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CHLORAMBEN

DRAFT

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

I. INTRODUCTION

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

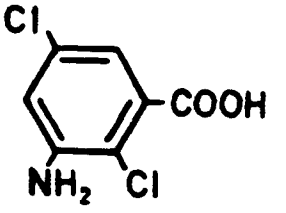
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as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

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

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 133-90-4

Structural Formula:



3-Amino-2-5-dichlorobenzoic acid

Synonyms

- Acp-m-728; Ambiben; Abiben; Amibin; Amoben; Chlorambed; Chlorambene; NCI-C00055 ornamental weeder; Ornamental weeder; Vegaben; Vegiven (U.S. EPA, 1985).

Uses

- Pre-emergent herbicide for weed control (Meister, 1983).

Properties (U.S. EPA, 1985; CHEMLAB, 1985)

Chemical Formula	$C_7H_5O_2NCl_2$
Molecular Weight	206.02
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	200-201°C
Density	--
Vapor Pressure	7×10^{-3} mm Hg (100°C)
Specific Gravity	--
Water Solubility (25°C)	700 mg/L
Log Octanol/Water Partition Coefficient	2.32
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Samples were collected at 5 surface water locations and 188 ground water locations, and chloramben was found in only 1 state. The 85th percentile of all nonzero samples was 2.1 ug/L in surface water and 1.7 ug/L in ground water sources. The maximum concentration found was 2.3 ug/L in surface water and 1.7 ug/L in ground water (STORET, 1987).

Environmental Fate

- Sodium chloramben appears to be resistant to hydrolysis. Limited studies indicate that there is no loss of phytotoxicity when aqueous solutions of chloramben are kept in the dark (Registrant CBI data).

- Photodegradation of aqueous solutions of sodium chloramben appears to occur readily in sunlight. Total loss of phytotoxicity occurs in 2 days. Loss of phytotoxicity on dry soil is somewhat slower, about 30% in 48 hours (Registrant CBI data).

- Soil bacteria bring about a loss of phytotoxicity in sodium chloramben after several weeks. It appears that this is due to a decarboxylation. The rate of reaction appears to be independent of soil pH within the range of 4.3 to 7.5 (Registrant CBI data).

- The mobility of sodium chloramben is governed principally by its high solubility in water and its apparent limited strength of adsorption to soil particles. It appears to easily leach down in most soil types by rainfall (Registrant CBI data).

- Probably all plants grown in contact with sodium chloramben take up the compound. In some plants the subsequent movement of compound away from the roots is very slow, whereas in others it readily spreads throughout the plant. The fate of chloramben in plants includes decomposition, a detoxifying conjugation which proceeds fairly rapidly, and a detoxifying conjugation which goes slowly, if at all (Registrant CBI data).

- The methyl ester of chloramben acid appears to have the expected properties of a carboxylic acid ester. It is apparently not hydrolysed after a short period in contact with water at slightly acid pH values (5 to 6). Bacteria-mediated hydrolysis appears to be quick: approximately 50% of the ester is converted to the free acid in about 1 week when in contact with wet soil. A subsequent and slower bacterial reaction, shown by a loss of phytotoxicity, is probably a decarboxylation, as with sodium chloramben (Registrant CBI data).

- The leaching behavior of the methyl ester is governed by its aqueous solubility, which is much lower than that of the sodium salt (120 ppm and 250,000 ppm, respectively). For a given rainfall the ester seems to leach down about 15% of the distance travelled by the sodium salt (Registrant CBI data).

III. PHARMACOKINETICS

Absorption

- Chloramben is rapidly absorbed from the gastrointestinal tract of Sprague-Dawley female rats (Andrawes, 1984). Based on radioactivity recovered in urine (96.7%) and expired air (0.2%), about 97% of an oral dose (5 uCi/rat) of chloramben is absorbed.

Distribution

- Andrawes (1984) reported low levels (up to 0.5% of the administered dose) of chloramben in liver, kidney, lung, muscle, plasma and red blood cells of rats 96 hours after a single oral dose (by gavage).

Metabolism

- In rats dosed by gavage, Andrawes (1984) reported that the parent compound accounted for 70% of the applied dose in 24-hour urine.
- Andrawes (1984) identified 5 of 24 urinary metabolites: 3-amino-5-chlorobenzoic acid; 3-aminobenzoic acid; 2,5-dihydroxybenzoic acid; 3,5-dihydroxybenzoic acid; and 2,5-dichloroaniline. Together, these constituted 1.4% of the administered dose.
- Metabolism of chloramben in rats proceeded through dechlorination, deamination, decarboxylation and hydroxylation. Metabolism through oxidative ring cleavage was negligible (Andrawes, 1984).

Excretion

- Rats administered chloramben (5 uCi/rat) by gastric intubation excreted over 99% of the dose within 3 to 4 days, mostly within the first 24 hours (Andrawes, 1984). Approximately 96.7% was eliminated in the urine, with lesser amounts in the feces (4.1%) and respiratory gases (0.2%). Only 0.6% remained in the carcass after 3 to 4 days.

IV. HEALTH EFFECTS

Humans

- No information was found in the available literature on the human health effects of chloramben.

Animals

Short-term Exposure

- Acute oral LD_{50} values for chloramben range from 2,101 mg/kg (Field, 1980a) to 5,000 mg/kg (Field, 1978a) in rats; the acute dermal LD_{50} in rabbits has been reported to be >2,000 (Field, 1980b) or >5,000 mg/kg (Field, 1978b).
- Rees and Re (1978) reported an acute (1 hr) LC_{50} of >200 mg/L in rat inhalation studies.
- Keller (1959) fed male Holtzman Sprague-Dawley rats (10/dose) chloramben (100% a.i.) for 28 days in the diet at dose levels of 0, 1,000, 3,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 50, 150 or 500 mg/kg/day. Body weights, food consumption, general appearance

and behavior and histopathology were evaluated. There were no statistically significant differences between the treated rats and untreated controls in any parameter measured. Based on this information, a No-Observed-Adverse-Effect-Level (NOAEL) of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

Dermal/Ocular Effects

- Gabriel (1969) applied chloramben (4 or 8 g/kg) to intact and abraded skin of 16 male albino rabbits (8/dose). Test animals were observed for 14 days. No evidence of skin irritation was observed under conditions of the study.

- In a study by Myers et al. (1982), a 1.0% (w/w) chloramben sodium salt suspension produced little or no sensitization reactions in male albino Hartley guinea pigs.

Long-term Exposure

- In studies by Beliles (1976), weanling Golden Syrian hamsters (12/sex/dose) were administered technical chloramben (purity not specified) at dose levels of 0, 100, 1,000 or 10,000 ppm (reported to be equivalent to 0, 11, 115 or 1,070 mg/kg/day) in the diet for 90 days. Food consumption, body and organ weights and histopathology were evaluated. No treatment-related adverse effects were reported for any parameter evaluated. Based on this information, a NOAEL of 10,000 ppm (1,070 mg/kg/day), the highest dose tested, was identified.

- In an 18-month feeding study (Huntingdon Research Center, 1978; cited in U.S. EPA, 1981), Crl:COBS CD-1 mice (50/sex/dose) were administered technical chloramben (purity not specified) at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 15, 150 and 1,500 mg/kg/day. No compound-related effects were observed in terms of survival, general appearance, behavior or changes in body weight. Statistically significant ($p < 0.05$) changes in organ weights included decreased liver weight in males at 100 ppm, decreased kidney weight in males at 10,000 ppm, and decreased kidney weight in females at 10,000 ppm. Since the values for these observations were within normal ranges for this species and no trends were established, the organ-weight changes were not attributed to compound administration. Histopathological examinations revealed alterations in the livers of all treated mice. The primary hepatocellular reaction was a histomorphological hepatocellular alteration compatible with that observed in enzyme induction. The typical cellular changes included hepatocyte hypertrophy, increased nuclear size and chromatin content, and dense granular eosinophilic cytoplasm. Other changes included scattered foci of individual or small groups of degenerating hepatocytes, hepatocyte vacuolation, cytoplasmic eosinophilic inclusions, and multiple focal small granulomas. Based on the reported hepatic effects, this study identifies a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 100 ppm (15 mg/kg/day).

- NCI (1977) administered technical-grade chloramben (90 to 95% active ingredient) to Osborne-Mendel rats (50/sex/dose) and B6C3F$_1$ mice (50/sex/dose) for 80 weeks at dietary levels of 10,000 or 20,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day and 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day for rats and 1,500 or 3,000 mg/kg/day for mice. Matched controls consisted of 10 animals per sex for each species. Pooled controls consisted of the matched controls plus 75 rats/sex and 70 mice/sex from similarly performed bioassays. Body weights and mortality did not differ between control and treatment groups for both species, and the various (unspecified) clinical signs observed were similar in the control and treatment groups for both species. Based on this information, a NOAEL of 20,000 ppm (1,000 mg/kg/day for rats and 3,000 mg/kg/day for mice), the highest dose tested, was identified for each species.

- In studies conducted by Paynter et al. (1963), albino rats (35/sex/dose) were administered chloramben (97% pure) in the diet for 2 years at dose levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 5, 50 or 500 mg/kg/day. Untreated rats (70/sex/dose) were observed concurrently. The general appearance and behavior, growth, food consumption, clinical chemistry, hematology and histopathology in the treated rats did not differ significantly from the untreated controls. Based on this information, a NOAEL of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

- Hazleton and Farmer (1963) administered technical chloramben (97% pure) in the feed to 16 young adult beagle dogs (4/sex/dose) for 2 years at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 2.5, 25 or 250 mg/kg/day. General appearance and behavior, food consumption, body weight, hematology, biochemistry, urinalysis and histopathology of the treated dogs did not differ significantly from the untreated controls. Based on this information, a NOAEL of 10,000 ppm (250 mg/kg/day), the highest dose tested, was identified.

- Johnston and Seibold (1979) administered technical chloramben to Sprague-Dawley rats for 2 years at dietary concentrations of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959) this corresponds to doses of 0, 5, 50 and 500 mg/kg/day. No compound-related effects were observed on any parameters measured including body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology and histopathology. Based on this information, a NOAEL of 10,000 ppm (500 mg/kg/day), the highest dose tested, was identified.

Reproductive Effects

- In a three-generation study (Gabriel, 1966), three groups of albino rats (8 females and 16 males/dose) were administered 0, 500, 1,500 or

4,500 ppm chloramben (purity not specified) in the diet for 9 weeks prior to breeding, during breeding and during weaning periods. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these dietary levels correspond to doses of about 0, 25, 75 or 225 mg/kg/day. Untreated animals served as controls. Following treatment, various parameters were measured, including indices of fertility, gestation, viability and lactation. No adverse effects were reported in any parameter measured. Based on this information, a NOAEL of 4,500 ppm (225 mg/kg/day), the highest dose tested, was identified for reproductive effects.

Developmental Effects

- Beliles and Mueller (1976) administered technical chloramben (purity not specified) to pregnant CFE rats (20/dose) by incorporation into the diets on days 6 through 15 of gestation. No compound-related changes were seen among dams treated at levels of 0, 500, 1,500 and 4,500 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 25, 75 or 225 mg/kg/day. Fetal mortality was increased, and data suggestive of decreased fetal skeletal development were observed in fetuses from dams treated at 4,500 ppm (225 mg/kg/day). At 1,500 ppm (75 mg/kg/day), there was no significant increase in embryo mortality; however, there was a generalized reduction in skeletal development. Fetuses of dams treated with 500 ppm (25 mg/kg/day) were similar in all respects to those of untreated control dams. Based on this information, a NOAEL of 4,500 ppm (225 mg/kg/day), the highest dose tested, was identified for maternal toxicity and teratogenicity. The NOAEL for fetotoxicity was identified as 500 ppm (25 mg/kg/day).

- Holson (1984) conducted studies in which New Zealand White rabbits (24/dose) were administered chloramben (sodium salt, 83% a.i. by weight) by gavage at dose levels of 0, 250, 500 or 1,000 mg/kg during days 6 through 18 of gestation. A NOAEL of 1,000 mg/kg/day, the highest dose tested, was identified, since the test compound did not produce maternal or fetal toxicity or teratogenic effects at any dose level tested. Other end points were not monitored.

Mutagenicity

- Chloramben was found to be negative in several indicator systems for potential mutagenic activity, including several microbial assays (Anderson et al., 1967; Eisenbeis et al., 1981; Jagannath, 1982), an *in vivo* bone marrow cytogenetic assay (Ivett, 1985) and primary rat hepatocytes unscheduled DNA synthesis test (Myhr and McKeon, 1982).

- Results were positive for the *in vitro* cytogenic test using Chinese hamster ovary cells (Galloway and Lebowitz, 1982).

Carcinogenicity

- In an 18-month feeding study (Huntingdon Research Center, 1978; cited in U.S. EPA, 1981), Crl:COBS CD-1 mice (50/sex/dose) were administered

technical chloramben (purity not specified) at dietary levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 15, 150 and 1,500 mg/kg/day (Lehman, 1959). Hepatocellular carcinomas (trabecular type) were present in 1/50 low-dose and 1/50 high-dose males. In no case was vascular invasion or secondary spread of the nodular carcinoma masses observed. Hepatocellular adenomas were present only in males as follows: 5/50 control, 2/50 low-dose, 2/48 intermediate-dose and 5/50 high-dose. However, due to a number of deficiencies in this study (e.g., missing data, significant tissue autolysis), no conclusion can be made regarding the oncogenic potential of the test material.

- NCI (1977) administered 10,000 or 20,000 ppm technical chloramben (90 to 95% active ingredient) in the feed to Osborne-Mendel rats (50/sex/dose) and B6C3F_1 mice (50/sex/dose) for 80 weeks followed by up to 33 weeks of postexposure observation. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day and 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day for rats and 1,500 or 3,000 mg/kg/day for mice. Under conditions of the study, no compound-related tumors were reported in male or female rats or male mice. Hepatocellular carcinomas were reported in female mice, but in a retrospective audit of this bioassay by Drill et al. (1982), it was reported that the incidence of hepatocellular carcinomas in both the low-dose and high-dose female mice was lower than the maximal incidence of corresponding tumors in historical groups. It was concluded that there was no association between chloramben and the occurrence of hepatocellular carcinomas under conditions of the assay. However, since exposure was for only 80 weeks, this study may not have been adequate to detect late-occurring tumors.

- Paynter et al. (1963) reported no evidence of carcinogenic activity in albino rats (35/sex/dose) that received chloramben (97% pure) in the diet for 2 years at dose levels of 0, 100, 1,000 or 10,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959) this corresponds to doses of 0, 5, 50 or 500 mg/kg/day.

- Johnston and Seibold (1979) reported no evidence of carcinogenic activity in Sprague-Dawley rats administered 0, 100, 1,000 or 10,000 ppm technical chloramben in the diet for 2 years. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 0, 5, 50 or 500 mg/kg/day. No compound-related effects were observed on any other parameters measured, including body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology and histopathology.

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 data were found in the available literature that were suitable for determination of the One-day HA value. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (2.5 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rat teratology study by Beliles and Mueller (1976) has been selected to serve as the basis for determination of the Ten-day HA value for a 10-kg child for chloramben. In this study, a NOAEL of 225 mg/kg/day, the highest dose tested, was identified for maternal toxicity and teratogenicity while a NOAEL of 25 mg/kg/day was identified for fetotoxicity (skeletal development) in rats exposed on days 6 to 15 of gestation. There is some question as to whether it is appropriate to base a Ten-day HA for the 10-kg child on fetotoxicity observed in a teratology study. However, this study is of appropriate duration and the fetus may be more sensitive than the 10-kg child.

The studies by Keller (1959) and Holson (1984) have not been selected, since the NOAEL values identified in these studies (500 and 1,000 mg/kg/day, respectively) are much higher than the NOAEL identified by Beliles and Mueller (1976).

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

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

where:

25 mg/kg/day = NOAEL, based on the absence of systemic toxic effects in rats fed chloramben for 10 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 Advisories

No data were found in the available literature that were suitable for the determination of the Longer-term HA. It is, therefore, recommended that an adjusted DWEL for a 10-kg child (0.15 mg/L - 150 ug/L) and the DWEL for a 70-kg adult (0.525 mg/L - 525 ug/L) be used at this time for the Longer-term HA values.

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 18-month feeding study by the Huntingdon Research Center (1978; cited in U.S. EPA, 1981) has been selected to serve as the basis for determination of the Lifetime HA for chloramben. In this study, Crl:COBS CD-1 mice were administered technical chloramben at dietary levels of 0, 100, 1,000 or 10,000 ppm (0, 15, 150 or 1,500 mg/kg/day). Hepatocellular alterations were observed in mice in all treatment groups, and a LOAEL of 100 ppm (15 mg/kg/day) was identified. Other studies of appropriate duration identify NOAELs that are higher than the LOAEL of 15 mg/kg/day. For example, Hazleton and Farmer (1963) identified a NOAEL of 250 mg/kg/day in a 2-year study in dogs, and both Paynter et al. (1963) and Johnston and Siebold (1979) identified a NOAEL of 500 mg/kg/day in 2-year rat studies.

Using the LOAEL of 15 mg/kg/day, the Lifetime HA for chloramben is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(15\ mg/kg/day)}{(1,000)} = 0.015\ mg/kg/day$$

where:

15 mg/kg/day = LOAEL, based on hepatic effects in mice exposed to chloramben via the diet for 18 months.

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

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

$$DWEL = \frac{(0.015\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.525\ mg/L\ (525\ ug/L)$$

where:

0.015 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 = (0.525 mg/L) (20%) = 0.105 mg/L (105 ug/L)

where:

0.525 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- NCI (1977) evaluated the carcinogenic potential of orally administered chloramben (10,000 or 20,000 ppm, equivalent to 500 or 1,000 mg/kg/day) to Osborne-Mendel rats (50/sex/dose) and B6C3F$_1$ mice (20/sex/dose) for 80 weeks. It was concluded in a retrospective audit of this assay (Drill et al., 1982) that under conditions of this study, chloramben is not carcinogenic. Since exposure was for only 80 weeks, this experiment may not have been adequate to detect late-occurring tumors. Johnston and Seibold (1979) reported no evidence of carcinogenic activity in Sprague-Dawley rats that received chloramben in the diet for 2 years at concentrations up to 500 mg/kg/day. The Huntingdon Research Center (1978; cited in U.S. EPA, 1981) reported no evidence of carcinogenicity in Crl:COBS CD-1 mice that received chloramben in the diet for 18 months at concentrations up to 1,500 mg/kg/day. However, due to a number of deficiencies in this study, no conclusion can be made regarding the oncogenic potential

of the test material. Paynter et al. (1963) reported no evidence of carcinogenicity in albino rats that received chloramben in the diet for 2 years at concentrations up to 500 mg/kg/day.

- The International Agency for Research on Cancer has not evaluated the carcinogenicity of chloramben.

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

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS has determined an Acceptable Daily Intake of 0.25 mg/kg/day with a Suggested-No-Adverse-Effect-Level of 1.75 mg/L (U.S. EPA, 1985).

- The U.S. EPA has established a residue tolerance for chloramben in or on raw agricultural commodities of 0.1 ppm (CFR, 1985).

VII. ANALYTICAL METHODS

- Chloramben may be analyzed using a gas chromatographic (GC) method applicable to the determination of chlorinated acids, ethers and esters in water samples (U.S. EPA, 1986b). 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 as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron-capture (EC) gas chromatography. The method detection limit has not been determined for this compound.

VIII. TREATMENT TECHNOLOGIES

- No data were found for the removal of chloramben from drinking water by conventional treatment.

- No data were found for the removal of chloramben from drinking water by activated carbon treatment. However, due to its low solubility and its high molecular weight, chloramben probably would be amenable to activated carbon adsorption.

- No data were found for the removal of chloramben from drinking water by ion exchange. However, chloramben is an acidic pesticide and these compounds have been readily adsorbed in large amounts by ion exchange resins. Therefore, chloramben probably would be amenable to an ion exchange.

- No data were found for the removal of chloramben from drinking water by aeration. However, the Henry's Coefficient can be estimated from available data on solubility (700 mg/L at 25°C) and vapor pressure (7×10^{-3} mm Hg at 100°C). Due to its estimated Henry's Coeeficient of 0.15 atm, chloramben probably would not be amenable to aeration or air stripping.

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