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MALEIC HYDRAZIDE

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.

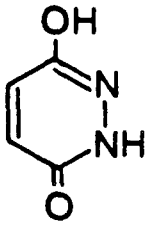
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 123-33-1

Structural Formula



1,2-Dihydro-3,6-pyridazinedione

Synonyms

- Antergon; Chemform; De-Sprout; Retard; Slo-Gro; Sucker-Stuff; (Meister, 1983).

Uses

- Plant growth retardant (Meister, 1983).

Properties (Meister, 1983; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_4H_4O_2N_2$
Molecular Weight	112.09
Physical State (25°C)	Crystalline solid
Boiling Point	--
Melting Point	292°C
Density	1.60
Vapor Pressure (50°C)	0 mm Hg
Specific Gravity	--
Water Solubility (25°C)	6,000 mg/L
Log Octanol/Water Partition Coefficient	-3.67 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No information was found in the available literature on the occurrence of maleic hydrazide.

Environmental Fate

- Maleic hydrazide is very soluble in water (6,000 ppm) and in most organic solvents (>1,000 ppm). The vapor pressure is essentially zero (Registrant CBI data; WSSA, 1983).

- Salts of maleic hydrazide will dissociate in solutions above pH 4.5 and exist only as maleic hydrazide. Maleic hydrazide is stable to hydrolysis at pHs of 3, 6 and 9. Photolysis potential has not been addressed (Registrant CBI data; WSSA, 1983).

- In field dissipation studies using various soils from the eastern, southern and midwestern U.S., the half-lives were reported to be between 14 and 100 days. There is no pattern, but the half-life may be related to organic matter content. Degradation by soil micro-organisms appears to be rapid (Registrant CBI data; WSSA, 1983).

- There is some indication that maleic hydrazide is highly mobile in unaged soils. Aerobic aging of maleic hydrazide results in a lowering of leaching potential (Registrant CBI data; WSSA, 1983).

III. PHARMACOKINETICS

Absorption

- Mays et al. (1968) administered single oral doses of ^{14}C-labeled maleic hydrazide to rats. After 6 days, only 12% had been excreted in the feces, indicating that 88% had been absorbed.

Distribution

- Kennedy and Keplinger (1971) administered ^{14}C-labeled maleic hydrazide to pregnant rats in daily doses of either 0.5 or 5.0 mg/kg. Fetuses from dams sacrificed on day 20 were found to contain label equivalent to 20 to 35 ppb of the parent compound at the 0.5-mg/kg dose level, and 156 to 308 ppb at the 5.0-mg/kg dose level. Pups from females that were allowed to litter were sacrificed at 8 and at 24 hours, and stomach coagulum was analyzed to determine transfer through the milk. At the 0.5 mg/kg dose, the coagulum contained 4 to 7 ppb at 8 hours and 2 ppb at 24 hours; at the 5.0 mg/kg dose, the figures for 8 and 24 hours were 79 to 89 ppb and 7 to 8 ppb, respectively. These results showed that maleic hydrazide crossed the placenta and was also transmitted to the pups via the milk.

Metabolism

- Barnes et al. (1957) reported that rabbits administered a single oral dose of 100 mg/kg of maleic hydrazide excreted 43 to 62% of the dose, unchanged, within 48 hours. The route of excretion (urinary or fecal) was not stated. The results were similar following a dose of 2,000 mg/kg, and no glucuronide or ethereal sulfate conjugates were found.

- Oral administration of maleic hydrazide labeled with ^{14}C to rats resulted in excretion of 0.2% labeled carbon dioxide in the expired air over a 6-day observation period (Mays et al., 1968). Urinary products (77% of the total dose) were largely unchanged maleic hydrazide (92 to 94% of the urinary total) and conjugates of maleic hydrazide (6 to 8%).

Excretion

- Mays et al. (1968) administered single oral doses of ^{14}C-maleic hydrazide to rats. Over a 6-day observation period, the animals excreted 0.2% of the label as carbon dioxide in the expired air, 12% in the feces and 77% in the urine. Only trace amounts were detected in tissues and blood after 3 days.

IV. HEALTH EFFECTS

Humans

- No information on human exposure to maleic hydrazide was found in the available literature.

Animals

Short-term Exposure

- The acute oral toxicity of maleic hydrazide (purity not specified) in rats was determined with administration of four dose levels to groups of five animals, with a 15-day observation period (Reagan and Becci, 1982). At dose levels of 5,000, 6,300, 7,940 or 10,000 mg/kg, deaths occurring in the male animals were 0/5, 0/5, 1/5 and 5/5, respectively, while those for female animals were 1/5, 1/5, 4/5 and 5/5, respectively. The LD_{50} values were calculated to be 6,300 mg/kg for males, 6,680 mg/kg for females and 7,500 mg/kg for both sexes combined. Adverse effects noted included ataxia, diarrhea, salivation, decreased motor activity and blood in the intestines and stomach.

- Sprague-Dawley rats (five males and five females) were fasted for 16 hours and then given a single oral dose of technical maleic hydrazide (purity not specified) at a level of 5,000 mg/kg and observed for 14 days (Shapiro, 1977a). No deaths occurred during this period. Necropsies were not performed, and no details were given with respect to adverse effects that may have been observed.

- The acute oral toxicity of the diethanolamine salt of maleic hydrazide (MH-DEA) (purity not specified) was determined in rats and rabbits (Uniroyal Chemical, 1971). In both species, MH-DEA was lethal at a level of 1,000 mg/kg, while doses between 300 and 500 mg/kg showed no toxicity in either species. The LD_{50} value for both species was calculated to be 700 mg/kg.

- Rats were used for a comparison of the acute oral toxicity of the sodium and diethanolamine salts (purities not specified) of maleic hydrazide (Tate, 1951). The diethanolamine salt showed an LD_{50} value of 2,350 mg/kg, while the LD_{50} for the sodium salt (MH-Na) was 6,950 mg/kg. No details of the study were given.

- The acute oral LD_{50} value of technical-grade maleic hydrazide (purity not specified) for rabbits was greater than 4,000 mg/kg (Lehman, 1951). No details of the study were available.

° The acute oral toxicity of maleic hydrazide (purity not specified) in four species (mouse, rat, rabbit and dog) was studied by Mukhorina (1962). For all species, the LD_{50} was reported as 700 mg/kg, with an LD_{100} of 1,000 mg/kg and a toxicity range from 300 to 500 mg/kg. For rats and rabbits, adverse effects noted were cyanosis, tachypnea, convulsions and paralysis; no other details were given.

Dermal/Ocular Effects

° Technical-grade maleic hydrazide was tested on male and female New Zealand rabbits for both skin and eye irritation (Shapiro, 1977b,c). Applied at 0.5 mL, the maleic hydrazide was scored as a mild primary skin irritant. In the eye test, 100 mg of the material was used, and maleic hydrazide was judged not to be an eye irritant.

° The acute dermal toxicity of maleic hydrazide (purity and form not specified) was determined in five male and five female New Zealand rabbits (Shapiro, 1977d). The skin of two males and three females was abraded. A single dose of 20,000 mg/kg was applied, and the animals were observed for 14 days. On the first day, two males (one with abraded skin) and one female died. The animals that died exhibited ataxia, shallow respiration and were comatose.

° In an evaluation of the acute dermal toxicity of Royal MH-30 (30% MH-DEA) and maleic hydrazide-technical, both formulations were stated to be mild primary skin irritants and slight eye irritants (Uniroyal Chemical, 1977). Individual details of the study were not given.

Long-term Exposure

° Rats were fed MH-Na or MH-DEA (purity not specified) in the diet for 11 weeks (Tate, 1951). The MH-Na was given at dose levels of 0.5% or 5.0% (5,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 250 or 2,500 mg/kg/day. No significant mortality or other adverse effects were noted (no details given). The No-Observed-Adverse-Effect-Level (NOAEL) for MH-Na in this study is 2,500 mg/kg (the highest dose tested). The MH-DEA was fed at a level of 0.1% (1,000 ppm) for 11 weeks. This is equivalent to a dose of 50 mg/kg/day (Lehman, 1959). At the end of 11 weeks, 21/24 animals had died. The author stated that after further investigation (details not given), it was concluded that the observed mortality was due to the DEA component of the formulation.

° The toxicity of maleic hydrazide in the diet for 1 year (320 to 360 days) was investigated in rats and dogs (Mukhorina, 1962). Rats received oral doses of maleic hydrazide at 0.7, 1.5 or 3 mg/kg/day, and a fourth group received 7 mg/kg MH-DEA. Dogs were administered an oral dose of 0.7 mg/kg/day maleic hydrazide. Other details in this translation on study design and conduct were not clear. Rats exposed at the high dose had hyperemia and hemorrhage of the lungs, myocardium, liver and brain, abnormal glucose-tolerance curves, lowered liver glycogen, dystrophic changes in the liver, nephritis,

interstitial pneumonia, loss of hair and significant reduction in weight gain compared with the controls (at 4 months, controls had gained 30%; those fed MH-DEA at 3 mg/kg/day had gained only 21%). Dogs fed 0.7 mg/kg/day maleic hydrazide showed no significant adverse changes, and it appears that for both the rat and the dog the level of 0.7 mg/kg/day MH-DEA was a NOAEL.

- Mukhorina (1962) also reported on a study done in mongrel mice given 0.7 mg/kg/day maleic hydrazide (purity not specified) in the diet for 320 to 360 days. No pathological changes were found. Based on these data, the NOAEL for MH-DEA in the mouse is 0.7 mg/kg/day.

- In a study by Food Research Labs (1954), MH-Na was fed in the diet to rats (number not specified) from weaning for two years. Levels of MH-Na (expressed as the free acid) were 0.0, 0.5, 1.0, 2.0 or 5.0% (0, 5,000, 10,000, 20,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to doses of 0, 250, 500, 1,000 or 2,500 mg/kg/day. There were no changes in blood or urine and no dose- or time-dependent effects on longevity. Other study details were not presented. Based on these observations, the NOAEL identified from this study is 2,500 mg/kg/day (highest dose tested) for the rat.

- In a similar study in dogs (Food Research Labs, 1954) animals were fed doses of 0.0, 0.6, 1.2 or 2.4% maleic hydrazide (as MH-Na) in the diet for 1 year. Assuming 1% (10,000 ppm) in the diet of dogs corresponds to 250 mg/kg/day (Lehman, 1959), this is equivalent to a dose of 500 mg/kg/day. No effects attributable to exposure were detected.

- Van Der Heijden et al. (1981) fed technical maleic hydrazide, 99% active ingredient (a.i.) and containing less than 1.5 mg hydrazine/kg as an impurity to rats at dietary levels of 1.0 or 2.0% (10,000 or 20,000 ppm) for 28 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day. These two levels of maleic hydrazide in the diet caused proteinuria and increased the protein/creatinine ratio in the urine of both sexes, although there were no detectable histopathological changes in the kidney or the urinary tract. Based on the effects on kidney function, the no-effect level was considered by the authors to be lower than 1.0% maleic hydrazide in the diet of rats. On this basis, a Lowest-Observed-Adverse-Effect-Level (LOAEL) of 500 mg/kg is identified.

Reproductive Effects

- In a two-generation reproduction study by Kehoe and MacKenzie (1983), Charles River CD(SD)BR rats (15 males and 30 females/dose) were administered the potassium salt of maleic hydrazide (K-MH) (purity not specified) at dietary concentrations of 0, 1,000, 10,000 or 30,000 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 0, 50, 500 and 1,500 mg/kg/day. No adverse effects on reproductive indices were

observed at any dietary level. However, increased mortality was observed in F_1 parents that received 30,000 ppm. Also at this dose level, body weights were reduced in F_0 parents during growth and reproduction and in F_1 and F_2 pups during lactation. Based on the postnatal decrease in the body weight of pups, a reproductive NOAEL of 10,000 ppm (500 mg/kg/day) is identified.

- In a four-generation reproduction study in rats (Food Research Labs, 1954), animals were fed MH-Na (purity not specified) in the diet at dose levels of 0.5, 1.0, 2.0 or 5.0% (5,000, 10,000, 20,000 or 50,000 ppm) (expressed in terms of free acid). Assuming 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to 250, 500, 1,000 or 2,500 mg/kg/day. The authors reported that there were no effects on fertility, lactation or other reproductive parameters, but no data from the study were presented for an adequate assessment of these findings.

Developmental Effects

- Khera et al. (1979) administered maleic hydrazide (97% purity) to pregnant rats by gavage on days 6 to 15 of gestation at doses of 0, 400, 800, 1,200 or 1,600 mg/kg/day. Animals were sacrificed on day 22. No sign of toxicity or adverse effect on maternal weight gain was observed at any dose level tested. Values for corpora lutea, total implants, resorptions, dead fetuses, male/female ratio and fetal weight were within the control range. The number of live fetuses was decreased at the 1,200-mg/kg dose, but this was not statistically significant and did not occur at the highest dose tested. Fetuses examined for external, soft-tissue and skeletal abnormalities showed no increase in frequency of abnormalities at any dose level tested. Based on the results of this study, a NOAEL of 1,600 mg/kg/day (the highest dose tested) is identified for maternal effects, fetotoxicity and teratogenic effects.

- Hansen et al. (1984) studied the teratogenic effects of MH-Na and the monoethanolamine salt (MH-MEA) on fetuses from female rats exposed by gavage to doses of 500, 1,500 or 3,000 mg/kg/day in the diet at various stages of gestation. Replicate tests were run. No increased frequency of gross, skeletal or visceral abnormalities was observed in animals dosed by gavage on days 6 to 15 of gestation with 500 mg/kg/day of either MH-Na or MH-MEA. An increased frequency of minor skeletal variants (asymmetrical and bipartite sternebrae, wavy ribs, fused ribs, rudiment of cervical rib, single bipartite or other variations in thoracic vertebrae) was observed in animals receiving 1,500 ($p < 0.01$) or 3,000 ($p < 0.1$) mg/kg/day of MH-MEA on days 6 to 15, but this was observed neither in animals exposed to 3,000 mg/kg/day for days 1 to 21 of gestation nor in a replicate experiment. Similarly, MH-Na produced marginal increases in minor skeletal variants in one experiment at doses of 1,500 mg/kg/day for days 6 to 15 ($p < 0.1$) or 3,000 mg/kg/day for days 1 to 21 ($p < 0.1$), but this was not observed in a replicate experiment. Rats dosed with 3,000 mg/kg/day MH-MEA in the diet exhibited a significant decrease in maternal body weight and in weight gain compared to the controls. This effect was not observed

when 3,000 mg/kg was given on days 1 to 21 by gavage, and there was no significant effect on food intake. Exposure to 3,000 mg/kg in the diet caused a significant increase in resorptions ($p < 0.001$) and a decrease in mean fetal weight ($p < 0.001$). Similar but less pronounced effects were observed when this dose was given by gavage. In addition, postimplantation loss was increased significantly ($p < 0.01$) in both experiments. The authors theorized that the more severe effects observed when the MH-MEA was fed in the diet (versus gavage) could be due to an alteration in the palatability of the diet, resulting in decreased food consumption. In contrast to the results with MH-MEA, MH-Na had no adverse effects on the dams except for a reduction in food consumption for days 1 to 6 in the group exposed from days 1 to 21 at 3,000 mg/kg. There were significant differences in body weight of the pups (up to age 35 days) of dams administered MH-MEA by gavage at 3,000 mg/kg/day from day 6 of gestation through day 21 of lactation; a significant delay in the pups' startle response to an auditory stimulus, significantly higher brain weight in both male and female pups, and a delay in unfolding of the pinna were noted also. The authors attributed the increase in relative brain weight to the lower body weight. The delay in the startle response in MH-MEA dosed offspring was considered the most significant effect, since it was observed in both sexes, but the authors noted that it cannot be explained. Based on these data, maternal, fetotoxic and teratogenic NOAELs of 1,500, 1,500 and 500 mg/kg/day, respectively, were identified for both MH-MEA and MH-Na.

- Aldridge (1983, cited in U.S. EPA, 1985a) administered K-MH by gavage at doses of 0, 100, 300 or 1,000 mg/kg/day to Dutch Belted rabbits (16/dose) on days 7 through 27 of gestation. No signs of maternal toxicity were reported, and the NOAEL for this effect is identified as 1,000 mg/kg/day (the highest dose tested). Malformed scapulae were observed in fetuses from the 300- and 1,000-mg/kg/day dose groups. An evaluation of this study by the Office of Pesticide Programs (U.S. EPA, 1985a) concluded that scapular malformations are rare and considered to be a major skeletal defect. Historical data for Dutch Belted rabbits from the testing laboratory (IRDC) indicated that scapular anomalies were observed in only 1 of 1,586 fetuses examined from 264 litters. Based on this information, a NOAEL of 100 mg/kg/day is identified for developmental effects.

Mutagenicity

- The mutagenic activity of maleic hydrazide and its formulations has been investigated in a number of laboratories. These studies are complicated by the fact that hydrazine (a powerful mutagen) is a common contaminant of these preparations, and N-nitrosoethanolamine (also a mutagen) may be present in MH-DEA. Present data are inadequate to determine with certainty whether any mutagenic activity of maleic hydrazide is due to impurities and not the maleic hydrazide itself.

- Tosk et al. (1979) reported that maleic hydrazide (purity not specified), at levels of 5, 10 and 20 mg, was not mutagenic in Salmonella typhimurium (TA 1530). However, two formulations (MH-30

and Royal MH), at 50, 100 and 200 uL (undiluted), were highly mutagenic in this system.

- Moriya et al. (1983) reported that maleix hydrazide was not mutagenic in five strains of S. typhimurium.

- Ercegovich and Rashid (1977) observed a weak mutagenic response with maleic hydrazide (purity not specified) in five strains of S. typhimurium.

- Shiau et al. (1980) reported that maleic hydrazide was mutagenic, with and without activation, in several Bacillus subtilis strains.

- Epstein et al. (1972) reported that maleic hydrazide (500 mg/kg) was not mutagenic in a dominant-lethal assay in the mouse.

- Nasrat (1965) reported a slight increase in the frequency of sex-linked recessive lethals in the progeny of Drosophila melanogaster males reared on food containing 0.4% maleic hydrazide.

- Manna (1971) indicated that exposure to a 5% aqueous solution of maleic hydrazide produced chromosomal aberrations in the bone marrow of mice in a manner similar to that produced by x-rays and other known mutagens.

- Chaubey et al. (1978) reported that intraperitoneal injection of 100 or 200 mg/kg maleic hyerazide (purity not specified) did not affect the incidence of bone marrow erythrocyte micronuclei or the ratio of poly- to normochromatic erythrocytes in male Swiss mice.

- Sabharwal and Lockhard (1980) reported that at concentrations above 100 ppm, maleic hydrazide induced dose-related increases in sister chromated exchange (SCE) in human lymphocytes and V79 Chinese hamster cells. Commercial formulations of maleic hydrazide (Royal MH and MH-30) at the 250- and 500-mg/kg doses did not cause an increase in micronucleated polychromatic erythrocytes in a mouse micronucleus test.

- Stetka and Wolff (1976) reported that maleic hydrazide (11 and 112 mg/L; purity not specified) caused no significant effect in an SCE assay.

- Nishi et al. (1979) reported that maleic hydrazide (1,000 ug/L; purity not specified), MH-DEA (20,000 ug/mL) and MH-K (20,000 ug/mL) produced cytogenetic effects in Chinese hamster V79 cells in vitro.

- Paschin (1981) reported that in the concentration range of 1,800 to 2,500 mg/L maleic hydrazide (purity not specified) was mutagenic for the thymidine kinase locus of mouse lymphoma cells.

Carcinogenicity

- The carcinogenicity of maleic hydrazide (purity not specified) was evaluated in two hybrid strains of mice (C57BL/6 x AKR and C57BL/6 x C3H/Anf) (Kotin et al., 1968; Innes et al., 1969). Beginning at 7 days of age, mice were given maleic hydrazide at 1,000 mg/kg/day

(suspended in 0.5% gelatin) by stomach tube. After 28 days of age, they were given maleic hydrazide in the diet at 3,000 ppm for 18 months. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to a dose of 450 mg/kg/day. These were the maximum tolerated doses. No evidence of increased tumor frequency was detected in gross or histologic examination.

- Barnes et al. (1957) fed maleic hydrazide at a level of 1% (10,000 ppm) in the diet of rats and mice (10 to 15/sex/dose) for a total of 100 weeks. Assuming that 1 ppm in the diet corresponds to 0.05 mg/kg/day in rats and 0.15 mg/kg/day in mice (Lehman, 1959), this is equivalent to a dose of 500 mg/kg/day in rats and 1,500 mg/kg/day in mice. A concurrent study was conducted in which the maleic hydrazide (500 mg/kg/week, corresponding to 71 mg/kg/day) was injected subcutaneously (sc) for the same length of time. No increase in the incidence of tumors was observed in animals exposed by either route when compared with controls (data were pooled).

- Cabral and Ponomarkov (1982) administered maleic hydrazide by gavage in weekly doses of 510 mg/kg in 0.2 mL olive oil to male and female C57BL/B6 mice for 120 weeks. Controls received 0.2 mL olive oil alone, and a third group served as untreated controls. A simultaneous study was conducted using sc injection as the route of administration. There was no evidence of carcinogenicity in the study.

- Van Der Heijden et al. (1981) fed maleic hydrazide (99% pure) containing less than 1.5 mg hydrazine/kg as impurity to rats at dietary levels of 1.0 or 2.0% (10,000 or 20,000 ppm) for 28 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 500 or 1,000 mg/kg/day. Histological examination revealed no increase in the tumor incidence in exposed animals compared with the control group.

- In a study by Uniroyal Chemical (1971), mice were administered maleic hydrazide (0.5% in water) by gavage twice weekly beginning at 2 months of age (weight 15 to 18 g) for a total of 2 years. A parallel study was conducted using sc administration. No carcinogenic effect was reported, but specific details of the study were not presented.

- Uniroyal Chemical (1971) reported a 2-year study in Wistar-derived rats in which MH-Na was included in the diet at levels of 0, 0.5, 1,0, 2.0 or 5.0% (0, 5,000, 10,000, 20,000 or 50,000 ppm). Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to doses of 0, 250, 500, 1,000 or 2,500 mg/kg/day. Although no experimental details were presented, it was concluded that the MH-Na resulted in no blood dyscrasias or tissue pathology, and no indication of carcinogenic potential was detected.

- Epstein and Mantel (1968) used random-bred infant Swiss mice (ICR/Ha) to assess the carcinogenic effects of maleic hydrazide when administered during the neonatal period. The free acid form of maleic hydrazide (containing 0.4% hydrazine impurity) was prepared as an

aqueous solution of 5 mg/mL, or as a suspension in redistilled tricaprylin at a concentration of 50 mg/mL. The mice were given injections in the nape of the neck on days 1, 7, 14 and 21 following birth. Six litters received the maleic hydrazide aqueous solution (total dose: 3 mg), and 16 litters received the maleic hydrazide suspension (total dose: 55 mg). One litter received one injection of the suspension at a higher dose (100 mg/mL, total dose: 10 mg), but this was lethal to all mice. A total of 16 litters served as controls (treated with solvents alone). The experiment was terminated between 49 and 51 weeks. The mice that received a total dose of 55 mg in the 3-week period had a high incidence of hepatomas: 65% of 26 male mice alive at 49 weeks, in contrast to solvent controls in which hepatomas occurred in 8% of 48 male mice. The males that received 3 mg total had an 18% incidence of hepatomas. In addition to these lesions, hepatic "atypia" was observed in five males (at 55 mg) and eight females, which the authors judged might be preneoplastic. At the 3-mg level, one atypia was seen in each sex. It was concluded that maleic hydrazide was highly carcinogenic in the male mice. The authors also noted that since there was a complete absence of multiple pulmonary adenomas and pulmonary carcinomas, it was unlikely that the carcinogenicity of maleic hydrazide was due to hydrazine (either present as trace contamination or formed by metabolism), since hydrazine is a potent lung carcinogen in several species of rats and mice (including CBA mice).

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).

Several studies (Tate, 1951; Mukhorina, 1962; Hansen et al., 1984) indicate that the DEA ion is toxic and may contribute to the toxicity of the MH-DEA salt. For this reason, studies involving MH-DEA have not been considered as candidates in calculating HA values for maleic hydrazide.

One-day Health Advisory

No information was found in the available literature that was suitable for deriving a One-day HA value for maleic hydrazide. It is, therefore, recommended that the Ten-day HA value for a 10-kg child (10 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The developmental toxicity study by Aldridge (1983, cited in U.S. EPA, 1985a) has been selected to serve as the basis for the Ten-day HA. In this study, the potassium salt of maleic hydrazide (K-MH) was administered by gavage at doses of 0, 100, 300 or 1,000 mg/kg/day to Dutch Belted rabbits (16/dose) on days 7 through 27 of gestation. Malformed scapulae were observed in fetuses from the 300- and 1,000-mg/kg/day dose groups. Although the incidence of these malformations was not statistically significant and did not occur in a dose-related fashion, malformed scapulae are a rare, major skeletal defect. Additionally, historical data for this breed of rabbits indicate that scapular anomalies were observed in only 1 of 1,586 fetuses examined from 264 litters. For these reasons U.S. EPA (1985a) concluded that the possibility of teratogenic activity at these dose levels cannot be ruled out. The NOAEL for teratogenic effects is identified as 100 mg/kg/day.

Although a teratogenic response is clearly a reasonable basis upon which to base an HA for an adult, there is some question about whether the Ten-day HA for a 10-kg child can be based upon such a study. However, a teratogenic study is of appropriate duration and does supply some information concerning fetotoxicity. Since the fetus may be more sensitive to the chemical than a 10-kg child and since a teratogenic study is of appropriate duration, it is judged that, though possibly overly conservative, it is reasonable in this case to base the Ten-day HA for a 10-kg child on a developmental toxicity study.

Using a NOAEL of 100 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(100 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 10 \text{ mg/L } (10{,}000 \text{ ug/L})$$

where:

100 mg/kg/day = NOAEL, based on the absence of teratogenic effects in rabbits exposed to K-MH by gavage on days 7 to 27 of gestation.

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 studies were found that were adequate for calculation of Longer-term HA values for maleic hydrazide. An 11-week feeding study in rats by Tate (1951) identified a NOAEL of 2,500 mg/kg/day, and 2-year feeding studies in rats and dogs by Food Research Laboratories (1954) identified NOAEL values of 2,500 and 500 mg/kg/day, respectively. These studies have not been selected because they provided too little experimental detail to be suitable for calculation of an HA value. It is, therefore, recommended that the Drining Water Equivalent Level (DWEL) of 17.5 mg/L, calculated below, be used as a conservative estimate of the Longer-term HA for a 70-kg adult and that the modified DWEL of 5 mg/L (adjusted for a 10-kg child) be used as a conservative estimate of the Longer-term HA for a 10-kg child.

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 28-month feeding study in rats by Van Der Heijden et al. (1981) has been selected to serve as the basis for the Lifetime HA value for maleic hydrazide. Based on proteinuria (in the absence of visible histological effects in kidney), a LOAEL of 500 mg/kg/day was identified. This is a conservative selection, since 2-year feeding studies in dogs and rats by Food Research Laboratories (1954) identified NOAEL values of 500 and 2,500 mg/kg/day, respectively; those studies were not selected, however, because few data or details were provided.

Using the LOAEL identified by Van Der Heijden et al. (1981), the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(500\ mg/kg/day)}{(1,000)} = 0.5\ mg/kg/day$$

where:

500 mg/kg/day = LOAEL, based on decreased amino acid resorption in kidney of rats exposed to maleic hydrazide in the diet for 28 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)

$$DWEL = \frac{(0.5\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 17.5\ mg/L\ (17,500\ ug/L)$$

where:

0.5 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 = (17.5 mg/L) (20%) = 3.5 mg/L (3,500 ug/L)

where:

17.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic activity was detected in five studies in which maleic hydrazide was administered orally to mice or rats for periods from 18 to more than 2 years (Kotin et al., 1968; Innes et al., 1969; Barnes et al., 1957; Cabral and Ponomarkov, 1982; Van Der Heijden et al., 1981; Uniroyal Chemical, 1971). Increased incidence of hepatomas has been reported in mice exposed by sc injection during the first 3 weeks of life (Epstein and Mantel, 1968).

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

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

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1985b) has established residue tolerances for maleic hydrazide in or on raw agricultural commodities that range from 15.0 to 50.0 ppm.

VII. ANALYTICAL METHODS

- There is no standardized method for the determination of maleic hydrazide in water samples. A procedure has been reported for the estimation of maleic hydrazide residues on various foods (U.S. FDA, 1975). In this procedure, the sample is boiled in an alkaline solution to drive off volatile basic interferences. Distillation with zinc and a nitrogen sweep expel hydrazine liberated from maleic hydrazide. Hydrazine is reacted in acid solution with p-dimethylaminobenzaldehyde to form a yellow compound that is measured spectrophotometrically.

VIII. TREATMENT TECHNOLOGIES

- Currently available treatment technologies have not been tested for their effectiveness in removing maleic hydrazide from drinking water.

IX. REFERENCES

Aldridge, D.* 1983. Teratology study in rabbits with potassium salt of maleic hydrazide. Unpublished report prepared by International Research and Development Corporation for Uniroyal Chemical Company. Accession No. 250523. Cited in: U.S. EPA. 1985. U.S. Environmental Protection Agency. Memorandum dated 3/7/85 from G. Ghali to R. Taylor concerning EPA Reg. Numbers 400-84, 400-94 and 400-165; Maleic Hydrazide, K-Salt.

Barnes, J.M., P.N. Magee, E. Boyland, A. Haddow, R.D. Passey, W.S. Bullough, C.N.D. Cruickshank, M.H. Salaman and R.T. Williams. 1957. The non-toxicity of maleic hydrazide for mammalian tissues. Nature. 180:62-64.

Cabral, J.R.P., and V. Ponomarkov. 1982. Carcinogenicity study of the pesticide maleic hydrazide in mice. Toxicology. 24:169-173.

Chaubey, R.C., B.R. Kavi, P.S. Chauhan and K. Sundaram. 1978. The effect of hycanthone and maleic hydrazide on the frequency of micronuclei in the bone-marrow erythrocytes of mice. Mutat. Res. 57:187-191.

CHEMLAB. 1985. The Chemical Information System, CIS, Inc., Bethesda, MD.

Epstein, S.S., E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288-325.

Epstein, S.S., and N. Mantel. 1968. Hepatocarcinogenicity of the herbicide maleic hydrazide following parenteral administration to infant swiss mice. Intl. J. Cancer. 3:325-335.

Ercegovich, C.D., and K. A. Rashid. 1977. Mutagenesis induced in mutant strains of Salmonella typhimurium by pesticides. (Abstract of Paper) Am. Chem. Soc. 174:Pest 43.

Food Research Labs, Inc.* 1954. Chronic toxicity studies with sodium maleic hydrazide. Unpublished report. MRID 00112753.

Hansen, E., O. Meyer and E. Kristiansen. 1984. Assessment of teratological effect and developmental effect of maleic hydrazide salts in rats. Bull. Environ. Contam. Toxicol. 33:184-192.

Innes, J.R.M, B.M. Ulland, M.G. Valerio, L. Petrucelli, L. Fishbein, E.R. Hart, A.J. Pallotta, R.R. Bates, H.L. Falk, J.J. Gart, M. Klein, I. Mitchall and J. Peters. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. J. Natl. Cancer Inst. 42:1101-1114.

Kehoe, D.F., and K.M. MacKenzie.* 1983. Two-generation reproduction study with KMH in rats. Study No. 81065 prepared by Hazleton Raltech, Inc. for Uniroyal Chemical Company. Accession No. 250522. Cited in: U.S. EPA. 1985. U.S. Environmental Protection Agency. Memorandum dated 3/7/85 from G. Ghali to R. Taylor concerning EPA Reg. Numbers 400-84, 400-94 and 400-165; Maleic Hydrazide, K-Salt.

Kennedy G., and M.L. Keplinger.* 1971. Placental and milk transfer of maleic hydrazide in albino rats. Unpublished report. MRID 00112778.

Khera, K.S., C. Whalen, C. Trivett and G. Angers. 1979. Teratologic assessment of maleic hydrazide and daminozide, and formulations of ethoxyquin, thiabendazole and naled in rats. J. Environ. Sci. Health (B). 14:563-577.

Kotin, P., H. Falk and A.J. Pallotta.* 1968. Evaluation of carcinogenetic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals. Unpublished report. MRID 0017801.

Lehman, A.J. 1951. Chemicals in food: A report to the Association of Food and Drug Officials. Assoc. Food Drug Off. U.S.Q. Bull. 15:122. Cited in Ponnampalam R., N.I. Mondy and J.G. Babish. 1983. A review of environmental and health risks of maleic hydrazide. Regul. Toxicol. Pharmacol. 3:38-47.

Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Association of Food and Drug Officials of the United States.

Manna, G.K. 1971. Bone marrow chromosome aberrations in mice induced by physical, chemical and living mutagens. J. Cytol. Genet. (India) Congr. Suppl. 144-150.

Mays, D.L., G.S. Born, J.E. Christian and B.J. Liska. 1968. Fate of C^{14}-maleic hydrazide in rats. J. Agric. Food Chem. 16:356-357. Cited in Swietlinska Z and J. Zuk. 1978. Cytotoxic effects of maleic hydrazide. Mutat. Res. 55:15-30.

Meister, R., ed. 1983. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116:185-216.

Mukhorina, K.V.* 1962. Action of maleic hydrazide on animal organisms. Unpublished report (translation from Russian). MRID 00106969.

Nasrat, G.E. 1965. Maleic hydrazide, a chemical mutagen in Drosophila melanogaster. Nature. 207:439.

Nishi, Y., M. Mori and N. Inui. 1979. Chromosomal aberrations induced by maleic hydrazide and related compounds in Chinese hamster cells in vitro. Mutat. Res. 67:249-257.

Paschin, Y.V. 1981. Mutagenicity of maleic acid hydrazide for the TK locus of mouse lymphoma cells. Mutat. Res. 91:359-362.

Reagan E. and P. Becci.* 1982. Acute oral LD_{50} in rats of Royal-DRI-60-DG. Food and Drug Research Labs. Unpublished report. MRID 00110459.

Registrant Confidential Business Informathion data.* Complete citation not available.

Sabharwal, P.S., and J.M. Lockard. 1980. Evaluation of the genetic toxicity of maleic hydrazide and its commercial formulations by sister chromatid exchange and micronucleus bioassays. In Vitro. 16(3):205.

Shapiro, R.* 1977a. Acute oral toxicity: Report no. T-235. Unpublished report. MRID 00079657.

Shapiro, R.* 1977b. Primary skin irritation: Report no. T-212. Unpublished report. MRID 00079660.

Shapiro, R.* 1977c. Eye irritation: Report no. T-220. Unpublished report. MRID 00079661.

Shapiro, R.* 1977d. Acute dermal toxicity: Report no. T-242. Unpublished report. MRID 00079658.

Shiau, S.Y., R.A. Huff, B.C. Wells and I.C. Felkner. 1980. Mutagenicity and DNA-damaging activity for several pesticides with Bacillus subtilis mutants. Mutat. Res. 71:169-179.

Stetka, D.G., and S. Wolff. 1976. Sister chromatid exchange as an assay for genetic damage induced by mutagen-carcinogens. II. In vitro test for compounds requiring metabolic activation. Mutat. Res. 41:343-350.

Tate, H.D.* 1951. Progress report on mammalian toxicity studies with maleic hydrazide. Unpublished report. MRID 00106972.

TDB. 1985. Toxicity Data Bank. MEDLARS II. National Library of Medicine's National Interactive Retrieval Service.

Tosk, J., I. Schmeltz and D. Hoffmann. 1979. Hydrazines as mutagens in a histidine-requiring auxotroph of Salmonella typhimurium. Mutat. Res. 66:247-252.

Uniroyal Chemical Co., Bethany, Connecticut.* 1971. Summary of toxicity studies on maleic hydrazide: Acute oral toxicity in rats and rabbits. Unpublished report. MRID 00087385.

Uniroyal Chemical Co., Bethany, Connecticut.* 1977. Results from acute toxicology tests run with Royal MH-30(R) and MH Technical (R). Unpublished report. MRID 00079651.

U.S. EPA. 1985a.* U.S. Environmental Protection Agency. Memorandum dated 3/7/85 from G. Ghali to R. Taylor concerning EPA Reg. Numbers 400-84, 400-94 and 400-165; Maleic Hydrazide, K-Salt.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.175. July 1, p. 277.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

U.S. FDA. 1975. U.S. Food and Drug Administration. Pesticide analytical manual. Vol. II. Washington, DC.

Van Der Heijden, C.A., E.M. Den Tonkelaar, J.M. Garbis-Berkvens and G.J. Van Esch. 1981. Maleic hydrazide, carcinogenicity study in rats. Toxicology. 19:139-150.

WSSA. 1983. Weed Science Society of America. Herbicide handbook, 5th ed.

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