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DRAFT

SIMAZINE

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

I. INTRODUCTION

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

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

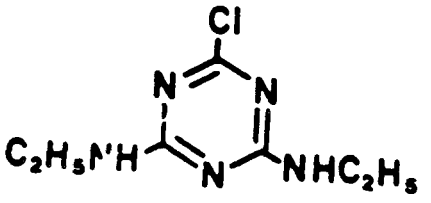
Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from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

The information used in preparing this Health Advisory was collected primarily from the open literature and the Simazine Registration Standard (U.S. EPA, 1983).

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 122-34-9

Structural Formula



2-Chloro-4,6-bis(ethylamino)-1,3,5-triazine

Synonyms

- Aquazine, Cekusan, Framed (discontinued by Farmoplant), G-27692, Gesatop, Primatol, Princep, Simadex, Simanex, Tanzene (Meister, 1984).

Uses

- Simazine is used as a selective preemergence herbicide for control of most annual grasses and broadleaf weeds in corn, alfalfa, established bermuda grass, cherries, peaches, citrus, different kinds of berries, grapes, apples, pears, certain nuts, asparagus, certain ornamental and tree nursery stock, and in turf grass soil production (Meister, 1984). It is also used to inhibit the growth of most common forms of algae in aquariums, ornamental fish ponds and fountains. At higher rates, it is used for nonselective weed control in industrial areas.

Properties (Berg, 1984; Freed, 1976; Windholz et al., 1983)

Chemical Formula	$C_7H_{12}ClN_5$
Molecular Weight	201.69
Physical State (room temperature)	White, crystalline solid
Boiling Point	--
Melting Point	225 to 227°C
Density	1.302 g/cm^3
Vapor Pressure (20°)	6.1 x 10^{-9} mm Hg
Water Solubility (20°)	3.5 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Simazine has been found in 877 of 5,067 surface water samples analyzed and in 229 of 2,282 ground water samples (STORET, 1987). Samples were collected at 472 surface water locations and 1,730 ground water locations, and simazine was found in 22 states. The 85th percentile of all non-zero samples was 2.18 ug/L in surface water and 1.60 ug/L in ground water sources. The maximum concentration found in surface water was 1,300 ug/L, and in ground water it was 800 ug/L.

- Simazine has been found in ground water in California, Pennsylvania and Maryland; typical positives were 0.2 to 3.0 ppb (Cohen et al., 1986).

Environmental Fate

- Simazine did not hydrolyze in sterile aqueous solutions buffered at pH 5, 7 or 9 (20°C) over a 28-day test period (Gold et al., 1973).
- Under aerobic soil conditions, the degradation of simazine depends largely on soil moisture and temperature (Walker, 1976). In a sandy loam soil, half-lives ranged from 36 days to 234 days. Simazine applied to loamy sand and silt loam soils and incubated (25 to 30°C) for 48 weeks, dissipated with half-lives of 16.3 and 25.5 weeks, respectively (Monsanto Company, date not available). Simazine degradation products, 2-chloro-4-ethylamino-6-amino-s-triazine (G-28279), 2-chloro-4,6bis(amino)-s-triazine, and several unidentified polar compounds were detected 32 and 70 days after a sandy loam soil had been treated with ^{14}C-simazine (Beynon et al., 1972). The degradates 2-hydroxy-4,6=bis(ethylamino)-s-triazine and 2-hydroxy-4-ethylamino-6-amino-s-triazine were also detected in aerobic soil (Keller, 1978).

- Under anaerobic conditions, ^{14}C-simazine had a half-life of 8 to 12 weeks in a loamy sand soil (Keller, 1978). The treated soil (10 ppm) was initially maintained for 1 month under aerobic conditions, followed by 8 weeks under anaerobic conditions (flooded with water and nitrogen). Degradates found included G-28279, 2-chloro-4,6-bis(amino)-s-triazine, 2-hydroxy-4,6-bis(ethylamino)-s-triazine, and 2-hydroxy-4-ethylamino-6-amino-s-triazine.

- Simazine is expected to be slightly to very mobile in soils ranging in texture from clay to sandy loam based on column leaching, soil thin-layer chromatography (TLC), and adsorption/desorption (batch equilibrium) studies. Using batch equilibrium tests, K_d values determined for 25 Missouri soils ranged from 1.0 for a sandy loam to 7.9 for a silty loam (Talbert and Fletchall, 1965). Simazine adsorption was correlated with soil organic matter content and, to a lesser extent, with cation exchange capacity (CEC) and clay content (Talbert and Fletchall, 1965; Helling and Turner, 1968; Helling, 1971). Simazine exhibited low mobility in peat and peat moss (K_d more than 21) and a higher mobility in clay fractions (K_d values ranged from 0.0 for kaolinite to 12.2 for montmorillonite (Talbert and Fletchall, 1965). Freundlich K and n values were determined to be 7.25 and 0.88, respectively, for a silty clay loam soil.

- Simazine, as determined by soil TLC, is mobile to very mobile in sandy loam soil (R_f 0.80 to 0.96), and of low to intermediate mobility in loam and silty clay loam (R_f 0.45), sandy clay loam (R_f 0.51), silt loam (R_f 0.16 to 0.51), clay loam (R_f 0.32 to 0.45) and silty clay (R_f 0.36) soils. R_f values were positively correlated with soil organic matter and clay content (Helling, 1971; Helling and Turner, 1968).

- Based on results of soil column leaching studies, simazine phytotoxic residues were slightly mobile to mobile in soils ranging in texture from clay loam to sand (Rodgers, 1968; Harris, 1967; Ivey and Andrews, 1965). Upon application of 18 inches of water to 30-inch soil columns containing clay loam, loam, silt loam or fine sandy loam soils, simazine phytotoxic residues leached to depths of 4 to 6, 10 to 12, 22 to 24, and 26 to 28 inches, respectively (Ivey and Andrews, 1965).

- In field studies, simazine had a half-life of about 30 to 139 days in sandy loam and silt loam soils (Walker, 1976; Martin et al., 1975; Mattson et al., 1969). The degradate, 2-chloro-4-ethylamino-6-amino-s-triazine (G-28279) was detected at the 0- to 6-inch depth and at the 6- to 12-inch depth (Martin et al., 1975; Mattson et al., 1969).

- Simazine residues (uncharacterized) may persist up to 3 years in soil under aquatic field conditions. Dissipation of simazine in pond and lake water was variable, with half-lives ranging from 50 to 700 days. The degradation compound G-28279 was identified in lake water samples, but was no more persistent than the parent compound (Flanagan et al., 1968; Kahrs, 1969; Larsen et al., 1966; LeBaron, 1970; Kahrs, 1977; Smith et al., 1975).

III. PHARMACOKINETICS

Absorption

- No quantitative information on the gastrointestinal absorption of simazine in monogastric mammals was located. Bakke and Robbins (1968) reported that in goats and sheep, from 67 to 77% of a dose of ^{14}C-simazine (given orally in gelatin capsules) was excreted in urine. This suggests that absorption was approximately 70%.

Distribution

- No studies providing data on the tissue distribution of absorbed simazine in monogastric mammals were found in the available literature.

Metabolism

- Bradway and Moseman (1982) administered simazine to male Charles River rats by gavage. Two doses of 0.017, 1.7, 17 or 167 mg/kg were given 24 hours apart. In 24-hour urine samples, the di-N-dealkylated metabolite (2-chloro-4,6-diamino-s-triazine) appeared to be the major product, ranging from 1.6% at the 1.7 mg/kg-dose to 18.2% at

the 167-mg/kg dose, while the mono-N-dealkylated metabolite ranged from 0.35% at the 1.7-mg/kg dose to 2.8% at the 167-mg/kg dose.

- Similar results were obtained by Bohme and Bar (1967), who fed simazine (formulation and purity not stated) at levels of 200 or 800 mg/kg to albino rats and at 240 to 400 mg/kg to rabbits. Of the several metabolites identified, all retained the triazine ring intact. The principal species were the mono- and di-N-dealkylated metabolites.

- Bakke and Robbins (1968) administered ^{14}C-simazine orally by gelatin capsules to goats and sheep. The sheep were given simazine labeled on the triazine ring or on the ethylamino side-chain, while goats were given the ring-labeled compound only. Based on the metabolites identified in the urine of animals receiving the ring-labeled compound, there was no evidence to suggest that the triazine ring was metabolized. In sheep that received chain-labeled triazines, at least 40% of the ethylamino side-chains were removed. Using ion-exchange chromatography, 18 labeled metabolites were found in urine.

- Bohme and Bar (1967) and Larsen and Bakke (1975) observed that rat and rabbit urinary metabolites from the 2-chloro-s-triazines were all 2-chloro analogs of their respective parent molecules and none of the metabolites contained the 2-hydroxy moiety. Total N-dealkylation, partial N-dealkylation, and N-dealkylation with N-alkyl oxidation were suggested as the major routes of the metabolism of 2-chloro-s-triazines in rats and rabbits.

Excretion

- No quantitative study of simazine excretion routes in monogastric animals was found in the available literature.

- Bakke and Robbins (1968) studied the excretion of ^{14}C-simazine in goats and sheep using triazines labeled on the ring or on the ethylamino side-chains. Approximately 67 to 77% of the administered ring-labeled activity was found in the urine, and 13 to 25% was found in the feces. Negligible residue was present in the milk immediately after treatment and within 48 hours of treatment.

- Hapke (1968) reported that simazine residues were present in the urine of sheep for up to 12 days after administration of a single oral dose. The maximum concentration in the urine occurred from 2 to 6 days after administration.

IV. HEALTH EFFECTS

Humans

Long-term Exposure

- There were 124 cases of contact dermatitis noted by Yelizarov (1977) in the Soviet Union among workers manufacturing simazine and propazine.

Mild cases lasting 3 or 4 days involved pale pink erythema and slight edema. Serious cases lasting 7 to 10 days involved greater erythema and edema, and also a vesiculopapular reaction that sometimes progressed to the formation of bullae.

Animals

Short-term Exposure

- Oral LD_{50} values for simazine have been reported to be greater than 5,000 mg/kg in the rat (Martin and Worthing, 1977), the mouse and the rabbit (USDA, 1984).

- Mazaev (1965) administered a single oral dose of simazine (formulation and purity not stated) to rats at 4,200 mg/kg. Anorexia and weight loss were observed, with some of the animals dying in 4 to 10 days. When 500 mg/kg was administered daily, all the animals died in 11 to 20 days, with the time of death correlating with the loss of weight.

- Sheep and cattle seem to be much more susceptible than laboratory animals to simazine toxicity. Hapke (1968) reported that a single oral dose of simazine, 50% active ingredient (a.i.), as low as 500 mg/kg was fatal to sheep within 6 to 25 days after administration. The animals that survived the exposure were sick for 2 to 4 weeks after treatment and showed loss of appetite, increased intake of water, incoordination, tremor and weakness. Some of the animals exhibited cyanosis and clonic convulsions.

- Palmer and Radeleff (1969) orally exposed cattle by drench to 10 doses of simazine 80W (purity not stated) at 10, 25 or 50 mg/kg/day and sheep by drench or capsule to 10 doses at 25, 50 or 100 mg/kg. The number of test animals in each group was not stated, and the use of controls was not indicated. Anorexia, signs of depression, muscle spasms, dyspnea, weakness and uncoordinated gait were commonly observed in treated animals. Necropsy showed congestion of lungs and kidneys, swollen, friable livers, and small, hemorrhagic spots on the surface of the lining of the heart.

- Palmer and Radeleff (1964) found that repeated oral administration of simazine 80W (purity not stated) at either 31 daily doses of 50 mg/kg or 14 daily doses of 100 mg/kg was fatal to sheep. Simazine was also lethal when administered at 100 mg/day for 14 days by drench (Palmer and Radeleff, 1969).

- The acute inhalation LC_{50} value of simazine is reported to be more than 2.0 mg/L of air (4-hour exposure) (Weed Science Society of America, 1983).

Dermal/Ocular Effects

- The acute dermal toxicity in rabbits is greater than 8,000 mg/kg (NAS, 1977).

- In a 21-day subacute dermal toxicity study in rabbits, Ciba-Geigy (1980) reported that 15 dermal applications of technical simazine at doses up to 1 g/kg produced no systemic toxicity or any dose-related alterations of the skin.

- In primary eye irritation studies in rabbits, simazine at 71 mg/kg caused transient inflammation of conjunctivae (USDA, 1984).

Long-term Exposure

- Tai et al. (1985a) conducted a 13-week subacute oral toxicity study in Sprague-Dawley rats fed technical simazine at 0, 200, 2,000 or 4,000 ppm in their diets. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of about 0, 10, 100 or 200 mg/kg/day. Significant dose-related reductions in food intake, mean body weight and weight gain occurred in all treated groups. Significant weight loss occurred in mid- and high-dose animals during the first week of dosing. At 13 weeks, various dose-related effects were noted in hematological parameters (decreased mean erythrocyte and leukocyte counts and increased neutrophil and platelet counts), clinical chemistry (lowered mean blood glucose, sodium, calcium, blood urea nitrogen (BUN), lactic dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT) and creatinine and increased cholesterol and inorganic phosphate levels), and urinalysis determinations (elevated ketone levels and decreased protein levels). Relative and absolute adrenal, brain, heart, kidney, liver, testes and spleen weights increased, and overy and heart weights decreased. Necropsies revealed no gross lesions attributable to simazine. A dose-related incidence of renal calculi and renal epithelial hyperplasia were detected microscopically in treated rats, primarily in the renal pelvic lumen and rarely in the renal tubules. Microscopic examinations revealed no other lesions that could be attributed to simazine. It appeared to the authors that reduced mean food intake in treated rats was most likely due to the unpalatability of simazine. Lower individual body weights and reduced body weight gains paralleled mean food intake in treated rats. The majority of the alterations in clinical chemistry values may have been related to reduced food consumption. Since these dietary levels of simazine seriously affected the nutritional status of treated rats, the results of this study are of limited value.

- Tai et al. (1985b) also conducted a 13-week dietary study with beagle dogs fed technical simazine at 0, 200, 2,000 or 4,000 ppm. Based on Lehman (1959), these levels correspond to doses of about 0, 5, 50 or 100 mg/kg/day. As in the previously described study in rats, reduced daily food consumption was attributed to the palatability of simazine in the diet and corresponded with weight loss, decreased weight gain and various effects on hematology, clinical chemistry, and urinalysis determinations. Changes in these parameters were generally similar to those noted in the rat study (Tai et al., 1985a). Due to the seriously affected nutritional status of the test animals, the results of this study are of limited value.

- Dshurov (1979) studied the histological changes in the organs of 21 sheep following exposures to simazine (50% a.i.) by gavage at 0, 1.4, 3.0, 6.0, 25, 50, 100 or 250 mg/kg/day for various time durations up to about 22 weeks. Fatty and granular liver degeneration, diffuse granular kidney degeneration, neuronophagia, diffuse glial proliferation and degeneration of ganglion cells in the cerebrum and medulla were found. In sheep that died, spongy degeneration, hyperemia and edema were observed in the cerebrum; the degree of severity was related to the dose of simazine and the duration of exposure. The thyroid showed hypofunction after daily doses of 1.4 to 6.0 mg/kg was administered for periods of 63 to 142 days. The most severe antithyroid effect followed one or two doses of 250 mg/kg, which in one sheep produced parenchymatous goiter and a papillary adenoma. This type of goiter was also seen in sheep administered simazine at 50 or 100 mg/kg once per week for approximately 22 weeks. Based on these data, a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 1.4 mg/kg can be identified; however, it is not clear from the study details whether the authors considered the 50% formulation when providing the dosage levels.

Reproductive Effects

- Woodard Research Corporation (1965) reported that no adverse effects on reproductive capacity were observed in a three-generation study in rats. In this study, two groups of 40 weanling rats (20/sex) were used; one served as the control and the other was fed simazine 80W at 100 ppm. This corresponds to a dose of about 5 mg/kg/day, based on the assumptions that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959). After 74 days of dosing, animals were paired and mated for 10 days, resulting in F_{1a} litters. After weaning first litters, parents were remated to produce F_{1b} litters. Weanlings of parents in the 100 ppm group were divided into two groups and fed simazine at 50 ppm (approximately 2.5 mg/kg/day) or at 100 ppm. After 81 days they were mated to produce the F_{2a} and F_{2b} litters. F_{2b} weanlings were fed the same dietary levels of simazine (0, 50 or 100 ppm). F_{2b} rats were mated to produce F_{3a} and F_{3b} litters. Reproductive performance of rats fed simazine was basically similar to that of controls, and no developmental changes were detected. The No-Observed-Adverse-Effect-Level (NOAEL) for this study is approximately 5 mg/kg/day.

- Dshurov (1979) reported that repeated administration of simazine (50% a.i.) to sheep (6.0 mg/kg for 142 days or 25 mg/kg for 37 to 111 days) caused changes in the germinal epithelium of the testes and disturbances of spermatogenesis.

Developmental Effects

- No treatment-related developmental effects were observed by Newell and Dilley (1978) in the offspring of rats exposed to simazine at 0, 17, 77 and 317 mg/m^3 via inhalation for 1 to 3 hours/day on days 7 through 14 of gestation.

- Woodard Research Corporation (1965), as described above in Reproductive Effects, conducted a three-generation study in which rats were fed simazine 80W in mixed dosage groups of 50 and 100 ppm (approximately 2.5 and 5 mg/kg/day). No developmental effects were noted in the offspring.

Mutagenicity

- Simazine has shown negative results in a variety of microbial mutagenicity assay systems including tests with the following organisms: Salmonella typhimurium (Simmons et al., 1979; Commoner, 1976; Eisenbeis et al., 1981; Anderson et al., 1972); Escherichia coli (Simmons et al., 1978; Fahring, 1974); Bacillus subtilis (Simmons et al., 1978); Serratia marcescens (Fahring, 1974); and Saccharomyces cerevisiae (Simmons et al., 1978).

- Simazine induced lethal mutations in the sex-linked recessive lethal test using the fruitfly Drosophila melanogaster (Valencia, 1981). In a study reported by Murnik and Nash (1977), simazine increased X-linked lethals when injected into male D. melanogaster, but failed to do so when fed to larvae.

- There are contradictory data concerning the ability of simazine to cause DNA damage. According to Simmons et al. (1979), simazine induced unscheduled DNA synthesis in a human lung fibroblast assay. However, in the same test conducted by Waters et al. (1982), simazine showed a negative response.

- Simazine does not produce chromosomal effects as indicated by the sister-chromatid exchange test and mouse micronucleus assay (Waters et al., 1982).

Carcinogenicity

- Simazine was not tumorigenic in an 18-month feeding study in mice at the highest tolerated dose of 215 mg/kg/day (Innes et al., 1969). In this bioassay of 130 compounds, male and female mice of two hybrid strains (C57BL/6 x C3H/Anf)F_1 and (C57BL/6 x AKR)F_1 were exposed to simazine (purity not stated) at the maximum tolerated dose of 215 mg/kg by gavage from ages 7 to 28 days. For the remainder of the study, the animals were maintained on a diet with simazine at 215 mg/kg/day. Based on information presented only in tabular form, gross necropsy and histological examination revealed no significant increase in tumors related to treatment with simazine. Other toxicological data were not provided. This study is not considered to provide adequate data to fully assess the carcinogenic potential of simazine.

- Hazelton Laboratories (1960) conducted a 2-year dietary study in Charles River rats administered simazine 50W (49.9% a.i.) in the feed at 0, 1, 10 and 100 ppm (expressed on the basis of 100% a.i.). Based on the dietary assumptions of Lehman (1959), these levels are equivalent to approximately 0, 0.05, 0.5 and 5 mg/kg/day. These authors reported an excess of thyroid and mammary tumors in high-dose females. However,

complete histopathological details were not provided and statistical significance was not evaluated. Furthermore, the high incidence of respiratory and ear infections in all groups renders this study unsuitable for evaluating the carcinogenic potential of simazine.

- Simazine was found to produce sarcomas at the site of subcutaneous injection in both rats and mice (Pliss and Zabezhinsky, 1977; abstract only).

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

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

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

where:

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

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

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

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

One-day Health Advisory

No suitable studies were found in the available literature for the determination of the One-day HA value for simazine. It is therefore recommended that 0.05 mg/L (50 ug/L), the Drinking Water Equivalent Level (DWEL) calculated below and adjusted for a 10-kg child, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

No suitable studies were found in the available literature for the determination of the Ten-day HA value for simazine. It is therefore recommended that the adjusted DWEL for a 10-kg child of 0.05 mg/L (50 ug/L) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

No suitable studies were found in the available literature for the determination of the Longer-term HA values for simazine. It is therefore recommended

that the adjusted DWEL of 0.05 mg/L (50 ug/L) be used at this time as a conservative estimate of the Longer-term HA value for a 10-kg child and that the DWEL of 0.175 mg/L (175 ug/L) 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 for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The three-generation reproduction study in rats by Woodard Research Corporation (1965) has been selected to serve as the basis for calculation of the DWEL and Lifetime HA for simazine. In this study, two groups of 40 weanling rats (20/sex) were used; one served as the control, and the other was fed simazine 80W at 100 ppm (approximately 5 mg/kg/day). After 74 days of dosing, animals were paired and mated for 10 days, resulting in F_{1a} litters. After weaning first litters, parents were remated to produce F_{1b} litters. Weanlings of parents in the 100 ppm group were divided into two test groups: one group was fed simazine at 50 ppm (about 2.5 mg/kg/day) and the other at 100 ppm. After 81 days of dosing, animals were mated to produce the F_{2a} and F_{2b} litters. The F_{2b} weanlings were then divided into 50- and 100-ppm dosage groups. F_{2b} rats were mated to produce F_{3a} and F_{3b} litters. Reproductive performance of rats fed simazine was the same as that of controls, and no teratological changes were detected. The NOAEL for this study is approximately 5 mg/kg/day.

It is important to note that, in this study, rats in the F_0 generation were exposed to simazine at the high dose (100 ppm) only. However, considering that the F_1 and F_2 generations treated with 100 ppm did not reflect any adverse reproductive effects, this feature of the study design did not seem to affect the results. Therefore, the NOAEL of 5 mg/kg/day is used for calculation of the RfD.

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{5 \text{ mg/kg/day}}{(1,000)} = 0.005 \text{ mg/kg/day}$$

where:

5 mg/kg/day = NOAEL for reproductive and developmental effects in a three-generation rat study.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

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

$$DWEL = \frac{(0.005 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.175 \text{ mg/L } (175 \text{ ug/L})$$

where:

0.005 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

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

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.175 mg/L) (20%) = 0.035 mg/L (35 ug/L)

where:

0.175 mg/L = DWEL.

20% = Assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Based on the available data, there is no evidence to show that simazine is carcinogenic, and no calculations of carcinogenic risk factors for simazine have been performed. Neither the study in mice by Innes et al. (1969) nor the study in rats by Hazelton Laboratories (1960) is considered adequate for assessment of the carcinogenicity of this substance.

- Simazine is a chloro-s-triazine derivative, with a chemical structure analogous to atrazine and propazine. Both these two structurally-related compounds were found to significantly ($p > 0.05$) increase the incidence of mammary tumors in rats. The structure-activity relationship of this group of chemicals indicates that simazine is likely to reflect a similar pattern of oncogenic response in rats as atrazine and propazine. However, a conclusion on this issue must await the completion of a new 2-year oncogenic study in rats.

° Applying the criteria described in EPA's guidelines for the assessment of carcinogenic risk (U.S. EPA, 1986a), simazine 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

° A tolerance level of 10 ug/L has been established for simazine and its metabolites in potable water when present as a result of application to growing aquatic weeds (U.S. FDA, 1979).

° Residue tolerances have been established for simazene alone and the combined residues of simazine and its metabolites in or on various raw agricultural commodities (U.S. EPA, 1986b). These tolerances range from 0.02 ppm (negligible) in animal products to 15 ppm in various animal fodders.

VII. ANALYTICAL METHODS

° Analysis of simazine is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (U.S. EPA, 1986c). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for this compound but it is estimated that the detection limits for the method analytes are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

° Treatment technologies which will remove simazine from water include activated carbon adsorption; ion exchange; and chlorine, chlorine dioxide, ozone, hydrogen peroxide and potassium permanganate oxidation. Conventional treatment processes were relatively ineffective in removing simazine (Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in simazine removal (ESE, 1984; Miltner and Fronk, 1985a).

° Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed upon the rapid sand filters at the Fremont, Ohio water treatment plant and had been in service for 30 months, reduced the simazine levels by 35 to 89% in the water from the Sandusky River. Miltner and Fronk (1985a) developed adsorption capacity data using spiked, distilled water treated with Filtrasorb 400. The following Freundlich isotherm values were reported for simazine: $K = 490$ mg/g; $1/n = 0.56$.

° At the Bowling Green, Ohio water treatment plant, PAC in conjunction with conventional treatment achieved an average reduction of 47% of

the simazine levels in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985b) monitored simazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 43 to 100% removal of simazine with higher percent removals reflecting higher PAC dosages. Andersen (1968) reported that activated charcoal (wood charcoal, 300-mesh A.C. from Harrison Clark, Ltd.) was effective in "inactivating" simazine when mixed into simazine-treated soils, though no quantitative data on simazine concentrations were reported.

- Rees and Au (1979) reported that an adsorption column containing XAD-2 resin removed 81 to 95% of the simazine in spiked tap water.

- Turner and Adams (1968) reported that, in a study on the adsorption of simazine by ion exchange resins (Sheets, 1959), duolite C-3 cation exchange resin removed from solution up to 2,000 ug of simazine per gram of resin. Little adsorption was observed with Duolite A-2 anion exchange resin.

- Miltner and Fronk (1985b) reported the bench scale testing results of the addition of various oxidants to spiked, distilled water. Chlorine oxidation achieved 62 to 74 percent removal of simazine. However, when spiked Ohio River water was treated with smaller chlorine dosages during shorter time intervals, less than 17% removal was achieved. Chlorine dioxide oxidation of spiked, distilled water achieved only a 22% removal and achieved 8 to 27% removal of simazine in spiked Ohio River water when applied at a smaller dosage over a shorter time interval. Ozonation of spiked, distilled water resulted in a 92% removal of simazine. Oxidation of spiked, distilled water with hydrogen peroxide obtained a 19 to 42% removal of simazine, and in spiked Ohio River water, a smaller dosage over a shorter time interval obtained a simazine removal of 1 to 25%. Potassium permanganate oxidized up to 26% of the simazine present in spiked distilled water.

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