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GLYPHOSATE

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.

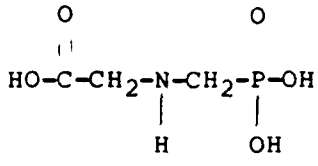
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 1071-83-6

Structural Formula



Glycine, N-(Phosphonomethyl)

Synonyms

Rodeo®; Roundup®.

Uses

- Herbicide for control of grasses, broad leaved weeds and woody brush (U.S. EPA, 1986b).

Properties (Meister, 1983)

Chemical Formula	$C_3H_8NO_5P$
Molecular Weight	169.07
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	200°C
Density	1.74
Vapor Pressure	--
Water Solubility	10 g/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Glyphosate has been found in none of the surface water samples and in only 1 of the ground water samples (in the state of California) analyzed from 64 samples taken at 61 locations (STORET, 1987).

Environmental Fate

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) and aminomethylphosphonic acid were stable in sterile buffered water at pH 3, 6, and 9 during 35 days of incubation in the dark at 5 and 35°C (Brightwell and Malik, 1978).

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) was adsorbed to Drummer silty clay loam, Ray silt, Spinks sandy loam,

Lintonia sandy loam, and Cattail Swamp sediment with Freundlich-K values of 62, 90, 70, 22, and 175, respectively (Brightwell and Malik, 1978). For each soil preparation, the maximum percentages of applied glyphosate desorbed were 5.3, 3.7, 3.6, 11.5, and 0.9%, respectively. At concentrations ranging from 0.21 to 50.1 ppm, ^{14}C-Glyphosate was highly adsorbed to five soils, with organic matter contents ranging from 2.40 to 15.50% (Monsanto Company, 1975). Adsorption of glyphosate ranged from 71 (Soil E, 2.4% organic matter, pH 7.29) to 99% (Soil C, 15.5% organic matter, pH 5.35).

- ^{14}C-Glyphosate (94% glyphosate, 5.9% aminomethylphosphonic acid) was slightly mobile to relatively immobile, with less than 7% of the applied ^{14}C detected in the leachate from 30-cm silt, sand, clay, sandy clay loam, silty clay loam, and sandy loam soil columns eluted with 20 inches of water (Brightwell and Malik, 1978). Aged (30 days) ^{14}C-glyphosate residues were relatively immobile in silt, clay and sandy clay loam soils with less than 2% of the radioactivity detected in the leachate following elution with 20 inches of water. Both glyphosate and aminomethylphosphonic acid were detected in the leachate of aged and un-aged soil columns.

III. PHARMACOKINETICS

Absorption

- Feeding studies with chickens, cows and swine showed that ingestion of up to 75 ppm glyphosate resulted in nondetectable glyphosate residue levels (<0.05 ppm) in muscle tissue and fat (Monsanto Company, 1983). The duration of exposure was not reported in this report. Glyphosate residue levels were not detectable (<0.025 ppm) in milk and eggs from cows and chickens on diets containing glyphosate.

Distribution

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

Metabolism

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

Excretion

- After a single oral or intraperitoneal dose, less than 1% of the administered dose was retained after 120 hours of treatment (U.S. EPA, 1986b). In rats fed 1, 10 or 100 ppm of ^{14}C-glyphosate for 14 days, a steady-state equilibrium between intake and excretion of label was reached within about 8 days. The amount of radioactivity excreted in the urine decreased rapidly after withdrawal of treatment. Ten days after withdrawal, radioactivity was detectable in the urine and feces of rats fed 10 or 100 ppm of the test diet. Minimal residues

of 0.1 ppm or less remained in the tissues of high-dose rats after 10 days of withdrawal. No single tissue showed a significant difference in the amount of label retained.

IV. HEALTH EFFECTS

Humans

° No information on the health effects of glyphosate in humans was found in the available literature.

Animals

Short-term Exposure

° An oral LD_{50} of 5,600 mg/kg in the rat is reported for glyphosate (Monsanto Company, 1982a).

° Bababunmi et al. (1978) reported that daily intraperitoneal administration of 15, 30, 45 or 60 mg/kg to rats for 28 days resulted in reduced daily body weight gain, decreased blood hemoglobin, decreased red blood cell count and hematocrit values and elevated levels of serum glutamic-pyruvic transaminase and leucine-amino peptidase during the experimental period. The investigators did not specify the dose levels at which these effects were observed.

Dermal/Ocular Effects

° A dermal LD_{50} for glyphosate in the rabbit was reported to be >5,000 mg/kg (Monsanto Company, 1982a).

Long-term Exposure

° In subchronic studies reported by the Weed Science Society of America (1983), technical-grade glyphosate was fed to rats at dietary levels of 20, 60 or 200 mg/kg/day and to dogs at 50, 150 or 500 mg/kg/day for 90 days. Mean body weights, food consumption, behavioral reactions, mortality, hematology, blood chemistry and urinalysis did not differ significantly from controls. There were no relevant gross or histopathological changes. No other details or data were provided.

° Bio/dynamics, Inc. (1981a) conducted a study in which glyphosate was administered in the diet to four groups of Sprague-Dawley rats (50/sex/dose) at dose levels of 0, 3.1, 10.3 or 31.5 mg/kg/day to males or 0, 3.4, 11.3 or 34.0 mg/kg/day to females. After 26 weeks, body weight, organ weight, organ-to-body weight ratios and hematological and clinical chemistry parameters were evaluated. No significant differences between control and exposed animals were observed at any dose level.

Reproductive Effects

- Bio/dynamics, Inc. (1981b) investigated the reproductive toxicity of glyphosate in rats. The glyphosate (98.7% purity) was administered in the diet at dose levels of 0, 3, 10 or 30 mg/kg/day to Charles River Sprague-Dawley rats for three successive generations. Twelve males and 24 females (the F_0 generation) were administered test diets for 60 days prior to breeding. Administration was continued through mating, gestation and lactation for two successive litters (F_{1a}, F_{1b}). Twelve males and 24 females from the F_{1b} generation were retained at weaning for each dose level to serve as parental animals for the succeeding generation. The following indices of reproductive function were measured: fetal, pup and adult survival; parental and pup body weight; food consumption; and mating, fertility or gestation. Necropsy and histopathologic evaluation were performed as well. No compound-related changes in these parameters were observed when compared to controls, although an addendum to the pathological report for this study reported an increase in unilateral focal tubular dilation of the kidney in the male F_{3b} pups when compared to concurrent controls. Based on data from this study, the authors concluded that the highest dose tested (30 mg/kg/day) did not affect reproduction in rats under the conditions of the study.

Developmental Effects

- Glyphosate was also administered to pregnant rabbits (route not specified) at dose levels of 75, 175 or 350 mg/kg/day on days 6 through 27 of gestation (Monsanto Company, 1982a). No evidence of fetal toxicity or birth defects in the offspring was observed. However, at dose levels of 350 mg/kg/day, death, soft stools, diarrhea and nasal discharge were observed in the animals.

Mutagenicity

- The Monsanto Company (1982a) reported that glyphosate did not cause mutation in microbial test systems. A total of eight strains (seven bacterial and one yeast), including five Salmonella typhimurium strains and one strain of Bacillus subtilis, Escherichia coli and Saccharomyces cerevisiae, were tested. No mutagenic effects were observed in any strain.

- Njagi and Gopalan (1980) found that glyphosate did not induce reversion mutations in Salmonella typhimurium histidine auxotrophs.

Carcinogenicity

- Bio/dynamics, Inc. (1981b) conducted a study to assess the oncogenicity of glyphosate (98.7% purity). The chemical was given in the diet to four groups of Sprague-Dawley rats at dose levels of 0, 3.1, 10.3 or 31.5 mg/kg/day to males or 0, 3.4, 11.3 or 34.0 mg/kg/day to females. After 26 weeks, animals were sacrificed and tissues were examined for histological lesions. A variety of benign and malignant tumors were observed in both the treated and control groups, the most common tumor

occurring in the pituitary of both sexes and in the mammary glands of females. The total number of rats of both sexes that developed tumors (benign and malignant) was 72/100 (low dose), 79/100 (mid dose), 85/100 (high dose) and 87/100 (control). An increased rate of interstitial cell tumors of the testes was reported in the high-dose males when compared to concurrent controls (6/50 versus 0/50), but this was not considered to be related to compound administration. Based on the data from this study, the authors concluded that the highest dose level tested (31.5 and 34.0 mg/kg/day for males and females, respectively) was not carcinogenic in rats.

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 glyphosate. It is, therefore, recommended that the Ten-day HA value be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The teratology study in pregnant rabbits has been selected to serve as the basis for determination of the Ten-day HA for the 10-kg child. In this study, pregnant rabbits that received glyphosate at dose levels of 0, 75, 175 or 350 mg/kg/day on days 6 through 27 of gestation showed effects at 350 mg/kg/day; however, no treatment-related effects were reported at lower dose levels. The No-Observed-Adverse-Effect-Level (NOAEL) identified in this study is, therefore, 175 mg/kg/day. While a developmental end point may not be the most appropriate basis for derivation of an HA for a 10-kg child, use of this study provides an extra margin of safety.

Using a NOAEL of 175 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(175 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 17.50 \text{ mg/L } (17{,}500 \text{ ug/L})$$

where:

175 mg/kg/day = NOAEL, based on absence of altered physical changes and mortality in rabbits.

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

No information was found in the available literature that was suitable for determination of the Longer-term HA value for glyphosate. It is, therefore, recommended that the adjusted DWEL for a 10-kg child 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 study by Bio/dynamics (1981b) has been selected to serve as the basis for determination of the Lifetime HA value for glyphosate. In this study, the reproductive toxicity of glyphosate in rats was investigated over

three generations. Even though no compound-related changes in the reproductive indices were observed when compared to controls at a dose level of 30 mg/kg/day, there were pathological changes of renal focal tubular dilation in male F_{3b} weanling rats at this level. Therefore, the lower dose level of 10 mg/kg/day was identified as the NOAEL.

Using a NOAEL of 10 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10 \text{ mg/kg/day})}{(100)} = 0.1 \text{ mg/kg/day}$$

where:

10 mg/kg/day = NOAEL, based on absence of renal focal tubular dilation in rats.

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)

$$DWEL = \frac{(0.1 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 3.5 \text{ mg/L } (3{,}500 \text{ ug/L})$$

where:

0.1 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 = (3.5 mg/L) (20%) = 0.70 mg/L (700 ug/L)

where:

3.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

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

- The evidence of carcinogenicity in animals is considered equivocal by the Science Advisory Board (Pesticides), and has been classified in Category D [Office of Pesticide Programs has requested the manufacturer to conduct another study in animals (U.S. EPA, 1986)].

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No other criteria, guidelines or standards were found in the available literature pertaining to glyphosate.

- Tolerance of 0.1 ppm has been established for the combined residues of glyphosate and its metabolite in or on raw agricultural commodities (U.S. EPA, 1985a).

VII. ANALYTICAL METHODS

- Analysis of glyphosate is by a high-performance liquid chromatographic (HPLC) method applicable to the determination of glyphosate in water samples (U.S. EPA, 1985B). In this method, a known volume of sample is applied to a Bio-Rad prefilled AG 50W-X8 column. The column effluent is injected via an auto injector onto a primary column packed with a cation exchange resin, but used in an anion-exclusion mode to eliminate interferences. The effluent from this column flows onto a strong anion-exchange column where the analytical separation is accomplished. Detection and quantitation are made with a spectrophotometer at 570 nm. The method detection limit for glyphosate is 5 ug/L.

VIII. TREATMENT TECHNOLOGIES

- No information was found in the available literature on treatment technologies capable of effectively removing glyphosate from contaminated water.

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*Confidential Business Information submitted to the Office of Pesticide Programs.