toxicity study by Walker et al. (1968) was performed using groups of 10 male and 10 female CFE rats, 5 weeks of age, receiving diets containing 1, 10 or 100 ppm cyanazine (75% or 97% a.i.) for 4 weeks; These doses are equivalent to 0.05, 0.5 or 5 mg/kg/day (Lehman, 1959). A control group of 20 animals/sex was used. After 4 weeks, urine samples were collected for 16 hours (overnight), and blood samples were used to determine the kidney function. Reductions in body weight and food intake were noted at the high-dose level. Osmolal clearance decreased in males, and this change was associated with a decrease in free water clearance in both the low- and mid-dose groups. In females, decreased urine and increased serum osmolality were observed in the mid-dose group, and both creatinine clearance and urine potassium concentrations increased in the low-dose group. The LOAEL in this study appeared to be 0.05 mg/kg/day (lowest dose tested) based on kidney function tests, although additional information was not available to determine if any other significant adverse effects were noted at this level.

Dermal/Ocular Effects

○ Cyanazine caused mild eye irritation at 100 mg (Young and Adamik 1979a) and slight skin irritation at 2,000 mg (Young and Adamik, 1979c) in rabbits. A skin sensitization test in guinea pigs was negative (Walker et al., 1974; Young and Adamik, 1979d).

Long-term Exposure

○ In a 13-week oral study in dogs (Walker and Stevenson, 1968x; Walker et al., 1974), groups of 5- to 7-month old beagle dogs, four animals/sex/treatment group, were given daily doses of 1.5, 5 or 15 mg/kg/day cyanazine in gelatin capsules. A control group of five animals/sex was given empty capsules. The test material caused emesis within the first hour of dosing in all of the high-dose males. Reduced body weight gain was also noted in the high-dose group during the second half of the study period as well as increased kidney and liver weights in the females of this group. Thus, the LOAEL was 15 mg/kg/day and the NOAEL was 5 mg/kg/day.

○ In a 13-week mouse feeding study (Fish et al., 1979), groups of 12 animals/sex/dose were fed diets containing 10, 50, 500, 1,000 or 1,500 ppm, equivalent to 1.5, 7.5, 75, 150 or 225 mg/kg/day (Lehman, 1959). The control group consisted of 24 animals/sex. Body weight gain reduction was observed in both sexes at 75 mg/kg/day and above. Statistically significant increases in liver weights were observed in both

sexes at 75 mg/kg/day and above. Thus, the LOAEL was 75 mg/kg/day and the NOAEL was 7.5 mg/kg/day.

○ An initial 13-week rat feeding study by Walker et al. (1968) was performed using 0.1, 1.0 or 100 ppm (equivalent to 0.005, 0.05 or 0.5 mg/kg/day; Lehman, 1959) of technical cyanazine (purity not specified: 97% or 75% a.i.) in feed. Each dosage group had 20 animals/sex; the control group had 40 animals/sex. Body weight gain decreased in all dosage groups in males and in the high-dose female group. A NOAEL was not reflected in this study for males, although it appeared to be 0.05 mg/kg/day for females.

○ Walker and Stevenson (1968b) repeated the above study in rats at dose levels of 1.5, 3, 6, 12, 25, 50 or 100 ppm; these levels are equivalent to 0.075, 0.15, 0.30, 1.25, 2.5 or 5 mg/kg/day (Lehman, 1959). Similar effects were noted; however, a NOAEL of 25 ppm (1.25 mg/kg/day) was identified.

○ In a 2-year study in dogs (Walker et al., 1970x), groups of 4- to 6-month-old beagle dogs were treated with technical cyanazine (97% a.i., in gelatin capsules) at dose levels of 0.625, 1.25 or 5 mg/kg/day. Each group consisted of four animals/sex. The control group consisted of six animals/sex and received empty gelatin capsules. Frequent emesis within 1 hour of dosing was observed throughout the study period in the high-dose group; this effect was associated with reduction of growth rate and serum protein. The NOAEL appeared to be 1.25 mg/kg/day; however, this NOAEL should be considered with reservations because the study did not provide adequate explanation relative to missing histological data on one of four female dogs in the 1.25-mg/kg/day dosage group. In addition, the reported data were limited to a summary report.

○ In a 2-year study in mice (Shell, 1981), cyanazine technical (purity not specified) was given in feed to CD mice at 10, 25, 50, 250 or 1,000 ppm, equivalent to 1.5, 3.75, 7.5, 37.5 or 150 mg/kg/day (Lehman, 1959); 50 animals/sex were used in the treatment groups, and 100 animals/sex were used as controls. Toxic effects reported at the two high-dose levels, 37.5 and 150 mg/kg/day, included poor appearance and skin sores, increased mortality in the female animals in both groups, increased relative brain weight in both sexes, increased relative liver weight in the two female groups, and decreased absolute and differential leukocyte values in both sexes. Anemia was noted at 150 mg/kg/day in the females, as well as increased blood protein and increased relative kidney weight. Cyanazine did not demonstrate an oncogenic potential in this study. The NOAEL for systemic toxicity in mice appeared to be 50 ppm (7.5 mg/kg/day).

○ Two chronic feeding studies in rats were available for review. In one study (Walker et al., 1970b; also cited in Walker et al., 1974), groups of 24 CFE rats/sex/dose received diets containing 6, 12, 25 or 50 ppm, equivalent to 0.3, 0.6, 1.25 or 2.5 mg/kg/day (Lehman, 1959) cyanazine (97% a.i.); 45 rats/sex were used as controls. The authors indicated that no effects due to cyanazine were noted in this study, although reduction in growth rate was noted in both sexes at 2.5 mg/kg/day and in females at 1.25 mg/kg/day. A review of this study (U.S. EPA, 1984b) indicated that cyanazine appeared to be tumorigenic in both male and female rats based on the increased incidences of thyroid tumors in all treatment groups as compared to the study's control group; increased incidences of adrenal tumors also were noted in all male treatment groups. However, this study was considered unacceptable because of several deficiencies: a limited number of tissues per animal were examined microscopically; the tumor incidences were calculated based on the number of animals tested rather than on the number of specific tissues histologically examined; gross examination and histologic findings for nonneoplastic lesions were not adequately reported; and only limited hematology, clinical blood chemistry and urinalyses data were presented.

○ Simpson and Dix (1973) repeated the above 2-year study using 1, 3 or 25 ppm, equivalent to 0.05, 0.15 or 1.25 mg/kg/day in the diet of rats (Lehman, 1959); however, convulsions were noted in the rats 3 months after the study initiation and throughout the remainder of the study period. Approximately 42% of the animals were affected, and the incidence was not considered to be dose-related. The incidence of

animals with convulsions was similar in both the control and high-dose male groups (21/48 and 11/24, respectively).

○ A recent one-year feeding study in dogs using atrazine (98% a.i.) by Dickie (1986) has been evaluated by the Agency. Five experimental groups of 6 animals/sex/group were exposed to the following doses: 0, 10, 25, 100 or 200 ppm. These doses were equivalent to actual consumption of 0, 0.27, 0.68, 3.20 or 6.11 mg/kg/day for males and 0, 0.28, 0.72, 3.02 or 6.39 mg/kg/day for females, respectively. No systemic toxicity was noted at 10 or 25 ppm. However, dose-related decreases in body weight and body weight gains were noted at 100 and 200 ppm, as well as elevated platelet counts, reduced levels of total protein, albumin and calcium in both sexes. At these two high-dose levels, there were also slight but not statistically significant decreases in spleen weights and increases in relative liver weights in females, and increases in liver weights and decreases in testes weights in males. Other noted changes in organ weights(i.e., heart, lung and kidneys) were not considered significant at these dose levels since they were not consistent with changes in the absolute and relative organ weight values. No gross or microscopic findings related to treatment were noted. Thus, in this study, the LOAEL is 3.1 mg/kg/day and the NOAEL is 0.7 mg/kg/day.

Reproductive Effects

○ A three-generation reproduction study in Long-Evans rats (Eisenlord et al., 1969) using technical cyanazine (unknown percentage a.i.) at dietary levels of 3, 9, 27 or 81 ppm (0.15, 0.45, 1.35 or 4.05 mg/kg/day based on the dietary assumptions of Lehman, 1959) did not reflect a significant effect on reproduction parameters. The NOAEL in this study appeared to be 1.35 mg/kg/day; the LOAEL was 4.05 mg/kg/day (highest dose tested) based on findings related to reduced body weight gain in parental animals, and increased relative brain weight and decreased relative kidney weight in F_{3b} female weanlings.

○ In a repeat two-generation reproduction study in Sprague-Dawley rats (WIL Research Laboratory, 1987), atrazine (100% a.i.) was administered in feed at 0, 25, 75, 150 or 250 ppm. These doses are equivalent to actual food consumption of 0, 1.8, 5.3, 11.1 or 18.5 mg/kg/day, respectively; however, these values changed during lactation to 0, 3.8, 11.2, 23.0 or 37.1 mg/kg/day, respectively. Dose-related decreases in pups' viability and body weights were noted at 75 ppm and above, therefore, the NOAEL for reproduction may be 25 ppm (3.8 mg/kg/day). However, this level, 25 ppm, (equivalent to 1.8 mg/kg/day during non-lactating periods of the study) may be considered as the LOAEL for parental animals due to the noted decreases in body weight and food consumption at this level.

Developmental Effects

○ Cyanazine appeared to cause teratogenic effects and developmental toxicity in two animal species, the rabbit and the rat (Bui, 1985b).

○ In the rabbit study (Shell Toxicology Laboratory, 1982), 7- to 11-month-old New Zealand White rabbits were orally dosed with cyanazine (98% a.i.) in gelatin capsules at levels of 0, 1, 2 or 4 mg/kg/day on gestation days 6 through 18 (22 dams/dose/group). At 2 and 4 mg/kg/day, maternal toxic effects included anorexia, weight loss, death and abortion. Alterations in skeletal ossification sites, decreased litter size, and increased postimplantation loss were observed at 2 and 4 mg/kg/day. Malformations were also noted at 4 mg/kg/day as demonstrated by anophthalmia/microphthalmia, dilated brain ventricles, domed cranium and thoracoschisis; however, these responses were observed at levels in excess of maternal toxicity. The maternal and developmental toxicity NOAELs were 1 mg/kg/day.

○ In a rat study by Lu et al. (1581, 1982), 122-day-old Fischer 344 rats (30 dams/group) were administered cyanazine (98.5% a.i.) by gavage at dose levels of 0, 1.0, 2.5, 10.0 or 25.0 mg/kg/day on gestation days 6 through 15; the dosages were suspended in a 0.2% Methocel emulsion as a vehicle. Maternal body weight reductions during dosing were noted at the 10- and 25-mg/kg/day levels.

Diaphragmatic hernia associated with liver protrusion, microphthalmia and anophthalmia were observed at the 25 mg/kg/day dose level. A teratogenic NOAEL could not be determined from this study at 10 mg/kg/day and a maternal toxicity NOAEL at 2.5 mg/kg/day.

○ The above study was repeated in the same strain of rats, Fischer 344, by Lochry et al. (1985) in order to further examine the malformations reported in the study by Lu et al. (1981). In this study, the dams (70/dosage group) were 86 days old. Cyanazine (98% a.i.) was administered by gavage in an aqueous suspension of 0.25% (w/v) methyl cellulose at dose levels of 0, 5, 25 or 75 mg/kg/day on days 6 through 15 of gestation. One-half of the dams in each group were selected for Cesarean delivery on day 20 of gestation. The remaining half of the dams in each group were allowed to deliver, and both they and their pups were observed for 21 days before sacrifice. Maternal body weight reductions during dosing were noted in all dosage groups and appeared to be partly associated with lower food intake during the dosing period. Alteration in skeletal ossification sites were also observed in the fetuses at all dose levels. Teratogenic effects were demonstrated at 25 and 75 mg/kg/day as anophthalmia/microphthalmia, dilated brain ventricles and cleft palate in the fetuses, and abnormalities of the diaphragm (associated with liver protrusion) in pups sacrificed at time of weaning. The maternal and developmental toxicity NOAELs were lower than 5 mg/kg/day (lowest dose tested), and the teratogenic NOAEL was 5 mg/kg/day (Bui, 1985a).

○ An additional study in Sprague-Dawley rats (Shell, 1983) did not reflect any maternal or developmental toxicity at the highest dose tested, 30 mg/kg/day.

Mutagenicity

○ The mutagenic potential of cyanazine has not been investigated adequately, and only limited information was available for evaluation.

○ A study by Dean et al. (1974a) using technical cyanazine (80% a.i.) in mice of both sexes did not reflect any increase in chromosomal aberrations in the bone marrow cells. The animals were examined at 8- and 24-hour intervals after oral dosing with 50 or 100 mg/kg cyanazine. However, the sensitivity of this test was potentially compromised because the positive control data did not reflect a significant number of aberrations: the percent of cells showing chromatid gaps in the positive control (cyclophosphamide) was not statistically significant at the $p < 0.05$ level (U.S. EPA, 1984b).

○ Dean et al. (1974b) used technical cyanazine (purity not specified) to induce dominant lethal effects in male CF 1 mice. The test was negative at the dose levels tested (80, 160 and 320 mg/kg). However, this study appeared to be invalid because there was no positive control for comparison of data, and a range-finding test was not performed to select the appropriate dosages used in this study (U.S. EPA, 1984b).

○ Cyanazine is a member of the triazine family of herbicides. It is known that the triazines follow similar metabolic pathways (i.e., N-dealkylation, S-dealkylation or O-dealkylation and conjugation with glutathion) that result in common or closely related metabolites. Waters, et al. (1980) noted that a triazine herbicide (atrazine) gave a positive mutagenic response in the Drosophila sex-linked recessive lethal test (DRL), although this chemical gave a negative response in an in vitro test battery with microorganisms. Hence, the potential for cyanazine to give a positive response in a similar test exists (U.S. EPA, 1984b).

Carcinogenicity

○ Cyanazine was not determined to have a carcinogenic potential in a 2-year mouse study (Shell, 1981).

○ Cyanazine was not oncogenic in 2-year rat studies by Walker et al. (1970b) or by Simpson and Dix (1973); however, these studies were deficient (see description of these studies under the section entitled

Long-term Exposure) and are considered to be inadequate by design to determine the oncogenic potential of cyanazine.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 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:

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

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 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 for determination of the One-day HA for cyanazine. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, calculated below as 0.10 mg/L (100 ug/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratology study in rabbits by Shell Toxicology Laboaratory (1982) has been selected as the basis for determination for the Ten-day HA for cyanazine because it provides a short-term NOAEL (1 mg/kg/day for 13 days) for both maternal and fetal toxicity. This study also reflects the lowest NOAEL when compared with the teratology studies in rats described earlier, two in Fischer 344 rats (Lu et al., 1981; Lochry et al., 1985) and one in Sprague-Dawley rats (Shell, 1983).

Using a NOAEL of 1 mg/kg/day, the Ten-day HA for a 10 kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(1 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.10 \text{ mg/L } (100 \text{ ug/L})$$

where:

1 mg/kg/day =	NOAEL based on maternal and fetal effects in rabbits exposed to technical cyanazine orally for 13 days.
10 kg =	assumed body weight of a child.
100 =	uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.
1 L/day =	assumed daily water consumption by a child.

Longer-term Health Advisory

No information was suitable for the determination of the Longer-term HA for cyanazine. It is, therefore, recommended that the adjusted Drinking Water Equivalent Level (DWEL) of 0.02 mg/L (20 ug/L) be used

for a 10-kg child as a conservative estimate for the Longer-term HA value and the DWEL of 0.07 mg/L (70 ug/L), calculated below, be used for 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 are not available, a value of 20% is assumed. 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, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Five chronic studies were available for evaluation: (1) a 2-year oncogenic study in mice (Shell, 1981) with a potential NOAEL of 50 ppm (approximately 7.5 mg/kg/day when using a conversion factor for food consumption of 15% of the body weight); (2) a 2-year feeding study in dogs (Walker et al., 1970a) with a NOAEL of 1.25 mg/kg/day; (3) a 2-year feeding/oncogenic study in rats (Walker et al., 1970b, also cited in Walker et al., 1974) with a NOAEL of 12 ppm (approximately 0.6 mg/kg/day when using a conversion factor for food consumption of 5% of the body weight); however, this study was considered unacceptable (U.S. EPA, 1984b) due to several deficiencies in the study report (see Long-term Exposure Section); (4) a second 2-year feeding study in rats (Simpson and Dix, 1973), which was also considered inadequate because the control group reflected an effect, i.e., convulsions, that was suggestive of cross-dosing; and recently, (5) a 1-year feeding study in dogs (Dickie, 1986) with a NOAEL of 25 ppm (approximately 0.7 mg/kg/day based on actual mean food consumption of males and females).

The NOAEL in the mouse study (7.5 mg/kg/day) can be considered for this calculation; however, this NOAEL is higher than the NOAEL in the Walker et al (1970a) dog study (1.25 mg/kg/day) or in the Walker et al. (1970b) rat study (0.6 mg/kg/day). Since this rat study is considered unacceptable and since the second rat study (Simpson and Dix, 1973) appeared to be flawed by the invalidity of the control group, the 2-year dog study (Walker et al., 1970a) was used previously for the Lifetime HA calculations, using a NOAEL of 1.25 mg/kg/day. This study was of marginal acceptability because only a summary report was available for evaluation and histopathological data were missing for 1/4 females at 1.25 mg/kg/day. However, this NOAEL was supported by a similar NOAEL from a 13-week rat subchronic feeding study by Walker and Stevenson (1968b). Thus using this NOAEL from both studies (i.e., the 2-year dog study and 13-week rat study) and applying a large uncertainty factor of 1,000-fold was appropriate for the calculation of the RfD and the Lifetime HA (in the absence of more adequate chronic studies at that time). At the present time, the new 1-year dog feeding study by Dickie (1986) is a more adequate study for these calculations.

The NOAEL of 25 ppm (equivalent to 0.7 mg/kg/day based on mean actual food consumption in male and female dogs) from the Dickie study (1986) is used in the calculation of the RfD. In this 1-year study, thirty male and female dogs (6 animals/sex/dose) were fed diets containing 0, 10, 25, 100 or 200 ppm cyanazine (98% a.i.). These doses were equivalent to actual mean intakes of 0, 0.27, 0.68, 3.20 or 6.11 mg/kg/day in males and 0, 0.28, 0.72, 3.02 or 6.39 mg/kg/day in females, respectively. No systemic toxicity was noted at

25 ppm (0.7 mg/kg/day) in both sexes. The LOAEL was 100 ppm (3.1 mg/kg/day) based on reduced body weights and body weight gains, elevated platelet counts, and reduced levels of total protein, albumin and calcium in males and females. There were also slight, not statistically significant, decreases in spleen weights and increases in liver weights in the females and increases in liver weights and decreases in testes weights in the males. No gross or microscopic findings related to treatment were noted.

Using a NOAEL of 0.7 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.7 \text{ mg/kg/day})}{(300)} = 0.002 \text{ mg/kg/day}$$

where:

0.7 mg/kg/day =	NOAEL based on absence of toxicity in the dog during the one-year feeding exposure.
100 =	uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a NOAEL from an animal study.
3 =	modifying factor used to compensate for the lack of a chronic rat study as required by the Office of Pesticide Programs.

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

$$\text{DWEL} = \frac{(0.002 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.07 \text{ mg/L (70 ug/L)}$$

where:

0.002 mg/kg/day =	RfD.
70 kg =	assumed body weight of an adult.
2 L/day =	assumed daily water consumption by an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.07 mg/L) (20%) = 0.014 mg/L (10 ug/L)

where:

0.07 mg/L =	DWEL.

Evaluation of Carcinogenic Potential

○ Available toxicity data indicate that cyanazine was not carcinogenic in mice (Shell, 1981) or rats (Walker et al., 1970b, 1974; Simpson and Dix, 1973); however, in the rat, some increases were noted in the incidences of both thyroid tumors (male and female rats) and adrenal tumors (male rats); however, these increases were not statistically significant.

○ Cyanazine is a chloro-s-triazine derivative that has a chemical structure analagous to atrazine, propazine and simazine. These three analogs were found to significantly ($p < 0.05$) increase the incidence of mammary tumors in rats and they are classified as group C oncogens Based on structure-activity relationship, cyanazine may reflect a similar pattern of toxicity in the rat. A new 2-year oncogenic study is required from the manufacturer of this chemical to fill this data gap in the toxicity profile of cyanazine.

○ Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), cyanazine may be classified in Group D: not classified. This category is used for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

○ U.S. EPA Office of Pesticide Programs (OPP) has established residue tolerances for cyanazine ranging from 0.05 to 0.10 ppm in or on raw agricultural commodities (U.S. EPA, 1985) based on a Provisional ADI (PADI) of 0.0013 mg/kg/day.

VII. ANALYTICAL METHODS

○ Analysis of cyanazine is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of cyanazine in water samples, Method #4 (U.S. EPA, 1986b). In this method, 1 L of sample is extracted with methylene chloride using a separatory funnel. The methylene chloride extract is dried and concentrated to a volume of 10 mL or less. HPLC is used to permit the separation of compounds and measurement is conducted with an ultraviolet (UV) detector. Using this method, the estimated detection limit for cyanazine is 0.3 ug/L.

VIII. TREATMENT TECHNOLOGIES

○ Available data indicate that granular-activated carbon (GAC) adsorption will remove cyanazine from water.

○ Whittaker (1980) experimentally determined adsorption isotherms for cyanazine on GAC.

○ GAC adsorption appears to be an effective method of cyanazine removal from water. However, selection of individual or combinations of technologies to attempt cyanazine removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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