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AMETRYN

DRAFT

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

I. INTRODUCTION

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

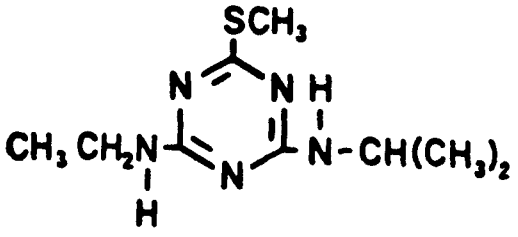
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as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

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

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 834-12-8

Structural Formula



2-(Ethylamino)-4-(isopropylamino)-6-(methylthio)-s-triazine

Synonyms

- N-ethyl-N'-(1-methylethyl)-6-(methylthio)-1,3,5-triazine-2,4-diamine; Ametrex; Ametryne; Cemerin; Crisatine; Evik 80W; Gesapax (WSSA, 1983; Meister, 1983).

Uses

- A selective herbicide for control of broadleaf and grass weeds in pineapple, sugarcane, bananas and plantains. Also used as a post-directed spray in corn, as a potato vine dessicant and for total vegetation control (WSSA, 1983).

Properties (WSSA, 1983)

Chemical Formula	$C_9H_{17}N_5S$
Molecular Weight	227.35
Physical State	Colorless crystals
Boiling Point	--
Melting Point	84 to 85°C
Density	--
Vapor Pressure	8.4×10^{-7} mm Hg
Specific Gravity	--
Water Solubility	185 mg/L
Log Octanol/Water Partition Coefficient	-1.72 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Ametryn has been found in 3 of 1,246 surface water samples analyzed and in 27 of 653 ground water samples (STORET, 1987). Samples were collected at 211 surface water locations and 544 ground water locations, and ametryn was found in 6 states. The 85th percentile of

all nonzero samples was 0.1 ug/L in surface water and 210 ug/L in ground water sources. The maximum concentration found was 0.1 ug/L in surface water and 450 ug/L in ground water.

Environmental Fate

- In aqueous solutions, ametryn is stable to natural sunlight, with a half-life of greater than 1 week. When exposed to artificial light for 6 hours, 75% of applied ametryn remained. One photolysis product was identified as 2-ethylamino-4-hydroxy-6-isopropylaminos-triazine (Registrant CBI data).

- Ametryn is stable to photolysis on soil (Registrant CBI data).

- Soil metabolism of ametryn, under aerobic conditions, proceeds with a half-life of greater than 2 to 3 weeks. Metabolic products include 2-amino-4-isopropylamino-6-methylthio-s-triazine, 2-amino-4-ethylamino-6-methylthio-s-triazine and 2,4-diamino-6-methylthio-triazine. Under anaerobic conditions the rate of metabolism decreases ($t_{1/2}$ = 122 days) (Registrant CBI data).

- Under sterile conditions ametryn does not degrade appreciably. Therefore, microbial degradation is a major degradation pathway (Registrant CBI data).

- Neither ametryn nor its hydroxy metabolite leach past 0 to 6 in. depth with normal rainfall. However, since both compounds are persistent they may leach under exaggerated rainfall or flood and furrow irrigation. This behavior is seen with other triazines (Registrant CBI data).

- Ametryn's Freundlich soil-water partition coeficient values, Kd, range from 0.6 in sands to 5.0 in silty clay soils. Specifically, the Kd for a sandy loam is 4.8, and for 2 silty loams, 3.8 and 2.8, respectively.

- In the laboratory, Ametryn has a half-life of 36 days. In the field, Ametryn degraded with a half-life of 125 to 250 days (Registrant CBI data).

III. PHARMACOKINETICS

Absorption

- Oliver et al. (1969) administered ^{14}C-labeled ametryn orally to Sprague-Dawley rats. Investigators stated that ametryn was administered by stomach tube to animals at dosage levels from 1 to 4 mg per animal. When the label was in the ring, 32.1% was excreted in the feces, indicating that over 70% had been absorbed. When the label was in the ethyl or isopropyl side chains, only 2 to 5% was excreted in the feces.

Distribution

- Oliver et al. (1969) administered ring-labeled ametryn orally to male and female Sprague-Dawley rats and measured distribution of label in tissues at 6, 48 and 72 hours after dosing. Tissue distribution at 6 hours was greatest in kidney, followed by liver, spleen, blood, lung, fat, carcass, brain, and muscle. Blood levels remained relatively constant for 72 hours after dosing, while all other tissue levels dropped rapidly to <0.1% of dose per gram of tissue.

Metabolism

- Oliver et al. (1969) administered ^{14}C-labeled ametryn orally to groups of six male and six female Sprague-Dawley rats. When the label was in the isopropyl side chain, 41.9% of the label appeared as CO_2. When the label was in the ethyl side chain, 18.1% of the label appeared as CO_2. This indicated that the side chains were extensively metabolized. When the ring was uniformly labeled with carbon-14 and the compound fed orally to rats, 58% was excreted in the urine but it was not determined whether excretion of the original compound or metabolites had occurred.

Excretion

- Oliver et al. (1969) studied the excretion of ametryn utilizing uniformly labeled compound with ^{14}C-ametryn in the ring or in the ethyl or isopropyl side chains. Forty-eight hours after oral dosing of six male and six female Sprague-Dawley rats, 57.6% of the ring labeled activity had been excreted in the urine with 32.1% excreted in the feces (total 89.7% of dose). When the fed compound was labeled in the side chains, however, much of the ^{14}C was excreted in expired air as carbon dioxide. When fed compound labeled in the isopropyl side chain, rats excreted 41.9% of the label in expired air 20% in the urine, 2% in the feces and 7% remained in the carcass (total 70.9%) at 48 hours. When the ethyl side chain contained the label, 18.1% of the label was excreted as carbon dioxide, 45% in the urine, 5% in the feces and 9% remained in the carcass (total 77.1% of dose). After 72 hours, total recovery was approximately 88% for both of the side-chain labeled compounds.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the health effects of ametryn in humans.

Animals

Short-term Exposure

- The following acute oral LD_{50} values for ametryn in rats were reported: Charles River CD rats, 1,207 mg/kg (males), 1,453 mg/kg

(females) (Grunfeld, 1981); mixed male and female rats (strain not specified), 1,750 mg/kg (Stenger and Planta, 1961a); male and female Wistar rats, 1,750 mg/kg (Consultox Laboratories Limited, 1974).

- Piccirillo (1977) reported the results of a 28-day feeding study in male and female mice. Animals were 5 weeks of age and weighed 21 to 28 g at the beginning of the study. Animals (five/sex/dose) were fed diets containing 0, 100, 300, 600, 1,000, 3,000, 10,000 or 30,000 ppm of ametryn (technical). Based on the assumption that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 15, 45, 90, 150, 450, 1,500 or 4,500 mg/kg/day. At 30,000 ppm in the diet, all animals died within 2 weeks. At 10,000 ppm, 3 of the 10 died within 2 weeks. No other deaths occurred at any other dose level. Clinical signs in the two highest dose groups included hunched appearance, stained fur and labored respiration. At the 3,000-ppm dose level, only 1 of the 10 animals showed clinical signs of toxicity. Body weight gain was comparable in all survivors by the end of week 4. Gross pathology in animals that died showed a dark-red mucosal lining of the gastro-intestinal tract and ulcerated areas of the gastric mucosa. There was no histopathological examination of tissues in this study.

- Stenger and Planta (1961b) reported a 28-day study of the toxicity of ametryn in rats. Dose levels of 100, 250 or 500 mg/kg/day were administered 6 days/week by gavage to groups of five male and five female rats. The study indicated that there was a control group but no data were given. At the 500-mg/kg/day dose level, animals became emaciated, weight gain was limited and 7 of 10 rats died. Histo-pathological examination of the animals that died indicated severe vascular congestion, centrilobular liver necrosis and fatty degeneration of individual liver cells. At 250 mg/kg/day, 1 of 10 rats died during the study and there was depressed growth rate in the survivors. Histological examination of liver, kidney, spleen, pancreas, heart, lung, intestine and gonads showed no major degenerative changes. No effects were reported in animals administered 100 mg/kg/day, which was identified as the No-Observed-Adverse-Effect-Level (NOAEL) in this study.

- Ceglowski et al. (1979) administered single oral doses of 88 or 880 mg/kg of ametryn to mice 5 days before, on the day of or 2 days after immunization with sheep erythrocytes (purity not specified). All mice receiving the highest dose (880 mg/kg) of ametryn had significant depression of splenic plaque-forming cell numbers when assayed 4 days later. Animals receiving the low dose showed no effect. Similarly, animals receiving 88 mg/kg for 8 or 28 consecutive days prior to immunization exhibited no significant reduction in antibody plaque formation.

Dermal/Ocular Effects

- Two of six rabbits showed mild skin irritation when ametryn was left in contact with intact or abraded skin (500 mg/2.5 cm^2) for 24 hours (Sachsse and Ullmann, 1977).

- In a sensitization study with Perbright White guinea pigs (Sachsse and Ullmann, 1977), 10 male and 10 female guinea pigs weighing 400 to 450 g received 10 daily intracutaneous 0.1-mL injections of 0.1% ametryn in polyethylene glycol:saline (70:30). Fourteen days after the last dose, animals were challenged by an occlusive dermal application of ametryn or by an intradermal challenge. Animals showed no sensitization reaction following the dermal application of the challenge dose but there was a positive response after the intradermal challenge.

- Kopp (1975) found that ametryn (technical grade) placed in the eyes of rabbits produced slight conjunctival redness at 24 hours. This cleared completely within 72 hours.

- Sachsse and Bathe (1976) applied 2,150 mg/kg or 3,170 mg/kg ametryn in suspension to the shaved backs of five male and five female rats weighing 180 to 200 g. The occlusive covering was removed at 24 hours, the skin was washed and animals were observed for 14 days. There was no local irritation or adverse reaction, and at necropsy there were no gross changes in the skin. The acute dermal LD_{50} in male and female rats was reported to be >3,170 mg/kg.

- Ametryn (2,000 mg/kg) was applied daily to the skin of five male and five female rats weighing approximately 200 g (Consultox Laboratories Limited, 1974). After 14 days of treatment, no deaths had occurred and no other effects were reported. The 14-day dermal LD_{50} was reported to be >2,000 mg/kg/day.

Long-term Exposure

- Domenjoz (1961) administered ametryn in water via stomach tube 6 days/week for 90 days to Meyer-Arendt rats (12/sex/dose). The initial material was 50% ametryn in a powder vehicle. Two dose levels of the material (20 or 200 mg/kg/day) provided dose levels of ametryn of 10 or 100 mg/kg/day. Two control groups were included; one group received water only and the other received the powder vehicle only suspended in water. Over the 90-day period, all animals gained weight at comparable rates and there was no visible effect on appearance or behavior. One control rat and one rat in the 100-mg/kg dosage group died. This death was not considered compound-related. At the 90-day necropsy, organ-to-body weight ratios were comparable to controls. Liver, kidney, spleen, heart, gonads, small intestine, colon, stomach, thyroid and lung were microscopically examined. The Lowest-Observed-Adverse-Effect-Level (LOAEL) was associated with fatty degeneration of the liver. Based on this study, a LOAEL of 100 mg/kg/day (the highest dose tested) was identified. All tissues were comparable to controls at the lowest dose (10 mg/kg/day), which was identified as the NOAEL.

Reproductive Effects

- No information was found in the available literature on the reproductive effects of ametryn.

Developmental Effects

- No information was found in the available literature on the developmental effects of ametryn.

Mutagenicity

- Anderson et al. (1972) reported that ametryn was not mutagenic in eight strains of Salmonella typhimurium. No metabolic activating system was utilized.

- Simmons and Poole (1977) also reported that ametryn was not mutagenic in five strains of Salmonella typhimurium (TA 98, 100, 1535, 1537 and 1538), with or without metabolic activation provided by an S9 fraction from rats pretreated with Aroclor 1254.

- Shirasu et al. (1976) reported ametryn was not mutagenic in the rec-assay system utilizing two strains of Bacillus subtilis, in reversion assays utilizing auxotrophic strains of Escherichia coli (WP2) and in S. typhimurium strains TA 1535, 1536, 1537 and 1538 (without metabolic activation).

Carcinogenicity

- No information was found in the available literature on the carcinogenic effects of ametryn.

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:

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

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 data were found in the available literature that were suitable for determination a One-day HA value for ametryn. It is, therefore, recommended that the Ten-day HA value for the 10-kg child (8.6 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The study by Stenger and Planta (1961b) has been selected to serve as the basis for determination of the Ten-day HA value for the 10-kg child. This study identified a NOAEL of 100 mg/kg/day, based on normal weight gain and absence of histological evidence of injury in rats following 28 days of exposure by gavage. The study also identified a LOAEL of 250 mg/kg/day, based on reduced body weight gain, although no major histological changes were noted. One death occurred in the 250-mg/kg/day group, but it could not be determined if this was compound-related. The NOAEL identified in this study (100 mg/kg/day) is supported by the 28-day feeding study in rats by Piccirillo (1977), which identifed a NOAEL of 150 mg/kg/day and a LOAEL of 450 mg/kg/day, and by the study of Ceglowski et al. (1979), which identified a NOAEL of 88 mg/kg/day and a LOAEL of 880 mg/kg/day.

Using the NOAEL of 100 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(100\ \text{mg/kg/day})\ (10\ \text{kg})\ (6/7)}{(100)\ (1\ \text{L/day})} = 8.6\ \text{mg/L}\ (8{,}600\ \text{ug/L})$$

where:

100 mg/kg/day = NOAEL, based on absence of effects on weight gain or histology in rats dosed by gavage for 28 days.

10 kg = assumed body weight of a child.

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

6/7 = conversion from 6 to 7 days.

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

Longer-term Health Advisory

The 90-day oral dosing study in rats by Domenjoz (1961) has been selected to serve as the basis for determination of the Longer-term HA. At two dose levels (10 or 100 mg/kg/day), no deaths were reported and no other effects were noted during the 90-day period. Terminal necropsy findings and histological examination of tissues from treated animals were comparable to controls. At the highest dose tested, there was fatty degeneration in the livers examined. Based on these data, a NOAEL of 10 mg/kg/day (the lowest dose tested) was identified.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})\ (6/7)}{(100)\ (1 \text{ L/day})} = 0.86 \text{ mg/L } (860 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on the absence of histological evidence of toxicity in rats exposed to ametryn via gavage for 90 days.

10 kg = assumed body weight of a child.

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

6/7 = conversion from 6 to 7 days of exposure.

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

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

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (70 \text{ kg})\ (6/7)}{(100)\ (2 \text{ L/day})} = 3 \text{ mg/L } (3{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on the absence of histological evidence of toxicity in rats exposed to ametryn via gavage for 90 days.

70 kg = assumed body weight of an adult.

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

6/7 = conversion from 6 to 7 days of exposure.

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

Lifetime Health Advisory

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

concentration equals 10% of influent concentration) occurred after 896 bed volumes (BV). When a bi-solute ametryn-propham solution was passed over the same column, ametryn breakthrough occurred after 240 BV.

- In a laboratory study (Nye, 1984) GAC was employed as a possible means of removing ametryn from contaminated wastewater. The results show that the column exhaustion capacity was 111.2 mg ametryn adsorbed on 1 g of activated carbon.

- Treatment technologies for the removal of ametryn from water are available and have been reported to be effective. However, selection of individual or combinations of technologies to attempt ametryn removal from water must be based on a case-by-case technical evaluation and an assessment of the economics involved.

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*Confidential Business Information submitted to the Office of Pesticide Programs.