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DRAFT

BROMACIL

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.

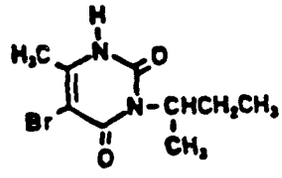
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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: 314-40-9

Structural Formula



5-Bromo-6-methyl-3-(1-methylpropyl)-2,4(1H,3H)-pyrimidinedione

Synonyms

- Borea; Borocil IV; Bromazil; Cynogan; Herbicide 976; Hyvar X-WS; Hyvar X; Hyvar X Weed Killer; Hyvar X-L; Hyvarex; Krovar II; Nalkil; Uragan; Urox HX; Urox B; Weed-Broom (Meister, 1983).

Uses

- Herbicide for general weed or brush control in noncrop areas; particularly useful against perennial grasses (Meister, 1983).

Properties (Windholz et al., 1983)

Chemical Formula	$C_9H_{13}O_2N_2Br$
Molecular Weight	261.11
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	158-160°C
Density	--
Vapor Pressure (100°C)	8×10^{-4} mm Hg
Specific Gravity	--
Water Solubility (20°C)	815 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Bromacil has been found in Florida ground water; a typical positive was 300 ppb (Cohen et al., 1986).

Environmental Fate

- Bromacil in aqueous solution was stable when exposed to simulated sunlight for 6 days (Moilanen and Crosby, 1974). Only one minor (<4%) photolysis product (5-bromo-6-methyluracil) was identified. An aqueous solution of bromacil at 1 ppm lost all herbicidal activity

after exposure to UV light for 10 minutes, but at 10 ppm and 15 minutes' irradiation herbicidal activity was still present (Kearney et al., 1964). However, bromacil in an aqueous solution (pH 9.4) containing the photosensitizer methylene blue was rapidly degraded under direct sunlight with a halflife of <1 hour (Acher and Dunkelblum, 1979).

- More than 26 soil fungi representative of several taxonomic groups, including Fungi Imperfecti, Ascomycetes and Zygomycetes, were capable of metabolizing bromacil as their sole carbon source (Wolf et al., 1975; Torgeson, 1969; Torgeson and Mee, 1967; Boyce Thompson Institute for Plant Research, 1971).

- Data from soil metabolism studies indicate that bromacil at 8 ppm had a half-life of about 6 months in aerobic loam soil incubated at 31°C (Zimdahl et al., 1970). However, 10% of applied bromacil at approximately 3 ppm was slowly degraded to CO_2 in an aerobic sandy loam soil after 330 days at 22°C (Wolf, 1974; Wolf and Martin, 1974). In anaerobic sandy loam soil, bromacil at approximately 3 ppm had a calculated half-life of approximately 144 days. No CO_2 evolved from the sterilized soil treated with bromacil within 145 days, indicating that degradation was microbial.

- Bromacil is mobile in soil. Phytotoxic residues of bromacil leached 19 cm in clay and silty clay loam soils eluted with the equivalent of 4.3 acre-inches of water (Signori et al., 1978). In mucky peat, loam and loamy sand soils eluted with the equivalent of 13 to 15 cm of water, bromacil leached to 10-, 25-, and to >30-cm depths, respectively (Day, 1976). Utilizing soil thin-layer chromatographic techniques ^{14}C-bromacil was evaluated to be mobile (R_f 0.7) in a silty clay loam soil (Helling, 1971). Bromacil is not adsorbed by montmorillonite, illite, or humic acid to any great extent [Freundlich K (adsorption coefficient) $\leq$10 at 25°C]; however, at 0°C bromacil was adsorbed (Freundlich K 126) to humic acid (Haque and Coshow, 1971; Volk, 1972). Adsorption appeared to increase with decreasing temperatures.

- Data from field dissipation studies showed that bromacil phytotoxic residues persisted in soils ranging in texture from sand to clay for >2 years following a single application of bromacil at $\geq$2.6 lb ai/A (active ingredient/acre) (Bunker et al., 1971; Stecko, 1971).

III. PHARMACOKINETICS

Absorption

- Workers who were exposed to bromacil during production, formulation and packaging excreted unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite in the urine (DuPont, 1966b). Unchanged bromacil and the metabolite were also detected in the urine of rats fed bromacil in the diet (DuPont, 1966a). Although these data indicate that bromacil is absorbed, sufficient information was not available to quantify the extent of absorption.

Distribution

- No information was found in the available literature on the distribution of bromacil.

Metabolism

- Workers at a bromacil production plant excreted unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite, present as the glucuronide and/or sulfonate conjugate, in urine (DuPont, 1966b).

- Gardiner et al. (1969) fed rats (age and strain not specified) food containing 1,250 ppm bromacil for 4 weeks. Assuming 1 ppm equals 0.05 mg/kg/day in the older rat (Lehman, 1959), this dietary level corresponds to about 62.5 mg/kg/day. Analysis of the urine of these rats revealed the presence of unchanged bromacil and the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite (primarily as the glucuronide and/or sulfonate conjugate). Five other minor metabolites were also detected: 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil; 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-hydroxymethyluracil; 3-sec-butyl-6-hydroxymethyluracil; 5-bromo-3-(3-hydroxyl-1-methylpropyl)6-methyluracil; and 3-sec-butyl-6-methyluracil. An unidentified bromine-containing compound with a molecular weight of 339 was also detected.

Excretion

- In humans exposed to bromacil during its formulation and packaging, urinary excretion products included 0.1 ppm parent compound and 6.3 ppm 5-bromo-3-sec-butyl-6-hydroxymethyluracil, present mostly as a conjugate (DuPont, 1966b).

- Rats were fed bromacil (1,250 ppm in the diet) for 4 weeks; urine was collected daily during weeks 3 and 4 of the study. Analysis of the urine revealed the presence of 20 ppm unchanged bromacil and 146 ppm of the 5-bromo-3-sec-butyl-6-hydroxymethyluracil metabolite (conjugated and unconjugated form) (DuPont, 1966a; Gardiner et al., 1969).

IV. HEALTH EFFECTS

Humans

- No information was located in the available literature on the health effects of bromacil in humans.

Animals

- Most of the animal data available are from unpublished studies identified prior to the published report by Sherman and Kaplan (1975). These authors stated that an 80% wettable bromacil powder was used in all tests discussed in their report except for eye irritation studies in which a 50% wettable bromacil powder was used. All dosages and

feeding levels, unless otherwise stated, were based on the active ingredient, bromacil.

Short-term Exposure

- The oral LD_{50} value for male ChR-CD rats was calculated to be 5,200 mg/kg (Sherman and Kaplan, 1975). Clinical signs of toxicity included rapid respiration, prostration and initial weight loss.

- In male mongrel dogs, a single oral dose of 5,000 mg/kg caused nausea, vomiting, fatigue, incoordination and diarrhea (Sherman and Kaplan, 1975). It was not possible to estimate a lethal oral dose for bromacil in dogs because vomiting occurred almost immediately, even at doses of 100 mg/kg.

- Sherman and Kaplan (1975) administered bromacil to groups of six male ChR-CD rats by gastric intubation at dose levels of 650, 1,035 or 1,500 mg/kg/day, 5 days/week for 2 weeks (10 doses). Four of six animals died at the high dose. Five of six survived exposure to 1,035 mg/kg/day, but showed gastrointestinal and nervous system disturbances, and there was focal liver cell hypertrophy and hyperplasia. All animals survived the low dose with similar, but less severe, pathological changes. The 650-mg/kg/day dose is identified as the Lowest-Observed-Adverse-Effect-Levels (LOAEL) in this study.

- Palmer (1964) reported that sheep that received bromacil at oral doses of 250 mg/kg for five days developed weakness in the legs and incoordination. Recovery from these symptoms usually took several weeks. Administration of 100 mg/kg/day for 11 days induced an 11% weight loss but no observable clinical symptoms.

Dermal/Ocular Effects

- Bromacil (applied as a 50% aqueous solution of the 80% wettable powder) was only mildly irritating to the intact and abraded skin of young guinea pigs exposed for periods of up to 3 weeks. It was more irritating to the skin of older animals. Bromacil did not produce skin sensitization (DuPont, 1962).

- Sherman and Kaplan (1975) reported that when bromacil was applied dermally to rabbits the lethal dose was greater than 5,000 mg/kg, the maximum feasible dose. No clinical signs of toxicity and no gross pathological changes were observed.

- Bromacil, as a 50% aqueous suspension, was mildly irritating to the skin of young guinea pigs, but only slightly more irritating to the skin of older animals. It was not a skin sensitizer (Sherman and Kaplan, 1975).

- Sherman and Kaplan (1975) reported that bromacil (0.1 mL of a 10% suspension in mineral oil) resulted in only mild temporary conjunctivitis in both the washed and unwashed eyes of rabbits. No corneal injury was observed when a dose of 10 mg dry powder was applied directly to the eye.

Long-term Exposure

- Zapp (1965) discussed a study, also reported by Sherman and Kaplan (1975), in which 10 male and 10 female ChR-CD rats were fed dietary levels of 0, 50, 500 or 2,500 ppm bromacil for 90 days. This corresponds to doses of about 0, 2.5, 25 or 125 mg/kg/day, assuming 1 ppm equals 0.05 mg/kg/day in an older rat (Lehman, 1959). Because no signs of toxicity were observed at any dose, the high dose was increased to 5,000 ppm (about 250 mg/kg/day) after 6 weeks; to 6,000 ppm (about 300 mg/kg/day) after 10 weeks; and to 7,500 ppm (about 375 mg/kg/day) after 11 weeks. This dosing pattern resulted in reduced food intake and mild histological changes in thyroid and liver. No compound-related effects on weight gain, hematology, urinalysis or histology were detected at the two lowest doses; 25 mg/kg/day was identified as the No-Observed-Adverse-Effect-Level (NOAEL) in this study.

- Sherman et al. (1966, also reported by Sherman and Kaplan, 1975) fed groups of 36 male and 36 female ChR-CD rats food containing 0, 50, 250 or 1,250 ppm bromacil for 2 years. This corresponds to doses of about 0, 2.5, 12.5 or 62.5 mg/kg/day, assuming 1 ppm equals 0.05 mg/kg/day in older rats (Lehman, 1959). Females at the highest dose showed decreased weight gain ($p < 0.001$). No other toxic effects were observed in a variety of parameters measured, including mortality, hematology, urinalysis, serum biochemistry, gross pathology, organ weight or histopathology, except for a slight thyroid hyperplasia at the high dose. This study identified a NOAEL of 12.5 mg/kg/day.

- Beagle dogs (three/sex/dose level) were fed a nutritionally complete diet containing 0, 50, 250 or 1,250 ppm bromacil for 2 years (Sherman et al., 1966; also reported by Sherman and Kaplan, 1975). This corresponds to doses of about 0, 1.25, 6.25 or 31.2 mg/kg/day, assuming 1 ppm equals 0.025 mg/kg/day in the dog (Lehman, 1959). No nutritional, clinical, hematological, urinary, blood chemistry or histopathologic evidence of toxicity was detected in any group. This study identified a NOAEL of 31.2 mg/kg/day.

- Kaplan et al. (1980) administered bromacil (approximately 95% pure) to CD-1 mice (80/sex/dose) for 78 weeks at dietary levels of 0, 250, 1,250 or 5,000 ppm. Based on information presented by the authors, these dietary levels correspond to doses of 0, 39.6, 195 or 871 mg/kg/day for males and 0, 66.5, 329 or 1,310 mg/kg/day for females. During the first year of the study, a compound-related decrease in body weight gain was observed in male mice receiving 5,000 ppm and in female mice receiving 1,250 ppm. The treatment and control groups exhibited no significant ($p < 0.05$) differences in food consumption. Mortality in the 5,000-ppm females was significantly ($p < 0.05$) greater than in the controls. Liver changes noted in treated mice consisted of increased mean and relative weights in the 1,250-ppm females and the 5,000-ppm males; an increased incidence of diffuse hepatocellular hypertrophy in the 1,250- and 5,000-ppm males and in the 5,000-ppm females; an increased incidence of centrilobular vacuolation in 250-ppm males; an increased incidence of scattered hepatocellular necrosis in

5,000-ppm males; and the presence of extravasated erythrocytes in the hypertrophied hepatocytes of the 1,250- and 5,000-ppm males. The authors felt that centrilobular vacuolation and hypertrophy were probably related to enzyme induction. The toxicological significance of extravasated erythrocytes in the hypertrophied hepatocytes was unclear. Compound-related changes in the testes of mice consisted of an increased incidence of spermatocyte necrosis, sperm calculi and mild interstitial-cell hypertrophy/hyperplasia in the 1,250- and 5,000-ppm males and a dose-related increase in the incidence of testicular tubule atrophy in all male treatment groups. Based on changes in testes, a LOAEL of 250 ppm (39.6 mg/kg/day) is identified for male mice. A NOAEL of 250 ppm (66.5 mg/kg/day) was identified for female mice.

Reproductive Effects

- Sherman et al. (1966; also reported by Sherman and Kaplan, 1975) reported the effects of bromacil on reproduction in a three-generation study in rats. Twelve male and twelve female weanling ChR-CD rats were fed bromacil in the diet at 0 or 250 ppm. This corresponds to doses of about 0 or 12.5 mg/kg/day, assuming 1 ppm in the diet equals 0.05 mg/kg/day for older rats (Lehman, 1959). Animals were bred after 12 weeks, and the F_{1b} and the F_{2b} generations were maintained on the same diets as their parents. No evidence of adverse effects on reproduction or lactation performance was observed. Examination of the F_{2b} generation revealed no evidence of gross or histopathological effects. This study identified a minimum NOAEL of 12.5 mg/kg/day.

Developmental Effects

- Paynter (1966; also reported by Sherman and Kaplan, 1975) administered bromacil to New Zealand White rabbits (8 or 9 per dosage) at dietary levels of 0, 50 or 250 ppm on days 8 through 16 of gestation. Assuming 1 ppm equals 0.03 mg/kg/day in the rabbit (Lehman, 1959), these dietary levels correspond to about 0, 1.5 or 7.5 mg/kg/day. No significant differences between the conception rates of the control and test groups were observed. Control and test group litters were comparable in terms of litter size, mean pup length, mean litter weight, number of stillbirths and number of resorption sites. No gross malformations were observed in any animals. Skeletal clearing revealed no abnormalities in bone structure in any animals. Based on reproductive and teratogenic end points, a NOAEL of 250 ppm (7.5 mg/kg/day) was identified.

- Pregnant rats (strain not specified) were exposed to aerosols of bromacil (165 mg/m^3) on days 7 to 14 of gestation. No prenatal changes or teratogenic effects were observed (no further details were provided) (Dilley et al., 1977).

Mutagenicity

- In a sex-linked recessive lethal test (Valencia, 1981), Drosophila melanogaster (Canton-S wild-type stock) were exposed to bromacil in

food at levels of 2, 3, 5 or 2,000 ppm. Bromacil was found to be weakly mutagenic at the 2,000-ppm dose level.

- Riccio et al. (1981) reported that bromacil (tested concentrations not specified) was not mutagenic with or without metabolic activation in assays conducted using Saccharomyces cerevisiae strains D3 and D7.

- Siebert and Lemperle (1974) reported that bromacil was not mutagenic when tested at a concentration of 1,000 ppm using S. cerevisiae strain D4.

- Simmon et al. (1977) reported that bromacil was not mutagenic in an in vivo mouse dominant-lethal assay and the following in vitro assays: unscheduled DNA synthesis in human fibroblasts (WI-38 cells); reverse mutation in Salmonella typhimurium strains TA1535, 1537, 1538 and 100, and in Escherichia coli WP2; mitotic recombination in S. cerevisiae; and preferential toxicity assays in E. coli (strains W3110 and p3478) and Bacillus subtilis (strains H17 and M45).

- In a modified Ames assay (Rashid, 1974), bromacil was not mutagenic in S. typhimurium strains TA1535 and 1538 when tested at concentrations up to 325 ug/plate.

- In an assay designed to test for thymine replacement in mouse DNA (McGahen and Hoffman, 1963), Swiss-Webster white mice received bromacil by oral intubation at 100 mg/kg twice daily for 2 days, followed by 50 mg/kg twice daily for 8 days. Under the conditions of the assay, bromacil was not recognized as a thymine analog by the mouse.

- Bromacil did not show any signs of mutagenicity in a variety of microbial test systems (Jorgenson et al., 1976; Woodruff et al., 1984).

- In the Ames test, bromacil (5% concentration) induced revertants in three of six Salmonella strains tested (Njage and Gopalan, 1980).

- Bromacil did not induce sex-linked recessive lethals in D. melanogaster (Gopalan and Njage, 1981).

Carcinogenicity

- Sherman et al. (1966) fed groups of 36 male and 36 female weanling ChR-CD rats bromacil in the diet for 2 years. Dietary levels were 0, 50, 250 or 1,250 ppm (about 0, 2.5, 12.5 or 62.5 mg/kg/day, based on Lehman, 1959). There was no effect on mortality, and the only treatment-related lesion detected by histological examination was a slight increase in the incidence of light-cell and follicular-cell hyperplasia in the thyroid at the high dose. One high-dose female was found to have follicular-cell adenoma. The authors stated that these observations suggest a compound-related effect.

- Kaplan et al. (1980) administered bromacil (approximately 95% pure) to CD-1 mice (80/sex/dose) for 78 weeks at dietary levels of 0, 250, 1,250 or 5,000 ppm. Based on information presented by the authors,

these dietary levels correspond to compound intake levels of 0, 39.6, 195 or 871 mg/kg/day for males and 0, 66.5, 329 or 1,310 mg/kg/day for females. In males, the combined incidences of hepatocellular adenomas plus carcinomas/number of animals examined were 10/74, 11/71, 8/71 and 19/70 ($p < 0.05$) at 0, 250, 1,250 and 5,000 ppm, respectively. Hepatocellular carcinoma incidences were 5/74, 4/71, 4/71 and 9/70 ($p > 0.05$) at 0, 250, 1,250 and 5,000 ppm, respectively. These tumors were found predominantly in mice that survived to terminal sacrifice. No effect on liver tumor incidence was observed in females.

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:

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

where:

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

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

UF = uncertainty factor (10, 100 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 studies were located which are suitable for derivation of a One-day HA for bromacil. The Ten-day HA, derived below, of 4.6 mg/L for a 10-kg child is proposed as a conservative One-day HA.

Ten-day Health Advisory

The 2-week oral study in rats by Sherman and Kaplan (1975) has been selected as the basis for the Ten-day HA for bromacil. Animals were dosed by gavage for 10 days over a period of 2 weeks. The lowest dose tested (650 mg/kg/day) produced mild pathological changes in the liver, and this value was identified as a LOAEL.

Using a LOAEL of 650 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(650 \text{ mg/kg/day}) (5/7) (10 \text{ kg})}{(1{,}000) (1 \text{ L/day})} = 4.6 \text{ mg/L } (4{,}600 \text{ ug/L})$$

where:

650 mg/kg/day = LOAEL, based on mild liver pathology in rats exposed by gavage to bromacil for 2 weeks.

5/7 = correction for dosing 5 days per week.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

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

Longer-term Health Advisory

The 90-day study by Zapp (1965) has been selected to serve as the basis for the Longer-term HA for bromacil. Rats were fed diets containing up to 500 ppm without any adverse effects. This study identified a NOAEL of 500 ppm (about 25 mg/kg/day).

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 2.5 \text{ mg/L } (2{,}500 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on the absence of any pathological evidence of toxicity in rats exposed to bromacil via oral feeding for 90 days.

10 kg = assumed body weight of 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.

Using a NOAEL of 25 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(25 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 8.7 \text{ mg/L } (8{,}700 \text{ ug/L})$$

where:

25 mg/kg/day = NOAEL, based on absence of any toxic effects in rats exposed to bromacil via oral feeding 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 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, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The chronic feeding study in rats by Sherman et al. (1966) has been selected to serve as the basis for the Lifetime HA. This study identified a dietary LOAEL of 1,250 ppm and a NOAEL of 250 ppm, based on weight gain and mild thyroid hyperplasia. This NOAEL corresponds to about 12 mg/kg/day. The same NOAEL is evident in a three-generation reproduction study in rats by Sherman et al. (1966). The long-term feeding studies in dogs by Sherman et al. (1966) and mice by Kaplan et al. (1980) were not selected, since the demonstrated NOAEL was the lowest in the rat study.

Using a NOAEL of 12 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(12 \text{ mg/kg/day})}{(100)} = 0.12 \text{ mg/kg/day}$$

where:

12 mg/kg/day = NOAEL, based on absence of hepatic effects in rats exposed to bromacil via the diet for 2 years.

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)

$$DWEL = \frac{(0.12 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 4.2 \text{ mg/L } (4{,}200 \text{ ug/L})$$

where:

0.12 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

$$\text{Lifetime HA} = \frac{(4.2 \text{ mg/L})\ (20\%)}{10} = 0.08 \text{ mg/L } (80 \text{ ug/L})$$

where:

4.2 mg/L = Lifetime HA at 100% contribution from drinking water.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy for use with a Group C carcinogen.

Evaluation of Carcinogenic Potential

- Bromacil has not been determined to be carcinogenic, although an increased incidence of hepatocellular adenomas plus carcinomas was observed in male CD-1 mice fed bromacil in the diet at a dose level of 871 mg/kg/day for 78 weeks (Kaplan et al., 1980).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of bromacil.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), bromacil is classified in Group C: possible human carcinogen. This category is for substances with limited evidence of carcinogenicity in animals in the absence of human data.
- The U.S. EPA has not published excess lifetime cancer risks for this material.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The NAS (1977) has calculated an acceptable daily intake (ADI) of 0.0125 mg/kg/day, based on a chronic NOAEL of 12.5 mg/kg/day in rats and an uncertainty factor of 1,000. A suggested-no-adverse-response level (SNARL) of 0.086 mg/L was calculated based on an assumed water consumption of 2 L/day by a 70-kg adult, with 20% contribution from water.

- The U.S. EPA Office of Pesticide Programs (EPA/OPP) previously calculated an ADI of 62.5 ug/kg/day, based on a NOAEL of 6.25 mg/kg/day in a 2-year feeding study in dogs (Sherman et al., 1966) and an uncertainty factor of 100. This was updated to 130 ug/kg/day based on a 2-year rat feeding study using a NOAEL of 12.5 mg/kg/day and a 100-fold uncertainty factor.

- A tolerance of 0.1 ppm bromacil in or on citrus fruits and pineapples has been set by the EPA/OPP (CFR, 1985). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment, and it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).

- The American Conference of Governmental Industrial Hygienists (ACGIH, 1984) has recommended a threshold limit value (TLV) of 1 ppm, and a short-term exposure limit (STEL) of 2 ppm.

VII. ANALYTICAL METHODS

- Analysis of bromacil is by a gas chromatographic (GC) method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1985). This method requires a solvent extraction of approximately 1 L of sample with methylene chloride using a separatory funnel. The methylene chloride extract is dried and exchanged to acetone during concentration to a volume of 10 mL or less. The compounds in the extract are separated by GC, and measurement is made with a thermionic bead detector. The method detection limit for bromacil is 2.38 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies used to remove bromacil from contaminated water.

IX. REFERENCES

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