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DRAFT

PICLORAM

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.

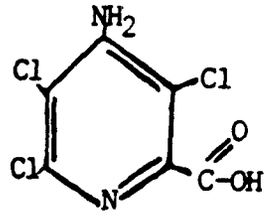
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 1918-02-01

Structural Formula



(4-amino-3,5,6-trichloropicolinic acid)

Synonyms

- Amdon; ACTP; Borolin; K-PIN; Tordon (Meister, 1987).

Uses

- Broad-spectrum herbicide for the control of broadleaf and woody plants in rangelands, pastures and rights-of-way for powerlines and highways (Meister, 1987).

Properties (Meister, 1987)

Chemical Formula	$C_6H_3Cl_3N_2O_2$
Molecular Weight	241.6
Physical State (Room Temp.)	White powder
Boiling Point	Decomposes
Melting Point	215°C (decomposes)
Density	--
Vapor Pressure (25°C)	6.2×10^{-7} mm Hg
Specific Gravity	
Water Solubility	0.043 g/100 mL (free acid) 40 g/100 mL (salts)
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	(Chlorine-like)
Conversion Factor	--

Occurrence

- Picloram has been found in 359 of 653 surface water samples analyzed and in 5 of 77 ground water samples (STORET, 1987). Samples were collected at 124 surface water locations and 49 ground water locations, and picloram was found in 7 states. The 85th percentile of all nonzero samples was 0.13 ug/L in surface water and 1.00 ug/L in ground water sources. The maximum concentration found was 4.6 ug/L in surface water and 1.00 ug/L in ground water.

Environmental Fate

- The main processes for dissipation of picloram in the environment are photodegradation and aerobic soil degradation. Field tests conducted in Texas with a liquid formulation of picloram have indicated that approximately 74% of the picloram originally contained in the test ecosystems, which included the soil, water and vegetation, was dissipated within 28 days after application (Scifres et al., 1977).

- Photodegradation of picloram occurs rapidly in water (Hamaker, 1964; Redemann, 1966; Youngson, 1968; Youngson and Goring, 1967), but is somewhat slower on a soil surface (Bovey et al., 1970; Merkle et al., 1967; Youngson and Goring, 1967). Hydrolysis of picloram is very slow (Hamaker, 1976).

- Laboratory studies have shown that under aerobic soil conditions, the half-life of picloram is dependent upon the applied concentration, and the temperature and moisture of the soil. The major degradation product is CO_2; other metabolites are present in insignificant amounts (McCall and Jefferies, 1978; Merkle et al., 1967; Meikle et al., 1970, 1974; Meikle, 1973; Hamaker, 1975). In the absence of light under anaerobic soil and aquatic conditions, picloram degradation is extremely slow (McCall and Jefferies, 1978).

- Following normal agricultural, forestry and industrial applications of picloram, long-term accumulation of picloram in the soil generally does not occur. In the field, the dissipation of picloram will occur at a faster rate in hot, wet areas compared to cool, dry locations (Hamaker et al., 1967). The half-life of picloram under most field conditions is a few months (Youngson, 1966). There is little potential for picloram to move off treated areas in runoff water (Fryer et al., 1979). Although picloram is considered to have moderate mobility (Helling, 1971a,b), leaching is generally limited to the upper portions of most soil profiles (Grover, 1977). Instances of picloram entering the ground water are largely limited to cases involving misapplications or unusual soil conditions (Frank et al., 1979).

III. PHARMACOKINETICS

Absorption

- Picloram is readily absorbed from the gastrointestinal (GI) tract of rats (Nolan et al., 1980). Within 48 hours after dosing rats with 1400 mg/kg body weight (bw), 80 to 84% of the dose was found in urine.

- A 500-kg Holstein cow was administered 5 mg/kg picloram in the feed for 4 days (approximately 0.23 mg/kg/day). Ninety-eight percent of the total dose was excreted in the urine, demonstrating nearly complete absorption (Fisher et al., 1965).

- Similar results were observed in three male Fischer CDF rats receiving ^{14}C-picloram (dose not specified), where 95% of the dose was absorbed (Dow, 1983).

Distribution

- Picloram appears to be distributed throughout the body, with the highest concentration in the kidneys (Redemann, 1964). In rats (strain, age and sex not specified) administered a single 20 mg/kg dose of ^{14}C-labeled picloram in food, radioactivity was found in abdominal fat, liver, muscle and kidneys with maximum levels occurring 2 to 3 hours after dosing.

- Hereford-Holstein steers fed picloram at daily doses of 3.2 to 23 mg/kg for 2 weeks had tissue concentrations of 0.05 to 0.32 mg/kg in muscle, 0.06 to 0.45 mg/kg in fat, 0.12 to 1.6 mg/kg in liver, 0.18 to 2.0 mg/kg in blood and 2 to 18 mg/kg in kidney (Kutschinski and Riley, 1969).

- In a similar study, two steers (strain not specified) fed 100 or 200 mg picloram (3 or 6 mg/kg bw/day) for 31 days had picloram concentrations of 4 or 10 mg/kg, respectively, in the kidneys, while concentrations in other tissues (muscle, omentum fat, heart, liver, brain) were less than 0.5 mg/kg (Leasure and Getzander, 1964).

Metabolism

- Picloram administered to rats or cattle was excreted in the urine in unaltered form (Fisher et al., 1965; Nolan et al., 1980; Dow, 1983), and no $^{14}CO_2$ was detected in expired air of rats given ^{14}C-carbon-labeled picloram (Redemann, 1964; Nolan et al., 1980; Dow, 1983). These studies indicate that picloram is not metabolized significantly by mammals.

Excretion

- Picloram administered to rats is excreted primarily in the urine (Redemann, 1964; Nolan et al., 1980; Fisher et al., 1965).

- Male (F344) rats that were administered a single oral dose of picloram at 1,400 mg/kg bw, within 48 hours excreted 80 to 84% of the dose in the urine, 15% in the feces, less than 0.5% in the bile and virtually no measurable amount as expired CO_2 (Nolan et al., 1980).

- One Holstein cow administered 5 ppm picloram in feed for 4 consecutive days excreted more than 98% of the dose in the urine (Fisher et al., 1965).

- In male F344 rats administered picloram at 10 mg/kg bw orally, clearance of picloram from the plasma was biphasic, showing half-lives of 29 and 228 minutes. When administered the same dose intravenously, biphasic clearance occurred with half-lives of 6.3 and 128 minutes (Nolan et al., 1980).

- Cattle excrete picloram primarily in the urine (Fisher et al., 1965), although small amounts may appear in the milk (Kutschinski and Riley, 1969). In Holstein cows fed picloram for 6 to 14 days at doses of

2.7 mg/kg/day or less, no picloram could be found in the milk, while cows fed picloram at doses of 5.4 to 18 mg/kg/day had milk levels up to 0.28 mg/L. This corresponds to 0.02% of the ingested dose. When picloram feeding was discontinued, picloram levels in milk became undetectable within 48 hours.

- Nolan et al. (1983) investigated the excretion of picloram in humans. Six male volunteers (40- to 51-years old) ingested picloram at 0.5 or 5 mg/kg in approximately 100 mL of grape juice. Seventy-six percent of the dose was excreted unchanged in the urine within 6 hours (half-life of 2.9 hours). The remainder was eliminated with an average half-life of 27 hours. The authors did not report observations, if any, of adverse effects. Thus, excretion of picloram in humans was biphasic as had been demonstrated in rats by Nolan et al. (1980).

IV. HEALTH EFFECTS

Humans

- No information on the health effects of picloram in humans was found in the available literature. In the excretion study by Nolan et al. (1983), described above, the authors did not address the presence of toxic effects in human volunteers ingesting picloram at 0.5 or 5 mg/kg.

Animals

Short-term Exposure

- The acute oral toxicity of picloram is low. Lethal doses have been estimated in a number of species, with LD_{50} values ranging from 2,000 to 4,000 mg/kg (NIOSH, 1980; Dow, 1983).

- In a 7- to 14-day study by Dow (1981), beagle dogs (number per group not specified) were administered picloram (79.4% Tordon) at dose levels of 0, 250, 500 or 1000 mg/kg/day. Based on 79.4% active ingredient, actual doses administered were 200, 400 or 800 mg/kg/day. The No-Observed-Adverse-Effect-Level (NOAEL) was determined to be 200 mg/kg/day, the lowest dose tested, based on the absence of reduced food intake.

- In a 9-day feeding study by Dow (1980a), picloram was fed to dogs (one/dose) at dose levels of 400, 800 or 1,600 mg/kg bw/day. Picloram was acutely toxic to female dogs at the higher doses and not toxic at 400 mg/kg/day (the lowest dose tested), which was identified as the NOAEL.

- In a 32-day feeding study by Dow (1980b), picloram was administered to mice at dose levels of 0, 90, 270, 580, 900 or 2,700 mg/kg/day. The NOAEL was 900 mg/kg/day, and the Lowest-Observed-Adverse-Effect-Level (LOAEL) was 2700 mg/kg/day, based on increased liver weight.

Dermal/Ocular Effects

- Most formulations of picloram have been evaluated for the potential to produce skin sensitization reactions in humans. Dow (1981) reported in summary data that Tordon 22K was not a sensitizer following an application as a 5% solution. A formulation of Tordon 101 containing 6% picloram acid and 2,4-D acid was not a sensitizer as a 5% aqueous solution in humans (Gabriel and Gross, 1964). However, when the triisopropanolamine salts of picloram and 2,4-D (Tordon 101) were applied as a 5% solution, sensitization occurred in several individuals; however, when applied alone, the individual components were nonreactive.

Long-term Exposure

- Subchronic studies with picloram have been conducted by Dow (1983) using three species (dogs, rats, mice) over periods of 3 to 6 months. A 6-month study was conducted with beagle dogs that received picloram at daily doses of 0, 7, 35 or 175 mg/kg/day (six/sex/dose group) (Dow, 1983). Increased liver weights were observed at the highest dose (175 mg/kg/day) for males and females, and at the intermediate dose (35 mg/kg/day) for males. Therefore, the 7-mg/kg/day dose level was considered to be a NOAEL.

- In a 13-week feeding study, CDF Fischer 344 rats (15/sex/dosage group) were fed picloram in their diet at dose levels of 0, 15, 50, 150, 300 or 500 mg/kg/day (Dow, 1983). Liver swelling was observed in both sexes at the 150- and 300-mg/kg/day dose levels. The NOAEL in this study was identified as 50 mg/kg/day.

- Osborne-Mendel rats receiving picloram at 370 or 740 mg/kg/day in the diet for 2 years had renal disease resembling that of the natural aging process (NCI, 1978). Increased indices of parathyroid hyperplasia, polyarteritis, testicular atrophy and thyroid hyperplasia and adenoma were observed. Polyarteritis may be indicative of an autoimmune effect.

- Ten male and female $B6C3F_1$ mice were administered picloram in their diet at dose levels of 0, 1,000, 1,400 or 2,000 mg/kg/day for 13 weeks (Dow, 1983). Liver weights were increased significantly (p values not reported) in females and males at all dose levels tested.

Reproductive Effects

- As described above in the 2-year feeding study by NCI (1978), testicular atrophy was observed in male Osborne-Mendel rats receiving picloram at 370 or 740 mg/kg/day.

- Groups of 4 male and 12 female rats were maintained on diets containing 0, 7.5, 25 or 75 mg/kg/day of Tordon (95% picloram) through a three-generation (two litters per generation) fertility, reproduction, lactation and teratology study (McCollister et al., 1967). The rats were 11-weeks old at the start of the study and were maintained on the test diets for 1 month prior to breeding to produce the F_{1a}

generation. Records were kept of numbers of pups born live, born dead or killed by the dam; litter size was culled to eight pups after 5 days. Lactation continued until the pups were 21-days old, when they were weaned and weighed. After a 7- to 10-day rest, the dam was returned for breeding the F_{1b} generation. The second generation (F_{2a} and F_{3b}) was derived from F_{2b} animals after 110 days of age. Two weanlings per sex per level of both litters of each generation were observed for gross pathology. Gross pathology was also performed on all parent rats and all females not becoming pregnant. Five male and five female weanlings from each group of the F_{3b} litter were selected randomly for gross and microscopic examination (lung, heart, liver, kidney, adrenals, pancreas, spleen and gonads). Picloram reduced fertility in the 75 mg/kg/day dose group. No other effects were noted. Based on these results, a NOAEL of 25 mg/kg/day was identified.

Developmental Effects

- In the McCollister et al. (1967) study described above, the F_{1c}, F_{2c} and F_{3c} litters were used to study the teratogenic potential of picloram. The dams were sacrificed on day 19 or 20 of gestation, and offspring were inspected for gross abnormalities, including skeletal and internal structures, and placentas were examined for fetal death or resorptions. None were observed at any dose level. Picloram reduced fertility in the 75-mg/kg/day dose group. Based on these results, a NOAEL of 25 mg/kg/day was identified.

- Thompson et al. (1972) administered picloram in corn oil to pregnant Sprague-Dawley rats on days 6 to 15 of gestation. Four groups of 35 rats (25 for the teratology portion and 10 for the postnatal portion of the study) received picloram at 0, 500, 750 or 1,000 mg/kg/day by gavage. Rats were observed daily for signs of toxicity. Prebreeding and gestation day 20 body weights were obtained on teratology rats and prebreeding and postpartum day 21 body weights were obtained for signs of maternal toxicity, while rats given 750 or 1,000 mg/kg/day developed hyperesthesia and mild diarrhea after 1 to 4 days of treatment; and 14 maternal deaths occurred between days 8 and 17 of gestation in these dose groups. Evidence of retarded fetal growth, as reflected by an increase in unossified fifth sternebrae, was observed in all treatment groups but not in a dose-related manner; i.e., the occurrence of bilateral accessory ribs was increased significantly in fetuses of dams given 1,000 mg/kg for 10 days during gestation. At this dose level, there was maternal toxicity and, therefore, no NOAEL was determined. The LOAEL was 500 mg/kg, the lowest dose tested.

Mutagenicity

- The mutagenic activity of picloram has been studied in a number of microbial systems. Ames tests in several Salmonella typhimurium strains indicated that picloram was not mutagenic with or without activation by liver microsomal fractions (Andersen et al., 1972; Torracca et al., 1976; Carere et al., 1978).

- One study using the same system as above found picloram to be weakly mutagenic (Ercegovich and Rashid, 1977).

- Picloram was shown to be negative in the reversion of bacteriophage AP72 to T_4 phenotype (Andersen et al., 1972), but positive in the forward mutation spot test utilizing Streptomyces coelicolor (Carere et al., 1978).

- Irrespective of a weak mutagenic response in the Salmonella typhimurium test (Ercegovich and Rashid, 1977) and a positive forward mutation, the authors take the position that picloram is not mutagenic. This view is supported by studies in male and female Sprague-Dawley rats fed picloram at dose levels of 20, 200 or 2,000 mg/kg/day in which no cytological changes in bone marrow cells were observed (Mensik et al., 1976).

Carcinogenicity

- Picloram (at least 90% pure) was administered by diet to Osborne-Mendel rats and B6C3F_1 mice (NCI, 1978; also reviewed by Reuber, 1981). Pooled controls from carcinogenicity studies run in the same laboratory (and room, at the Gulf South Research Institute) and overlapping this study by at least 1 year were used. Fifty male rats were dosed with picloram at 208 or 417 mg/kg/day and 50 female rats were dosed at 361 or 723 mg/kg/day. During the second year, rough hair coats, diarrhea, pale mucous membranes, alopecia and abdominal distention were observed in treated rats. In addition, a relatively high incidence of follicular hyperplasia, C-cell hyperplasia and C-cell adenoma of the thyroid occurred in both sexes. However, the statistical tests for adenoma did not show sufficient evidence for association of the tumor with picloram administration. An increased incidence of hepatic neoplastic nodules (considered to be benign tumors) was observed in treated animals. In male rats, the lesion appeared in only three animals of the low-dose treatment group and was not significant when compared to controls. However, the trend was significantly dose-related in females ($p = 0.016$). The incidence in the high-dose group was significant ($p = 0.014$) when compared with that of the pooled control group. The incidences of foci of cellular alteration of the liver were: female rats - matched controls 0/10, low-dose 8/50, high-dose 18/49; male rats - matched controls 0/10, low-dose 12/49, high-dose 5/49. Thus, there is evidence that picloram induced benign neoplastic nodules in the livers of rats of both sexes, but especially those of the females. Subsequent laboratory review by the National Toxicology Program (NTP) has questioned the findings of this study because animals with exposure to known carcinogens were placed in the same room with these animals and cross-contamination might have occurred. In the same study, NCI (1978), 50 male and 50 female mice received picloram at 208 or 417, and 361 or 723 mg/kg/day, respectively. Body weights of mice were unaffected, and no consistent clinical signs attributable to treatment were reported during the first 6 months of the study, except isolated incidences of tremors and hyperactivity. Later, particularly in the second year, rough hair coats, diarrhea, pale mucous membranes, alopecia and abdominal distention occurred. No tumors were found in male or female mice or male rats at incidences that could be significantly related to treatment. It was concluded that picloram was not a carcinogen for B6C3F_1 mice.

- Dow (1986) retested picloram (93% pure) in a 2-year chronic feeding/oncogenicity study in Fisher 344 rats. Rats (50/sex/dose) were fed 20, 60 or 200 mg/kg/day. Oncogenic effects above those of controls were absent in this study.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

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

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

where:

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

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

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

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

One-day Health Advisory

No information was found in the available literature that was suitable for determination of the One-day HA value for picloram. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (20 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The 7- to 14-day study in dogs by Dow (1981) has been selected to serve as the basis for the Ten-day HA value for picloram because dogs appear to be the most sensitive species. Doses of 200, 400 or 800 mg/kg/day were used and the dose of 200 mg/kg/day was identified as the NOAEL for short-term exposures based on reduced food intake. Other short-term studies include a 9-day study in dogs by Dow (1980a) with a NOAEL of 400 mg/kg/day and a 32-day study in mice by Dow (1980b) with a NOAEL of 900 mg/kg/day.

Using a NOAEL of 200 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(200 \text{ mg/kg/day}) \ (10 \text{ kg})}{(100) \ (1 \text{ L/day})} = 20 \text{ mg/L } (20{,}000 \text{ ug/l})$$

where:

200 mg/kg/day = NOAEL based on the absence of reduced feed intake in beagle dogs exposed to picloram for 7 to 14 days.

10 kg = assumed body weight of a child.

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

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

Longer-term Health Advisory

The study by Dow (1983) has been selected to serve as the basis for the Longer-term HA value for picloram because dogs have been shown to be the species most sensitive to picloram. In this study, picloram was fed for 6 months to beagle dogs (six/sex/group) in the diet at dose levels of 0, 7, 35 or 175 mg/kg/day. At 175 mg/kg/day, the following adverse effects were observed in both male and female dogs: decreased body weight gain, food consumption and alanine transaminase levels, increased alkaline phosphatase levels, absolute liver weight and relative liver weight. At 35 mg/kg/day, increased absolute and relative liver weights were noted in males. No compound-related effects were detected in females at 35 mg/kg/day or in males or females at 7 mg/kg/day. Based on these data, 7 mg/kg/day was identified as the NOAEL for dogs for a 6-month exposure.

Using this study, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(7 \text{ mg/kg/day})\ (10)}{(100)\ (1 \text{ L/day})} = 0.7 \text{ mg/L } (700 \text{ ug/L})$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

10 kg = assumed body weight of a child.

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

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

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

$$\text{Longer-term HA} = \frac{(7 \text{ mg/kg/day})\ (70)}{(100)\ (2 \text{ L/day})} = 2.45 \text{ mg/L } (2{,}450 \text{ ug/L})$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

70 kg = assumed body weight of an adult.

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

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

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Dow (1983), chosen for the Longer-term Health Advisory has also been chosen to calculate the Lifetime HA value for picloram. In this study, picloram was fed for 6 months to beagle dogs (six/sex/group) in the diet at dose levels of 0, 7, 35 or 175 mg/kg/day. At 175 mg/kg/day, the following adverse effects were observed in both male and female dogs: decreased body weight gain, food consumption and alanine transaminase levels, increased alkaline phosphatase levels, absolute liver weight and relative liver weight. At 35 mg/kg/day, increased absolute and relative liver weights were noted in males. No compound-related effects were detected in females at 35 mg/kg/day or in males or females at 7 mg/kg/day. Based on these data, 7 mg/kg/day was identified as the NOAEL for dogs for a 6-month exposure. Therefore, the Lifetime HA for picloram is determined as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(7\ mg/kg/day)}{(100)} = 0.07\ mg/kg/day$$

where:

7 mg/kg/day = NOAEL, based on the absence of relative and absolute liver weight changes.

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

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

$$DWEL = \frac{(0.07\ mg/kg/day)\ (70)}{(2\ L/day)} = 2.45\ mg/L\ (2450\ ug/L)$$

where:

0.07 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 = (2.45 mg/L) (20%) = 0.49 mg/L (490 ug/L)

where:

2.45 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The National Cancer Institute conducted studies on the carcinogenic potential of picloram in rats and mice (NCI, 1978; this study was also reviewed by Reuber, 1981). In the study with mice, there was no indication of an oncogenic response from dietary exposure which included levels of more than 5,000 ppm picloram (723 mg/kg/day) for the greater part of their lifetime. The rat study, however, was negative for oncogenic effects in males, while female rats exhibited a statistically significant increase in neoplastic nodules in the liver. On a time-weighted average, exposures ranged up to 14,875 ppm (743 mg/kg/day) picloram in the diet.

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

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), picloram may be classified in Group D: not classified. This group is generally used for substances with inadequate human and animal evidence of carcinogenicity or for which no data are available.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA Office of Pesticide Programs has set an RfD for picloram at 0.07 mg/kg/day (U.S. EPA, 1986b).

- Tolerances have been established for picloram in or on raw agricultural commodities (U.S. EPA, 1986c).

- The National Academy of Sciences (NAS, 1983) has calculated a chronic Suggested-No-Adverse-Response-Level (SNARL) of 1.05 mg/L for picloram. An uncertainty factor of 1,000 was used because the issue of carcinogenicity had not yet been resolved and also because the Johnson (1971) study used by NAS does not provide enough information for a complete judgment of its adequacy.

VII. ANALYTICAL METHODS

- Analysis of picloram is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1986d). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane. Excess reagent is removed, and the esters are determined by electron-capture gas chromatography. The method detection limit has not been determined for picloram.

VIII. TREATMENT TECHNOLOGIES

- The manufacture of this compound has been discontinued (Meister, 1987). No information was found on treatment technologies capable of effectively removing picloram from contaminated water.

IX. REFERENCES

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