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DRAFT

TERBACIL

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.

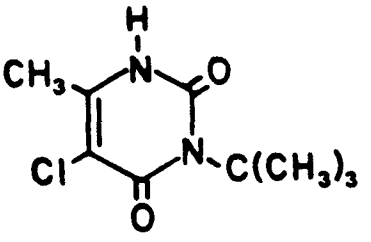
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 5902-51-2

Structural Formula



5-Chloro-3-(1,1-dimethylethyl)-6-methyl-2,4(1H,3H)-pyrimidinedione

Synonyms

° Sinbar; Turbacil (Meister, 1983).

Uses

° Herbicide used for the selective control of annual and perennial weeds in crops such as sugarcane, alfalfa, apples, peaches, blueberries, strawberries, citrus, pecans and mint (Meister, 1983).

Properties (Meister, 1983)

Chemical Formula	$C_9H_{13}O_2N_2Cl$
Molecular Weight	216.65
Physical State (at 25°C)	White crystals
Boiling Point (at 25 mm Hg)	--
Melting Point	175-177°C
Vapor Pressure (54°C)	5.4×10^{-6} mm Hg
Specific Gravity	--
Water Solubility (25°C)	710 mg/L
Log Octanol/Water Partition Coefficient	-1.41
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

° Terbacil was not sampled at any water supply stations listed in the STORET database (STORET, 1987). No information was found in available literature on the occurrence of terbacil.

Environmental Fate

- ^{14}C-Terbacil at 5 ppm was stable (less than 2% degraded) in buffered aqueous solutions at pH 5, 7, and 9 for 6 weeks at 15°C in the dark (Davidson et al. 1978).

- After 4 weeks of irradiation with UV light (300 to 400 nm), about 16% of the applied ^{14}C-terbacil (5 ppm) was photodegraded in distilled water (pH 6.2) (Davidson et al., 1978).

- Soil metabolism studies indicate that terbacil is persistent in soil. At 100 ppm, terbacil was slowly degraded in an aerobic sandy loam soil (80% remained after 8 months) (Marsh and Davies, 1978). Terbacil at 8 ppm had a half-life of about 5 months in aerobic loam soil (Zimdahl et al., 1970). ^{14}C-Terbacil at 2 ppm had a half-life of 2 to 3 months in aerobic silt loam and sandy loam soils (Rhodes, 1975; Gardiner, 1964; Gardiner et al., 1969). The formation of carbon dioxide is slow; for example, 28% of the applied ^{14}C-terbacil at 2.88 ppm on sandy loam soil degraded to carbon dioxide in 600 days (Wolf, 1973; Wolf, 1974; Wolf and Martin, 1974).

- Degradation of terbacil in an anaerobic soil environment is also slow. In anaerobic silt loam and sandy soils, ^{14}C-terbacil at 2.1 ppm was slightly degraded (less than 5% after 60 days) in the dark (Rhodes, 1975). Only trace amounts of ^{14}C-terbacil, applied at 2.88 ppm, were degraded to ^{14}C-carbon dioxide after 145 days in an anaerobic environment when metabolized by microbes in the dark (Rhodes, 1975). At least 90% of the lable remained as terbacil after 90 days of incubation in both sterile and nonsterile soils. Small amounts (0.8 to 1.5% of the label of carbon dioxide were evolved from nonsterile soil, whereas 0.01% was evolved from sterile soil (Rhodes, 1975).

- Terbacil was mobile in soil columns of sandy loam and fine sandy soil (Rhodes, 1975; Mansell et al., 1972). However, in a silt loam soil column, only 0.4% of the applied ^{14}C-terbacil leached with 20 inches of water (Rhodes, 1975). In an aged soil column leaching study of the leaching characteristics of degradates, about 52% and 4% of the applied radioactivity in aged sandy loam and silt loam soils leached, respectively (Rhodes, 1975). Terbacil phytotoxic residues were mobile to depths of 27.5 to 30 cm in a sandy soil column treated with terbacil at 5.6 kg/ha and eluted with 10 or 20 cm water (Marriage, 1977). Terbacil was negligibly adsorbed to soils ranging in texture from sand to clay (Davidson et al., 1978; Liu et al., 1971; Rao and Davison, 1979). Terbacil was adsorbed (54%) to a muck soil (36% organic matter) (Liu et al., 1971).

- Data from field dissipation studies showed that terbacil persistence in soil varied with application rate, soil type and rainfall. In the field, terbacil phytotoxic residues persisted in soil for up to 16 months following a single application of terbacil. Residues were found at the maximum depths sampled (3 to 43 inches) (Gardiner, undated a,b; Gardiner et al., 1969; Isom et al., 1969; Isom et al., 1970; Liu et al., undated; Mansell et al., 1977; Mansell et al., 1979; Morrow and McCarty, 1976; Rahman, 1977; Rhodes, 1975).

- Phytotoxic residues resulting from multiple applications of terbacil persisted for 1 to more than 2 years following the final application (Skroch et al., 1971; Tucker and Phillips, 1970; Benson, 1973; Doughty, 1978).

- Terbacil has not been found in ground water; however, its soil persistence and mobility indicate that it has the potential to get into ground water.

III. PHARMACOKINETICS

Absorption

- No information was found in the available literature on the absorption of terbacil.

Distribution

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

Metabolism

- No information was found in the available literature on the metabolism of terbacil.

Excretion

- No information was found in the available literature on the excretion of terbacil.

IV. HEALTH EFFECTS

Humans

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

Animals

Short-term Exposure

- It was not possible to perform an acute oral toxicity study in dogs because repeated emesis prevented dosing with terbacil in amounts in excess of 5,000 mg/kg (Paynter, 1966). However, in a dog receiving one oral dose of terbacil at 250 mg/kg followed 5 days later by a dose of 100 mg/kg, emesis, diarrhea and mydriasis were noted.

- In rats (details not available), the LD_{50} was between 5,000 and 7,500 mg/kg (Sherman, 1965). At 2,250 mg/kg, inactivity, weight loss and incoordination were noted.

Dermal/Ocular Effects

- Hood (1966) reported that no compound-related clinical or pathological changes were observed when terbacil was applied to the clipped dorsal skin of rabbits (five males, five females) at a dose level of 5,000 mg/kg (as a 55% aqueous paste), for 5 hours/day, 5 days/week for 3 weeks (15 applications). The parameters observed included body weight, dermal reaction, organ weights and histopathology.

- Reinke (1965) reported that no dermal reactions were observed when terbacil was administered to the intact dorsal skin of 10 guinea pigs as a 15% solution in 1:1 acetone:dioxane containing 13% guinea pig fat.

- Reinke (1965) reported no observed sensitization in ten albino guinea pigs when terbacil was administered nine times during a 3-week period, with half of the animals in each group receiving dermal applications on abraded dorsal skin and the others receiving intradermal injections. After 2 weeks, the animals were challenged by application of terbacil to intact and abraded skin. The challenge application was repeated 2 weeks later.

Long-term Exposure

- Wazeter et al. (1964) administered terbacil, 82.7% (a.i.), in the diet to Charles River pathogen-free albino rats (20/sex/level) at levels of 0, 100, 500 or 5,000 ppm of a.i. for 90 days. This corresponds to doses of about 0, 5, 25 or 250 mg/kg/day based on the dietary assumptions of Lehman (1959). The parameters observed included body weight, food consumption, hematology, liver function tests, urinalyses, organ weights and gross and histologic pathology. No adverse effects with respect to behavior and appearance were noted. All rats survived to the end of the study. No effect on body weight gain was observed in either sex when terbacil was administered at 5 or 25 mg/kg/day. Females administered 250 mg/kg/day gained slightly less weight (15%) than controls. Males at this level showed no effect. No compound-related hematological or biochemical changes were found, and urinalyses were normal at all times. No gross or microscopic pathological changes were noted in animals administered terbacil at 5 or 25 mg/kg/day. Morphological changes in animals receiving the highest dose level were limited to the liver and consisted of statistically significant increases in liver weights. This change was accompanied by a moderate-to-marked hypertrophy of hepatic parenchymal cells associated with vacuolation of scattered hepatocytes. Similar microscopic changes, but with reduced severity, were found in one rat at the 25 mg/kg/day level. This study identified a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 25 mg/kg/day and a No-Observed-Adverse-Effect-Level (NOAEL) of 5 mg/kg/day.

- Goldenthal et al. (1981) administered terbacil (97.8% a.i.) in the diet to CD-1 mice (80/sex/level) at levels of 0, 50, 1,250 or 5,000 to 7,500 ppm for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day; therefore, these levels correspond to doses of about 0, 7.5, 187 or

750 to 1,125 mg/kg/day. The 5,000-ppm dose level was increased slowly to 7,500 ppm by week 54 of the study. Mortality was significantly higher ($p < 0.05$) in mice at the high dosage levels throughout the study. No changes considered biologically important or compound-related occurred in the hematological parameters. An increased incidence of hepatocellular hypertrophy was seen microscopically in male and female mice administered 750 to 1,125 mg/kg/day and in male mice administered 187 mg/kg/day. An increased incidence of hyperplastic liver nodules also occurred in male mice administered 750 to 1,125 mg/kg/day. Female mice from the 187-mg/kg/day group and both male and female mice from the 7.5-mg/kg/day group were free of compound-related microscopic lesions. This study identified a LOAEL of 187 mg/kg/day and a NOAEL of 7.5 mg/kg/day.

- Wazeter et al. (1967b) administered terbacil (80% a.i.) in the diet to CD albino rats (36/sex/level) at levels of 0, 50, 250 or 2,500 ppm to 10,000 ppm of a.i. for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat corresponds to 0.05 mg/kg/day; therefore, these dietary levels correspond to doses of about 0, 2.5, 12.5 or 125 to 500 mg/kg/day. The 2,500 ppm level was increased slowly to 10,000 ppm by week 46 of the study. No adverse compound-related alterations in behavior or appearance occurred in any test group. No significant differences in body weight gain in males and females administered 2.5 or 12.5 mg/kg/day were observed. Rats administered 125 to 500 mg/kg/day exhibited a significantly lower rate of body weight gain. This difference occurred early and became more pronounced with time in the female rats than in the male rats. Maximum differences were 14 to 17% in the male rats and 24 to 27% in the females when compared to the controls. No compound-related gross pathological lesions were seen at necropsy in rats from any groups. The only compound-related variation in organ weights was a slight increase in liver weights among rats from the 125- to 500-mg/kg/day dose level at final sacrifice. Histological changes were observed in the livers of rats fed terbacil at 12.5 mg/kg/day for 1 year and in the high-dose group fed 125 to 500 mg/kg/day for 1 and 2 years. These changes consisted of enlargement and occasional vacuolation of centrilobular hepatocytes. No compound-related microscopic changes were observed in livers or in any tissues examined in rats from the 12.5-mg/kg/day group sacrificed after 2 years. Due to an outbreak of respiratory congestion observed in all study groups at week 27, all animals were placed on antibiotic treatment (tetracycline hydrochloride) at a dose level of 25 mg/kg/day in drinking water for 1 week. In the 29th week, all rats were administered 50,000 units of penicillin G intra-muscularly and 1/16 g of streptomycin. Some rats still exhibiting respiratory congestion were administered a second dose on the following day. This study identified a LOAEL of 125 to 500 mg/kg/day, based on irreversible histological changes in the liver, and a NOAEL of 12.5 mg/kg/day.

- Wazeter et al. (1966) administered terbacil (80% a.i.) in the diet to young purebred beagle dogs (4 to 6 months old, four/ sex/dose) at dose levels of 0, 50, 250 or 2,500 to 10,000 ppm of a.i. for 2 years. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet

of a dog corresponds to 0.025 mg/kg/day; therefore, these dietary levels correspond to approximately 0, 1.25, 6.25 or 62.5 to 250 mg/kg/day. The 2,500-ppm level was gradually increased to 10,000 ppm from week 26 to week 46 of the study. All animals underwent periodic physical examinations, hematologic tests, and determinations of 24-hour alkaline phosphatase, prothrombin time, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyrurate transaminase (SGPT) and cholesterol. No adverse compoundrelated alterations in behavior or appearance occurred among any of the control or treated dogs. No mortalities occurred during the 2-year course of treatment. Although there were some fluctuations in body weight throughout the study, these were not considered to be compound-related. No alterations in hematology, plasma biochemistry or urinalysis were observed. No compound-related gross or microscopic pathological changes were seen in any of the dogs sacrificed after 1 or 2 years of feeding. A slight increase in relative liver weights and elevated alkaline phosphatase occurred in dogs from the 62.5- to 250-mg/kg/day group and the 6.25-mg/kg/day group, which were sacrificed after 1 or 2 years. Also at 6.25 mg/kg/day, there was an increase in thyroid-to-body weight ratio. This study identified a NOAEL of 1.25 mg/kg/day (50 ppm) and a LOAEL of 6.25 mg/kg (250 ppm).

Reproductive Effects

- Wazeter et al. (1967a) administered terbacil (80% a.i.) in the diet to male and female rats of three generations (10 males and 10 females per level per generation) at dietary levels of 0, 50 or 250 ppm of a.i. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of a rat is equivalent to 0.05 mg/kg/day; therefore, these dietary levels correspond to doses of about 2.5 or 12.5 mg/kg/day. Each parental generation was administered terbacil in the diet for 100 days prior to mating. No abnormalities in behavior, appearance or food consumption of the parental rats were observed in any of the three generations. Males at the 12.5 mg/kg/day level in all three generations exhibited reduced body weight gains. Females in all three generations were similar to controls in body weight gain. No abnormalities were observed in the breeding cycle of any of the three generations relative to the fertility of the parental male and female rats, development of the embryos and fetuses, abortions, deliveries, live births, sizes of the litters, viability of the newborn, survival of the pups until weaning or growth of the pups during the nursing period. Gross examination of pups surviving at weaning from both litters of all three generations did not reveal any evidence of abnormalities. No compound-related histopathological lesions were observed in any of the tissues examined from weanlings of the F_{3b} litter. This study identified a NOAEL of 2.5 mg/kg/day and a LOAEL of 12.5 mg/kg/day.

Developmental Effects

- E.I. DuPont (1984a) administered terbacil by gavage as a 0.5% suspension in methyl cellulose to groups of 18 female New Zealand White rabbits (5 months old) from days 7 to 19 of gestation at dose levels

of 0, 30, 200 or 600 mg/kg/day. Maternal mortality was significantly increased ($p \leq 0.05$) at the 600-mg/kg/day level. Additional indicators of maternal toxicity at 600-mg/kg/day were a significant increase ($p \leq 0.05$) in adverse clinical signs (anorexia and liquid or semi-solid yellow, orange or red discharges found below the cages) and a significant decrease ($p < 0.05$) in body weight gain. Mean body weight gains and the incidence of adverse effects were similar in controls and in the 30- and 200-mg/kg/day groups. Fetal toxicity at doses of 600 mg/kg/day included a significant decrease ($p \leq 0.05$) in fetal body weight and a significant increase ($p \leq 0.05$) in the frequency of extra ribs and partially ossified and unossified phalanges and pubes. This increase was not due to a statistically significant increase in any specific malformation, and occurred only at a dosage level that was overtly toxic to the dams, suggesting to the authors that it may be the result of maternal toxicity. No increase in the incidence of adverse effects was noted among fetuses produced by animals administered 30 or 200 mg/kg/day terbacil. Based on maternal and fetal toxicity, this study identified a NOAEL of 200 mg/kg/day and a LOAEL of 600 mg/kg/day.

- Culik et al. (1980) administered terbacil (96.6% a.i.) in the feed to female rats from days 6 to 15 of gestation at levels of 0, 250, 1,250 or 5,000 ppm. Based on the measured food consumption, these dietary levels correspond to doses of about 0, 23, 103 or 391 mg/kg/day. Maternal parameters observed included clinical signs of toxicity and changes in behavior, body weight and food consumption. Statistically significant ($p \leq 0.05$), compound-related reductions in mean body weight, weight gain and food consumption were seen in animals administered 103 or 391 mg/kg/day. No other clinical signs or gross pathological changes were observed in any animals. The mean number of live fetuses per litter and mean final maternal body weight were significantly lower ($p \leq 0.05$) in the groups administered 103 or 391 mg/kg/day than in the control group; the mean number of implantations per litter was also significantly lower ($p \leq 0.05$) than in control animals. Anomalies occurred in the renal pelvis, and ureter dilation was found in all the treatment groups. This study identified a LOAEL of 23 mg/kg/day, based on anomalies of the renal pelvis and ureter dilation.

Mutagenicity

- E.I. DuPont (1984b) reported that terbacil did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes (0.01 and 1.0 uM), did not exhibit mutagenic activity in the CHO/HGPRT assay (0 to 5.0 uM) with or without metabolic activation, and did not produce statistically significant differences between mean chromosome numbers, mean mitotic indices or significant increases in the frequency of chromosomal aberrations when tested by *in vivo* bone marrow chromosome studies in Sprague-Dawley CD rats (15/sex/level) administered a single dose of terbacil by gavage at 0, 20, 100 or 500 mg/kg.

- Murnik (1976) reported that terbacil significantly elevated the rates of apparent dominant lethals when tested in *Drosophila melanogaster*, but the authors concluded that the significant reductions in egg hatch were probably due to physiological toxicity of the treatment,

since genetic assays did not indicate the induction of chromosomal breakage or loss.

Carcinogenicity

- Goldenthal et al. (1981) administered terbacil (97.8% a.i.) in the diet to CD-1 mice (80/sex/level) at levels of 0, 50, 1,250 or 5,000 to 7,500 ppm for 2 years. These levels correspond to doses of about 0, 7.5, 187 or 750 to 1,125 mg/kg/day (Lehman, 1959). The 5,000-ppm dose level was increased slowly to 7,500 ppm by week 54 of the study. The authors reported no increased incidence of cancer in the treated animals.

- Wazeter et al. (1967b) administered terbacil (80% a.i.) in the diet to CD albino rats (36/sex/level) at levels of 0, 50, 250 or 2,500 to 10,000 ppm of active ingredient for 2 years. These levels correspond to doses of about 0, 2.5, 12.5 or 125 to 500 mg/kg/day (Lehman, 1959). The authors reported no evidence of compound-related carcinogenic effects.

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 terbacil. It is, therefore, recommended that the Ten-day HA value for a 10-kg child, 0.24 mg/L (240 ug/L), calculated below, be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The dietary reproductive study in rats by Wazeter et al. (1967a) has been selected to serve as the basis for the Ten-day HA value for terbacil. It identifies a LOAEL of 12.5 mg/L, based on a reduced body weight gain in the males in all three generations, and a NOAEL of 2.5 mg/kg/day, yielding a Ten-day HA of 0.25 mg/L (see calculation below). The teratology study in rats by Culik et al. (1980) provides support for this conclusion. This teratology study identifies a LOAEL of 23 mg/L (no doses lower than 23 mg/kg/day were tested) and essentially the same Ten-day HA value (0.23 mg/L) can be derived from this LOAEL by using an uncertainty factor of 1,000.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(2.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.25 \text{ mg/L } (250 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

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 dietary reproductive study in rats by Wazeter et al. (1967a) has been selected to serve as the basis for the Longer-term HA values for terbacil. A NOAEL of 2.5 mg/kg/day is identified in this study. A 90-day subchronic study in rats (Wazeter et al., 1964) identifying a NOAEL of 5 mg/kg/day supports this conclusion.

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

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.25 \text{ mg/L } (250 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

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:

$$\text{Longer-term HA} = \frac{(2.5 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.875 \text{ mg/L } (875 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of reduced body weight gain in male rats.

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 2-year dog feeding study by Wazeter et al. (1966), selected to serve as the basis for the Lifetime HA value for terbacil, identifies a NOAEL of 1.25 mg/kg/day, based on relative liver weight increases and an increase in alkaline phosphatase. A number of other studies provide information that supports the conclusion that the overall NOAEL for lifetime exposure of rats, mice and dogs to terbacil is less than 25 mg/kg/day. These include a 2-year feeding study in mice that identifies a NOAEL of 7.5 mg/kg/day for liver changes (Goldenthal, 1981) and a 2-year feeding study in rats that identifies a NOAEL of 12.5 mg/kg/day for lower body weight gain and liver effects (Wazeter et al., 1967b).

Using a NOAEL of 1.25 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(1.25 \text{ mg/kg/day})}{(100)} = 0.0125 \text{ mg/kg/day}$$

where:

1.25 mg/kg/day = NOAEL, based on slight increase in relative liver weight and elevated alkaline phosphatase.

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)

$$DWEL = \frac{(0.0125 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.44 \text{ mg/L } (440 \text{ ug/L})$$

where:

0.0125 mg/kg/day = RfD.

70 kg = assumed body weight of adult.

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

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.44 mg/L) (20%) = 0.09 mg/L (90 ug/L)

where:

0.44 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of terbacil.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), terbacil may be classified in Group E: evidence of noncarcinogenicity for humans. This category is used for substances that show no evidence of carcinogenicity in at least two adequate animal tests or in both epidemiologic and animal studies. Studies by Goldenthal et al. (1981) and Wazeter et al. (1967b) reported no induction of any carcinogenic effect in mice or rats, respectively, administered terbacil in the diet for 2 years.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Tolerances have been established for residues of terbacil in or on many agricultural commodities by the U.S. EPA Office of Pesticide Programs (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of terbacil is by a gas chromatographic method applicable to the determination of certain organonitrogen pesticides in water samples (U.S. EPA, 1985b). 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 gas chromatography, and measurement is made with a thermionic bead detector. The method detection limit for terbacil has not been determined.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies currently available have not been tested for their effectiveness in removing terbacil from drinking water.

IX. REFERENCES

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