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DIPHENAMID

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.

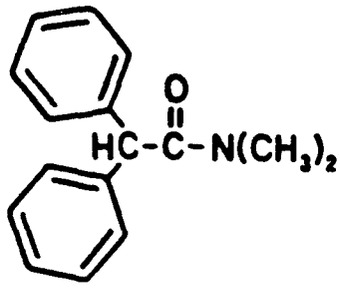
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 957-51-7

Structural Formula



N,N-dimethyl-alpha-phenyl-benzeneacetamide

Synonyms

- Dymid; Enide (Meister, 1983).

Uses

- Pre-emergent and selective herbicide for tomatoes, peanuts, alfalfa, soybean, cotton and other crops (Meister, 1986).

Properties (Windholz et al., 1983)

Chemical Formula	$C_{16}H_{17}ON$
Molecular Weight	239.30
Physical State (at 25°C)	White crystalline solid
Boiling Point	--
Melting Point	135°C
Density	--
Vapor Pressure (25°C)	--
Specific Gravity	--
Water Solubility (27°C)	260 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Diphenamid has not been found in any of the water samples collected and analyzed from 567 ground water locations (STORET, 1987).

Environmental Fate

- Diphenamid is stable to hydrolysis at pH 5, 7 and 9 for 7, 12 and 10 days, respectively, at elevated temperature (49°C or 120°F) (NOR-AM, 1986).

- Diphenamid is intermediately mobile (class 3) on silt loam and silty clay loam soil TLC plates; on sandy loam, it is in class 5, indicating that it would leach readily in this soil (Helling and Turner, 1968).

III. PHARMACOKINETICS

Absorption

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

Distribution

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

Metabolism

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

Excretion

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

IV. HEALTH EFFECTS

Humans

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

Animals

Short-term Exposure

- RTECS (1985) reported the acute oral LD_{50} values in the rat, mouse, dog, monkey and rabbit to be 600, 700, 1,000, 1,000 and 1,500 mg/kg, respectively.

Dermal/Ocular Effects

- Weddon and Brown (1976) applied a 90% wettable powder formulation of diphenamid to intact or abraded skin of New Zealand rabbits (two/sex/dose) for 24 hours at 0, 200, 1,000 or 2,000 mg/kg. No adverse responses were observed in any of the exposed animals.

Long-term Exposure

- Woodard et al. (1966b) administered technical diphenamid (purity not specified) in the feed to beagle dogs (three/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 103 weeks. No pathological effects were reported at 3 mg/kg/day for clinical chemistry, hematology, urinalysis, gross pathology and histopathology. Liver weights were slightly increased in the 10- and 30-mg/kg/day dosage groups of both sexes, and there were slight increases in numbers of portal macrophages and/or fibroblasts when compared to untreated controls. Liver enzyme levels were normal in all treated groups, except for elevation of serum glutamic-oxaloacetic transaminase (SGOT) after 8 weeks in one female dosed with 3 mg/kg/day. A No-Observed-Adverse-Effect-Level (NOAEL) of 3 mg/kg/day and a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 10 mg/kg/day were identified by this study.

- Hollingsworth et al. (1966) fed technical diphenamid (>98% pure) to rats (30/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 101 weeks. A slight increase in the mean absolute liver weights of males and the relative liver and thyroid weights of females in the high-dose groups was observed. No other adverse effects were reported at 10 mg/kg/day or less in general behavior, feed consumption, body and organ weights, hematology, gross pathology and histopathology. A NOAEL of 10 mg/kg/day was identified by this study.

Reproductive Effects

- In a three-generation reproduction study, Woodard et al. (1966a) supplied diphenamid to albino rats (10 males and 20 females/dose) at dose levels of 0, 10 or 30 mg/kg/day. No reproductive or pathological effects were observed for the parental generations (F_0, F_{1b}, F_{2b}) at any dose tested. Weanlings of the F_{3b} generation dosed with 30 mg/kg/day showed reversible liver changes, including slight congestion, glycogen depletion and irregular size of the hepatocytes. Based on reproductive end points, this study identifies a NOAEL of 30 mg/kg/day. Based on fetal toxicity, a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/kg/day are identified.

Developmental Effects

- Woodard et al. (1966a) reported no developmental effects in rat pups at any dose level. Reversible liver changes were observed in weanling pups of the F_{3b} generation dosed with 30 mg/kg/day. A NOAEL based on fetotoxicity of 10 mg/kg/day can be identified.

Mutagenicity

- Moriya et al. (1983) reported that diphenamid (up to 5,000 ug/plate) did not increase reversion frequency in *S. typhimurium* or *E. coli* test systems, either with or without metabolic activation.

- Shirasu et al. (1976) reported that diphenamid (1%) was not mutagenic in a recombination assay utilizing *B. subtilis* or in reversion assays with *E. coli* or *S. typhimurium*.

Carcinogenicity

- In a 2-year feeding study in rats by Hollingsworth et al. (1966), diphenamid was administered to albino rats (30/sex/dose) at dose levels of 0, 3, 10 or 30 mg/kg/day for 101 weeks. Based on histopathological examination of a variety of tissues and organs, the authors reported that the type and incidence of neoplasms were comparable in treated and control rats.

- In a 2-year feeding study in dogs by Woodard et al. (1966b), diphenamid was administered in the feed to beagle dogs (three/sex/dose) at dosage levels of 0, 3, 10 or 30 mg/kg/day for 103 weeks. Histopathological examinations were performed on a variety of tissues and organs, and no evidence of increased tumor frequency was reported.

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 diphenamid. It is therefore recommended that the Drinking Water Equivalent Level (DWEL), adjusted for a 10-kg child (0.3 mg/L, calculated below), be used at this time as a conservative estimate of the One-day HA value.

For a 10-kg child, the adjusted DWEL is calculated as follows:

$$DWEL = \frac{(0.03 \text{ mg/kg/day}) \ (10 \text{ kg})}{(1 \text{ L/day})} = 0.3 \text{ mg/L}$$

where:

0.03 mg/kg/day = RfD (see Lifetime Health Advisory Section).

10 kg = assumed body weight of a child.

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

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of the Ten-day HA value for diphenamid. It is therefore recommended that the DWEL, adjusted for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA value for diphenamid. It is therefore recommended that the DWEL value, adjusted for a 10-kg child (0.3 mg/L) be used at this time as a conservative estimate of the Longer-term HA value.

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 feeding study in dogs by Woodard et al. (1966b) has been selected to serve as the basis for determination of the Lifetime HA value for diphenamid. In this study, dogs were administered technical diphenamid (0, 3, 10 or 30 mg/kg/day) in the diet for 103 weeks. Based on clinical chemistry, hematology, urinalysis, gross pathology and histopathology, this study identified a NOAEL of 3 mg/kg/day and a LOAEL of 10 mg/kg/day. The study by Hollingsworth et al.

(1966), which identified a NOAEL of 10 mg/kg/day in a 101-week experiment in rats, was not selected, since the rat appears to be somewhat less sensitive than the dog (the NOAEL in the rat is the same as the LOAEL in the dog).

Using a NOAEL of 3 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(3\ mg/kg/day)}{(100)} = 0.03\ mg/kg/day$$

where:

3 mg/kg/day = NOAEL, based on absence of organ weight loss, clinical chemistry, hematology, urinalysis, gross pathology and histopathology in dogs exposed to diphenamid via the diet for 103 weeks.

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)

$$DWEL = \frac{(0.03\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 1.0\ mg/L\ (1{,}000\ ug/L)$$

where:

0.03 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 = (1.0 mg/L) (20%) = 0.2 mg/L (200 ug/L)

where:

1.0 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic potential was detected in rats (30/sex/dose) fed diphenamid in the diet for 2 years at a dose level of 30 mg/kg/day (Hollingsworth et al., 1966), or in dogs (three/sex/dose) fed diphenamid in the diet for 2 years, also at a dose of 30 mg/kg/day (Woodward et al., 1966b). These studies are limited by the low doses and the small number of animals employed.

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

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

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Tolerances in or on raw agricultural commodities of 0.01 ppm for milk to 2 ppm for peanut hay and forage have been set for diphenamid (U.S. EPA, 1985).

VII. ANALYTICAL METHODS

- Analysis of diphenamid is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for diphenamid but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular activated carbon (GAC) adsorption will remove diphenamid from water.

- Whittaker (1980) experimentally determined adsorption isotherms for diphenamid on GAC.

- Whittaker (1980) reported the results of GAC columns operating under bench-scale conditions. At a flow rate of 0.8 gpm/sq ft and an empty bed contact time of 6 minutes, diphenamid breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 500 bed volumes (BV). When two bi-solute diphenamid solutions were passed over the same column, diphenamid breakthrough occurred after 235 BV for diphenamid-propham solution and after 290 BV for diphenamid-fluometuron solution.

- GAC adsorption appears to be the most effective treatment technique for the removal of diphenamid from contaminated water. However, selection of individual or combinations of technologies to attempt diphenamid removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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