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DRAFT

PROPACHLOR

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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.

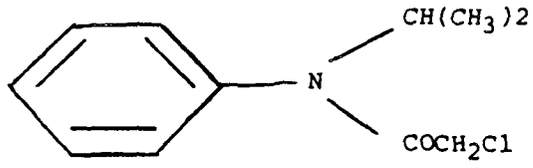
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 1918-16-7

Structural Formula



2-chloro-N-isopropylacetinilide

Synonyms

- Bexton; Prolex; Ramrod (Meister, 1983).

Uses

- Selective postemergence herbicide used for control of many grasses and certain broadleaf weeds (Meister, 1983).

Properties (Rao and Davidson, 1982; HSDB, 1986)

Chemical Formula	$C_{11}H_{14}ClNO$
Molecular Weight	211.69
Physical State (room temp.)	White crystalline solid
Boiling Point	110°C at 0.03 mm HG
Melting Point	67 to 76°C
Density (25°C)	1.13 g/mL
Vapor Pressure	2.3×10^{-4} mm Hg
Specific Gravity	--
Water Solubility (20°C)	700 mg/L
Log Octanol/Water Partition Coefficient	1.61
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Propachlor has been found in 132 of 1,144 surface water samples analyzed and in 2 of 76 ground water samples (STORET, 1987). Samples were collected at 314 surface water locations and 94 ground water locations, and propachlor was found in eight states. The 85th percentile of all nonzero samples was 2 ug/L in surface water and 0.12 ug/L in ground water sources. The maximum concentration found was 10 ug/L in surface water and 0.12 ug/L in ground water.

Environmental Fate

- Propachlor is degraded in aerobic soils in the laboratory and in the field with half-lives of 2 to approximately 14 days, when the soils are treated with propachlor at recommended application rates. However,

degradation was relatively slower in soil treated at 500 ppm, and 90% of the applied material remained after 21 days (Registrant CBI data).

° The major propachlor degradates produced under aerobic soil conditions are [(1-methylethyl)phenylamino]oxoacetic acid and [(2-methylethyl)-phenylamino]-2-oxoethane sulfonic acid. These degradates are recalcitrant to further degradation in soil under anaerobic conditions. The half-life of propachlor in anaerobic soil is <4 days (Registrant CBI data).

° Propachlor degrades very slowly (84.5% remaining after 30 days) in lake water (Registrant CBI data).

° Propachlor is moderately mobile to very mobile in soils ranging in texture from sand to clay. Mobility appears to be correlated with clay content and to a lesser degree with organic matter content and CEC. Aged ^{14}C-propachlor residues were mobile in a silt loam soil (Registrant CBI data).

° The rapid degradation of low levels of propachlor in soils is expected to result in a low potential for groundwater contamination by propachlor degradates. ^{14}C-Propachlor residues are taken up by rotated corn planted under confined conditions; <3% of the radioactivity remained in soil at the time of planting (Registrant CBI data).

III. PHARMACOKINETICS

Absorption

° No direct data on rate of gastrointestinal absorption of propachlor were found in the available literature. Based on recovery studies, propachlor appears to be rapidly absorbed by the oral route of administration. An estimated 68% of a single dose of 10 mg of ring-labeled ^{14}-C propachlor administered to 12 rats was recovered in urine 56 hours after compound administration (Malik, 1986). These results are supported by other studies in which 54 to 64% (Lamoureux and Davison, 1975) and 68.8% (Bakke et al., 1980) of the administered dose was recovered in urine 24 hours and 48 hours after dose administration, respectively.

Distribution

° Fifty-six hours following oral administration of 10 mg of ring-labeled ^{14}C-propachlor (purity not specified) to rats, no detectable levels of radioactivity were identified in any tissue samples (Malik, 1986).

Metabolism

° Metabolism of propachlor occurs by initial glutathione conjugation followed by conversion via the mercapturic acid pathway; oxidative metabolism also occurs (Lamoureux and Davison, 1975; Malik, 1986).

- Eleven urinary metabolites have been identified as the result of propachlor metabolism in rats. The primary metabolic end products of propachlor are mercapturic acid and glucuronic acid conjugates (approximately 20 to 25%), methyl sulfones (30 to 35%), and phenols and alcohols (Lamoureux and Davison, 1975; Malik, 1986).

Excretion

- Propachlor (purity not specified) was excreted in the form of metabolites in the urine (68%) and feces (19%) of rats within 56 hours after dosing with ring-labeled ^{14}C-propachlor. Methyl sulfonyl metabolites accounted for 30 to 35% of the administered dose (Malik, 1986).

- In studies with germ-free rats, 98.6% of the administered dose (not specified) for propachlor (purity not specified) was identified in the urine (68.8%) and feces (32.1%) within 48 hours. The major metabolite was mercapturic acid conjugate, which accounted for 66.8% of the administered dose (Bakke et al., 1980).

IV. HEALTH EFFECTS

Humans

- Schubert (1979) reported a case study in which occupational exposure to propachlor for 8 days resulted in erythemato-papulous (red pimply) contact eczema on the hands and forearms.

Animals

Short-term Exposure

- The acute oral LD_{50} values for technical-grade (approximately 96.5%) and wettable powder (WP) (65%) propachlor range from 1,200 to 4,000 mg/kg in rats. Technical-grade and wettable powder propachlor both produced a low LD_{50} value of 1,200 mg/kg (Keeler et al., 1976; Heenehan et al., 1979; Auletta and Rinehart, 1979; Monsanto, (undated).

- Beagle dogs (two/sex/dose) were administered propachlor (65% WP) in the diet for 90 days at dose levels of 0, 1.3, 13.3 or 133.3 mg/kg/day (Wazeter et al.. 1964). Body weight, survival rates, food consumption, behavior, general appearance, hematology, biochemical indices, urinalysis, histopathology and gross pathology were comparable in treated and control animals. The No-Observed-Adverse-Effect-Level (NOAEL) identified for this study is 133.3 mg/kg/day (the highest dose tested).

- Naylor and Ruecker (1985) fed propachlor [96.1% active ingredient (a.i.)] to beagle dogs (six/sex/dose) in the diet for 90 days at dose levels of 0, 100, 500 or 1,500 ppm. Based on the assumption that 1 ppm in food is equivalent to 0.025 mg/kg/day (Lehman, 1959), these doses are equivalent to 0, 2.5, 12.5 or 37.5 mg/kg/day. Clinical signs, ophthalmoscopic, clinicopathologic, gross pathology and

histopathologic effects were comparable for treated and control groups. The reduction in food consumption and concomitant reductions in body weight gain at all test levels were considered by the author to be due to poor diet palatability. Based on these responses, a NOAEL of 1,500 ppm (37.5 mg/kg/day) was identified.

Dermal/Ocular Effects

- The acute dermal LD_{50} value of technical propachlor and WP (65% propachlor) in the rabbit ranges from 380 mg/kg to 20 g/kg (Keeler et al., 1976; Monsanto, undated; Braun and Rinehart, 1978). Wettable powder produced the lowest LD_{50} in rabbits (380 mg/kg); the lowest LD_{50} produced by technical propachlor was between 1,000 and 1,260 mg/kg in rabbits.

- Propachlor (94.5% a.i.) (1 g/mL) applied to abraded and intact skin of New Zealand White rabbits (three/sex) for 24 hours produced erythema and slight edema at treated sites 72 hours post-treatment (Heenehan et al., 1979).

- Heenehan et al. (1979) instilled single applications (0.1 cc) of propachlor into one eye of tested New Zealand rabbits for 30 seconds. Corneal opacity with stippling and ulceration, slight iris irritation, conjunctival redness, chemosis, discharge and necrosis were reported at 14 days. Similar responses were reported by Keeler et al. (1976) for a corresponding observation period and by Auletta (1984) during 3 to 21 days post-treatment.

Long-term Exposure

- Albino rats (25/sex/dose) administered 0, 1.3, 13.3 or 133.3 mg/kg/day propachlor (65% WP = 65% a.i.) in the diet for 90 days showed decreased weight gain (10 to 12% less than control levels) in and increased liver weights in both sexes (10% greater than control levels) at 133.3 mg/kg/day (the highest dose tested) (Wazeter et al., 1964). The body and liver weights of rats of both sexes that received the low dose and mid dose were comparable to control levels. Survival, biochemical indices, hematology, urinalysis, gross pathology and histopathology did not differ significantly between treated and control groups. The NOAEL identified in this study is 13.3 mg/kg/day. The Lowest-Observed-Adverse-Effect-Level (LOAEL) is 133.3 mg/kg/day (the highest dose tested).

- Reyna et al. (1984a) administered propachlor (96.1% a.i.) to rats (30/sex/dose) in the diet for 90 days at mean dose levels of 0, 240, 1,100 or 6,200 ppm. Assuming that 1 ppm is equivalent to 0.05 mg/kg/day, these concentrations correspond to 0, 12, 55 or 310 mg/kg/day (Lehman, 1959). Body weights and food consumption were significantly decreased (no p value specified) at 55 mg/kg/day and 310 mg/kg/day in both sexes. Final body weights for females were 7 and 36% less than controls at the mid- and high-dose levels, respectively. In males, final body weights were 8 and 59% less than control levels for mid- and high-dose levels, respectively. However, histopathological examination showed no changes. Mid- and high-dose levels produced

increased platelet counts, decreased white blood cell counts and mild liver cell dysfunction. Mild hypochromic, microcytic anemia was reported at the high dose. A NOAEL of 12 mg/kg/day can be identified for this study.

- Albino mice (30/sex/dose) were fed propachlor (96.1% a.i.) in the diet for 90 days at mean dose levels of 0, 385, 1,121 or 3,861 ppm (Reyna et al., 1984b). Based on the assumption that 1 ppm in food is equivalent to 0.15 mg/kg/day (Lehman, 1959), these doses correspond to 0, 58, 168 or 579 mg/kg/day. Reduced body weight gain, decreased white blood cell count, liver and kidney weight changes and increased incidences of centrolobular hepatocellular enlargement were reported at the mid (168 mg/kg/day) and high (579 mg/kg/day) doses when compared to controls. Based on these responses, a NOAEL of 385 ppm (58 mg/kg/day) can be identified.

Reproductive Effects

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

Developmental Effects

- Miller (1983) reported no signs of maternal toxicity in New Zealand female rabbits (16/dose) that were administered propachlor (96.5%) orally by gavage at doses of 0, 5, 15 or 50 mg/kg/day on days 7 to 19 of gestation. Statistically significant increases in mean implantation loss with corresponding decreases in the mean number of viable fetuses were reported at 15 and 50 mg/kg/day when compared to controls. Two low-dose and one mid-dose rabbit aborted on gestation days 22 to 25. These effects, however, do not appear to be treatment-related since no abortions occurred in the high-dose animals. No treatment-related effects were present in the 5-mg/kg/day group (the lowest dose tested). The authors reported that the maternal and embryonic NOAELs were 50 and 5 mg/kg/day, respectively.

- Schardein et al. (1982) administered technical propachlor orally by gavage to rats (25/dose) at dose levels of 0, 20, 60 or 200 mg/kg/day during days 6 to 19 of gestation. There were no adverse fetotoxic or maternal effects reported at any dose level. Based on this information, the NOAEL identified in this study was 200 mg/kg/day (the highest dose tested).

Mutagenicity

- Technical propachlor was not genotoxic in assays of Salmonella typhimurium with or without plant and animal activation; however, genotoxic activity was reported in yeast assays (Saccharomyces cerevisiae) at 1.3×10^{-3} M and 3 mg per plate after plant activation (Plewa et al., 1984).

- In a cytogenic study, propachlor administered for 24 hours by intraperitoneal injection at dose levels of 0.05, 0.2 or 1.0 mg/kg to F344

rats did not induce chromosomal aberrations in bone marrow cells (*Ernst and Blazak, 1985*).

° Gene mutation was not detected in assays employing Chinese Hamster Ovary (CHO) cells. Primary rat hepatocytes exposed to 1,000 and 5,000 ug/mL technical-grade propachlor showed no effect on unscheduled DNA synthesis when compared to controls (Flowers, 1985; Steinmetz and Mirsalis, 1984).

Carcinogenicity

° No information was found in the available literature to evaluate the carcinogenic potential of propachlor. However, several chemicals analogous to this compound, i.e., alachlor and acetochlor, were found to be oncogenic in two animal species.

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 propachlor. It is therefore recommended that the Ten-day HA value for the 10-kg child (0.5 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The developmental toxicity study in rabbits by Miller (1983) has been selected as the basis for determination of the Ten-day HA value for propachlor. Pregnant rabbits administered propachlor (96.5%) by gavage at a dose level of

5 mg/kg/day showed no clinical signs of toxicity in the adult animals and no reproductive or developmental effects in the fetuses. The study identified a NOAEL of 5 mg/kg/day. These results are supported by a reproduction study reported by Schardein et al. (1982) in which rats were administered doses ranging from 20 to 200 mg/kg/day during gestation, with no adverse fetotoxic or maternal effects reported at any dose level. The NOAEL identified in that study was 200 mg/kg/day (the highest dose tested). However, since the rabbit appears to be the more sensitive species, the NOAEL identified in the rabbit study will be used to derive the Ten-day HA.

Using a NOAEL of 5 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.5 \text{ mg/L } (500 \text{ ug/L})$$

where:

5 mg/kg/day = NOAEL, based on the absence of clinical signs of toxicity and the lack of reproductive or teratogenic effects in rabbits exposed to propachlor by gavage for 12 days during gestation.

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

Because no suitable long-term studies were available to calculate a Longer-term HA, it was decided that it would be more appropriate to use the Reference Dose of 0.013 mg/kg/day and adjusting this number to protect a 10-kg child and a 70-kg adult. The resulting Longer-term HA thus becomes 0.13 mg/L and 0.46 mg/L for a 10-kg child and a 70-kg adult, respectively.

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, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 90-day study by Wazeter et al. (1964) has been selected to serve as the basis for determination of the Lifetime HA value for propachlor. Based on body and liver weight effects, a NOAEL of 13.3 mg/kg/day was identified. These results were further verified by the results of a similar study with rats conducted by Reyna et al. (1984a) in which a NOAEL of 12 mg/kg/day was identified.

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(13.3 \text{ mg/kg/day})}{(1{,}000)} = 0.013 \text{ mg/kg/day}$$

where:

13.3 mg/kg/day = NOAEL based on the absence of effects on body weight and liver weight in rats exposed to propachlor for 90 days.

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 Level (DWEL)

$$DWEL = \frac{(0.013 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.46 \text{ mg/L } (460 \text{ ug/L})$$

where:

0.013 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

$$\text{Lifetime HA} = (0.46 \text{ mg/L}) (20\%) = 0.092 \text{ mg/L } (92 \text{ ug/L})$$

where:

0.46 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No studies on the carcinogenic potential of propachlor were found in the available literature. However, other structurally similar compounds such as alachlor and acetochlor have been found to be potent carcinogens.

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

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Residue tolerances ranging from 0.02 to 10.0 ppm have been established for propachlor in or on agricultural commodities (U.S. EPA, 1985).

- NAS (1977) has recommended an ADI of 0.1 mg/kg/day and a Suggested-No-Adverse-Effect Level (SNARL) of 0.7 mg/L, based on a NOAEL of 100 mg/kg/day in a rat study (duration of study not available).

VII. ANALYTICAL METHODS

(to be provided by STB)

VIII. TREATMENT TECHNOLOGIES

- No data were found for the removal of propachlor from drinking water by conventional treatment or by activated carbon treatment.

- No data were found for the removal of propachlor from drinking water by aeration. However, the Henry's Coefficient can be estimated from available data on solubility (700 mg/L at 20°C) and vapor pressure (2.3×10^{-4} mm Hg at 25°C). Propachlor probably would not be amenable to aeration or air stripping because its Henry's Coefficient is approximately 0.0051 atm. Baker and Johnson (1984) reported the results of water and pesticide volatilization from a waste disposal pit. Over a 2-year period, approximately 66.4 mg of propachlor evaporated for every liter of water which evaporated and only 8.3% of the propachlor was removed. These results support the assumption that aeration would not effectively remove propachlor from drinking water.

- Propachlor is similar in structure to alachlor and has similar physical properties. The effectiveness of various processes for removing propachlor would probably be similar to that of alachlor.

- Alachlor is amenable to the following processes:

  - GAC (Miltner and Fronk, 1985; DeFilippi et al., 1980).

- PAC (Miltner and Fronk, 1985; Baker, 1983).
- Ozonation (Miltner and Fronk, 1985).
- Reverse osmosis (Miltner and Fronk, 1985).

° Chlorine and chlorine dioxide oxidation were partially effective in removing alachlor from drinking water (Miltner and Fronk, 1985).

° The following processes were not effective in removing alachlor from drinking water:

- Diffused aeration (Miltner and Fronk, 1985).
- Potassium permanganate oxidation (Miltner and Fronk, 1985).
- Hydrogen peroxide oxidation (Miltner and Fronk, 1985).
- Conventional treatment (Miltner and Fronk, 1985; Baker, 1983).

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*Confidential Business Information submitted to the Office of Pesticide Programs