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DRAFT

CARBOXIN

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.

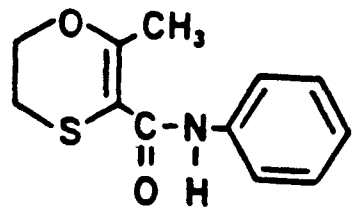
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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. 5234-68-4

Structural Formula



5,6-Dihydro-2-methyl-N-phenyl-1,4-Oxathin-3-carboxamide

Synonyms

- Carbathiin; Carboxine; D-735; DCMO; DMOC; F735; Vitavax (Meister, 1983).

Uses

- Systemic fungicide; seed protectant; wood preservative (Meister, 1983).

Properties (Meister, 1983; Windholz et al., 1983; Wo and Shapiro, 1983; Worthing, 1983; TDB, 1985)

Chemical Formula	$C_{12}H_{13}O_2NS$
Molecular Weight	235.31
Physical State (25°C)	Crystals
Boiling Point	--
Melting Point	93 to 95°C
Density	--
Vapor Pressure (20°C)	<1 mm Hg
Specific Gravity	--
Water Solubility (25°C)	170 mg/L
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

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

Environmental Fate

- Carboxin is rapidly metabolized (oxidized by flavin enzymes found in fungi mitochondria) in aerobic soil. When applied to soil (aerobic

conditions), more than 95% of the carboxin was degraded within 7 days. The major degradation product was carboxin sulfoxide, which represented 31 to 54% of the applied radioactivity at 7 days after treatment. Several minor degradation products were also formed (carboxin sulfone, p-hydroxy carboxin and $^{14}CO_2$). Carboxin was degraded in sterile soil but at a much slower rate than in nonsterile soil (46 to 72% degraded in 7 days). This would indicate that soil metabolism of carboxin under aerobic conditions is primarily by microbial processes. Carboxin sulfoxide is stable in anaerobic soil (Chin et al., 1972, 1969, 1970a,b; Dzialo and Lacadie, 1978; Dzialo et al., 1978; Spare, 1979).

° Carboxin sulfoxide, a major metabolite of carboxin, photodegrades to unknown compounds. After 7 days of incubation, 49% of the applied radioactivity was present as unknown compounds (Smilo et al., 1977).

° Carboxin does not readily adsorb to soil [K value (adsorption coefficient) <1] and both carboxin and carboxin sulfoxide are very mobile in soil with about half of the applied radioactivity leaching through 12-inch columns of clay loam soils (Lacadie et al., 1978; Dannals et al., 1976).

° In aqueous solution, carboxin was oxidized to carboxin sulfoxide and carboxin sulfone within 7 days (Chin et al., 1970a).

III. PHARMACOKINETICS

Absorption

° Waring (1973) administered carboxin (Vitavax) by gavage to groups of four to six female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) at 1 mmol/kg (235 mg/kg). In the rats, an average of 40% of the dose was excreted in the feces, mostly as unchanged carboxin. In the rabbits, an average of 10% was recovered in the feces. These data suggest that carboxin is not completely absorbed from the gut, especially in rats.

Distribution

° Waring (1973) administered single oral doses of carboxin (Vitavax, 6.3 uCi/rat) to female Wistar rats (age not specified; 200 to 250 g). Carboxin was labeled either in the heterocyclic or aromatic ring and distribution of label was assessed by autoradiography of whole-body sections. After 2 hours, label was localized in the liver, intestinal tract and salivary gland. After 6 hours, label was also present in the kidney. Only trace levels remained in any tissue after 48 hours. There were no differences in the distribution of the two labeled compounds.

° Nandan and Wagle (1980) fed carboxin to male albino rats (age not specified) for 28 days at dietary levels of 0, 100, 1,000 or 10,000

ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these levels correspond to 0, 5, 50 and 500 mg/kg/day. In animals fed the highest dose, maximum levels were detected in the liver (140 ug/g), with lower levels in the kidney (123 ug/g), heart (58 ug/g) and muscle (22 ug/g).

Metabolism

- In the study by Waring (1973), as described previously, female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) were given single oral doses of carboxin by gavage at 1 mmol/kg (235 mg/kg). The principal metabolic pathway was found to be ortho- or parahydroxylation, followed by glucuronidation. In the rats, 32% of the dose was excreted in urine as glucuronides and 7% as unconjugated phenols. In the rabbits, 85% of the dose was excreted in urine as glucuronides and 3% as free phenols. The pattern of phenolic metabolites was the same for carboxin labeled in either the heterocyclic or the aromatic rings, indicating that cleavage of the compound did not occur.

Excretion

- In the study by Waring (1973), as described previously, female New Zealand White rabbits (age not specified; 2.5 to 3 kg) and Wistar rats (age not specified; 200 to 250 g) were given single oral doses of carboxin by gavage at 1 mmol/kg (235 mg/kg). In the rats, 41% was excreted in the feces (largely unchanged carboxin) and 54% was excreted in the urine (15% parent compound, 32% glucuronides, 7% free phenols). In the rabbits, 10% was excreted in the feces and 90% was excreted in the urine (2% parent compound, 85% glucuronides, 3% free phenols).

IV. HEALTH EFFECTS

Humans

- A seven-year-old boy developed headaches and vomiting within 1 hour after ingesting several handfuls of wheat seed treated with carboxin. He was administered ipecac (an emetic) and was asymptomatic 2 hours later. No estimate of the ingested dose was provided (PIMS, 1980).

Animals

Short-term Exposure

- Reagan and Becci (1983) reported that the acute oral LD_{50} for technical carboxin (purity not specified) in young CD-1 mice (age not specified) was 4,150 mg/kg for males and 2,800 mg/kg for females. The average LD_{50} was reported to be 3,550 mg/kg.

- RTECS (1985) reported that the acute oral LD_{50} for carboxin (purity not specified) in the rat (age not specified) was 430 mg/kg.

- Nandan and Wagle (1980) fed carboxin to male albino rats (age not specified) for 28 days at dietary levels of 0, 100, 1,000 or 10,000 ppm. Based on the authors' measurements of food consumption and assuming average body weights of 0.1 kg, these levels corresponded to doses of about 0, 5.5, 59.0 or 311 mg/kg/day. A Lowest-Observed-Adverse-Effect-Level (LOAEL) of 100 ppm (5.5 mg/kg/day) was tentatively identified in this study based on fluid accumulation in the liver. However, due to a number of deficiencies in this study, it is not possible to accurately evaluate its validity. These deficiencies include a lack of information on the test animals (e.g., condition at study initiation, numbers used) and the absence of statistical analyses.

Dermal/Ocular Effects

- Holsing (1968a) applied carboxin (D-735; purity and vehicle not specified) to the intact or abraded abdominal skin of rabbits (10/sex/dose; age not specified) at concentrations of 1,500 or 3,000 mg/kg. Five animals of each sex served as controls. Test animals were exposed occlusively for 6 to 8 hours, 5 days per week, for 3 weeks (15 applications). No signs of dermal irritation were observed. The test material stained the skin and precluded readings for erythema.

Long-term Exposure

- Ozer (1966) administered carboxin (D-735; purity not specified) to weanling FDRL (Wistar-derived) rats (10/sex/dose; controls: 15/sex) for 90 days at dietary concentrations of 0, 200, 600, 2,000, 6,000 or 20,000 ppm, intended by the author to correspond to approximate dosage levels of 0, 10, 30, 100, 300 or 1,000 mg/kg/day. All animals survived the 90-day treatment period. Growth, food efficiency, hematology, blood chemistry and urinalysis were reported to be similar in all groups with the exception of increased blood urea nitrogen and decreased hemoglobin at the 12-week interval in females that received 20,000 ppm (1,000 mg/kg/day). No significant dose-related gross pathological changes were observed. Microscopically, a significant number of inflammatory degenerative renal changes were found in animals that received doses of 600 ppm (30 mg/kg/day) or higher. These changes included focal chronic inflammation, protein casts and cortical tubular degeneration. In two animals that received 2,000 ppm (100 mg/kg/day), some fibrosis in the medulla was observed. Based on renal changes, a LOAEL of 600 ppm (30 mg/kg/day) and a No-Observed-Adverse-Effect-Level (NOAEL) of 200 ppm (10 mg/kg/day) can be identified.

- Jessup et al. (1982) administered carboxin (technical Vitavax; purity not specified) to six-week old Charles River CD-1 mice (50/sex/dose; controls: 75/sex) for approximately 84 weeks at dietary concentrations of 0, 50, 2,500 or 5,000 ppm. The authors indicated that these dietary levels corresponded to doses of about 0, 8, 385 or 751 mg/kg/day for males and 0, 9, 451 or 912 mg/kg/day for females. No compound-related effects on general behavior or appearance were reported. Survival rates of females receiving 5,000 ppm (912 mg/kg/day) were significantly ($p < 0.01$) lower than controls. No compound-related

effects on body weight gain, food consumption, or various hematological parameters were reported. No gross pathologic lesions that were considered to be related to compound administration were observed at necropsy in any mice in any treatment group. Microscopically, compound-related effects on the liver, consisting of hypertrophy of the centrilobular parenchymal cells, were observed in mice in the 2,500- or 5,000-ppm dose groups (385 and 751 mg/kg/day for males; 451 and 912 mg/kg/day for females). No other nonneoplastic lesions that could be attributed to compound administration were observed. The NOAEL in this study is 50 ppm (8 mg/kg/day for males; 9 mg/kg/day for females) based on hepatic effects.

- Holsing (1969a) administered carboxin (technical D-735; considered to be 100% active ingredient) to Charles River rats (30/sex/dose; controls: 60/sex) for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these dietary levels correspond to dose levels of approximately 0, 5, 10 or 30 mg/kg/day. While the age of the animals was not specified, the weights of the male rats at initiation ranged from 65 to 88 g and the weight of the female rats ranged from 59 to 85 g. No compound-related effects in terms of physical appearance, behavior, hematology, blood chemistry or urinalysis were reported at any dose level. Observations at terminal necropsy did not reveal any compound-related gross or microscopic changes in the organs of animals at any dose level. At the 600-ppm level (30 mg/kg/day), body weight gain was significantly depressed in both sexes, and food consumption by males was lower than that of controls throughout most of the study (significantly lower during the first 26 weeks). Food consumption by females at all dose levels was generally comparable to controls. Compound-related effects included an increase in mortality at 18 months in males that received 600 ppm (30 mg/kg/day), and changes in absolute and relative organ weights at all dose levels, including increases in thyroid weight and decreases in kidney, heart and spleen weight and histopathological changes in the kidneys at the 12-month interval in both sexes at 200 and 600 ppm. Most of these effects were inconsistent and were not observed at the end of the study period. At the end of the 2-year study, decreased kidney weights were observed in males at 600 ppm (30 mg/kg/day). Therefore, based on the information presented in this study, a NOAEL of 200 ppm (10 mg/kg/day) was identified.

- Holsing (1969b) administered carboxin (technical D-735; considered to be 100% active ingredient) to young adult beagle dogs (4/sex/dose; controls: 6/sex) for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. Therefore, these dietary levels have been calculated to correspond approximately to 0, 2.5, 5.0 or 15.0 mg/kg/day. No treatment-related effects were reported on survival, body weight gain, food consumption, organ weights, organ-to-body weight ratios, hematological, blood chemistry or urinary parameters, liver and kidney function tests or gross and histopathological observations. Based on this information,

a NOAEL of 600 ppm (15 mg/kg/day; the highest dose tested) was identified.

Reproductive Effects

- In a three-generation reproduction study, Holsing (1968b) administered carboxin (technical D-735; 97% active ingredient) to Charles River rats (10 males/dose, 20 females/dose; controls: 15 males, 30 females) (age not specified) at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), these dietary levels have been calculated to correspond to dose levels of approximately 0, 5, 10 or 30 mg/kg/day. Criteria evaluated included fertility, gestation, live birth and lactation indices, litter size and the physical appearance and growth of the pups. No compound-related effects on reproductive performance were reported at any dose level. A compound-related effect on the progeny (moderate growth suppression in the nursing male and female pups of all three generations) was observed at the 600-ppm (30 mg/kg/day) dose level. Based on the information presented in this study, a NOAEL of 200 ppm (10 mg/kg/day) was identified.

Developmental Effects

- Schardein and Laughlin (1981) administered technical Vitavax (carboxin; 99% active ingredient) by gavage at doses of 0, 75, 375 or 750 mg/kg/day to seven- to eight-month-old Dutch Belted rabbits (10/dose) on days 6 through 27 of gestation. The compound was administered in a 0.5% carboxymethyl cellulose vehicle. No treatment-related effects on maternal mortality, appearance, behavior or body weight were reported. Four females aborted on days 27 and 28 of gestation (one at 375 mg/kg/day, three at 750 mg/kg/day). Examination for fetal malformations revealed no compound-related differences between the control and treatment groups. Based on the frequency of abortion, a NOAEL of 75 mg/kg/day and a LOAEL of 375 mg/kg/day were identified.

- Knickerbocker (1977) administered carboxin (technical Vitavax; purity not specified) in corn oil by gavage at doses of 0, 4, 20 or 40 mg/kg/day to sexually mature (age not specified) Sprague-Dawley rats (20/dose) on days 6 through 15 of gestation. No compound-related effects were observed on reproduction, gestation or in skeletal or soft tissue development. Based on the information presented, a NOAEL of 40 mg/kg/day (the highest dose tested) was identified.

Mutagenicity

- Brusick and Weir (1977) conducted a mutagenicity assay using Salmonella typhimurium strains TA 1535, 1537, 1538, 98 and 100, and Saccharomyces cerevisiae strain D4. Carboxin (purity not specified) was tested without activation at concentrations up to 500 ug/plate and with activation at concentrations up to 100 ug/plate. No mutagenic activity was detected in this assay.

- Byeon et al. (1978) reported that carboxin (Vitavax; purity not specified) tested at concentrations up to 1 mg/plate was not found to be mutagenic in an Ames assay using S. typhimurium strains TA 1535, 1538, 98 and 100.

- Brusick and Rabenold (1982) conducted an Ames assay using technical carboxin (Vitavax, 98% active ingredient) at concentrations up to 5,000 ug/plate. No mutagenic activity was detected, with or without activation, in S. typhimurium strains TA 1535, 1537, 1538, 98 and 100.

- Myhr and McKeon (1982) reported the results of a primary rat hepatocyte unscheduled DNA synthesis assay using carboxin (technical Vitavax; 98% active ingredient). The test compound produced significant increases in the nuclear labeling of primary rat hepatocytes over a concentration range of 5.13 to 103 ug/mL.

Carcinogenicity

- Holsing (1969a) administered carboxin (technical D-735; considered to be 100% active ingredient) to Charles River rats (30/sex/dose; controls: 60/sex) for 2 years at dietary concentrations of 0, 100, 200 or 600 ppm. Based on the dietary assumptions of Lehman (1959), 1 ppm in the diet of rats equals approximately 0.05 mg/kg/day. While the age of the animals was not specified, the weights of the male rats at initiation ranged from 65 to 88 g and the weights of the female rats ranged from 59 to 85 g. Therefore, dietary levels correspond to approximately 0, 5, 10 or 30 mg/kg/day. No evidence of increased tumor frequency was detected by either gross or histological examination of tissues.

- Jessup et al. (1982) administered carboxin (technical Vitavax; purity not specified) to six-week-old Charles River CD-1 mice (50/sex/dose; controls: 75/sex) for approximately 84 weeks at dietary concentrations of 0, 50, 2,500 or 5,000 ppm. The authors indicated that these dietary levels corresponded to dosage levels of approximately 0, 8, 385 or 751 mg/kg/day for males and 0, 9, 451 or 912 mg/kg/day for females. Survival rates of females receiving 5,000 ppm (912 mg/kg/day) were significantly ($p < 0.01$) lower than those of controls. No compound-related gross pathologic lesions were observed at necropsy in any treatment group. Microscopically, compound-related effects on the liver, consisting of hypertrophy of the centrilobular parenchymal cells, were observed in mice in the 2,500 or 5,000 ppm dose groups (385 and 751 mg/kg/day for males; 451 and 912 mg/kg/day for females). In males, the incidence of pulmonary adenoma/alveolar-bronchiolar adenoma was 13/75, 7/49, 7/50, and 17/50 at 0, 50, 2,500, and 5,000 ppm, respectively. The incidence at the high dose (34%) may have been compound-related based on comparison with the incidence in controls (17%). The difference was statistically significant ($p < 0.01$) using Cox's test for adjusted trend and the Kruskall Wallis tests for life-table data and adjusted incidence. However, based on the opinions of pathologists who reviewed the data and on historical data on tumor incidence in control Charles River CD-1 mice, the authors concluded that the increased incidence was not compound-related. Historical data indicate that in six 18-month studies, the incidence of lung adenomas ranged from 6.3 to

16.7%; in seven 20- to 22-month studies, the incidence of lung adenomas ranged from 4.0 to 31.1%.

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

Appropriate data for calculating a One-day HA value are not available. It is recommended that the Longer-term HA value for the 10-kg child (1.0 mg/L, calculated below) be used as the One-day HA value.

Ten-day Health Advisory

Appropriate data for calculating a Ten-day HA value are not available. The 22-day rabbit teratogenicity study by Schardein and Laughlin (1981) was considered for the development of the Ten-day HA. However, the NOAEL (75 mg/kg/day) identified in this study is far in excess of the NOAEL (10 mg/kg/day) identified in the 90-day rat feeding study reported by Ozer (1966) suggesting that the rat is the more sensitive species. It is, therefore, recommended that the Longer-Term HA value for the 10-kg child (1.0 mg/L, calculated below) be used as the Ten-day value.

Longer-term Health Advisory

The study by Ozer (1966) has been selected to serve as the basis for calculating the Longer-term HA for carboxin. In this study, weanling rats were exposed to carboxin in the diet for 90 days. At 30 mg/kg/day there was histological evidence of renal injury. At 10 mg/kg/day, no effects were detected on any parameter measured, including growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology. Based on these

data, a NOAEL of 10 mg/kg/day was identified. This value is supported by the subchronic (84 week) feeding study in mice by Jessup et al. (1982) which identified a NOAEL of 8 to 9 mg/kg/day, based on the absence of effects on appearance, behavior, mortality, weight gain, hematology, gross pathology and histopathology.

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

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.0 \text{ mg/L } (1{,}000 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology in rats exposed to carboxin in the diet for 90 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.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 3.5 \text{ mg/L } (3{,}500 \text{ ug/L})$$

where:

10 mg/kg/day = NOAEL, based on absence of effects on growth, hematology, blood chemistry, urinalysis, gross pathology and histopathology in rats exposed to carboxin in the diet for 90 days.

70 kg = assumed body weight of an adult.

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

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

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from

the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Holsing (1969a) has been selected to serve as the basis for calculation of the Lifetime HA for carboxin. In this study, rats were exposed to carboxin in the diet for 2 years. At 10 mg/kg/day, no significant effects were detected on appearance, behavior, body weight, mortality, hematology, blood chemistry, urinalysis, gross pathology or histopathology. Based on these data, a NOAEL of 10 mg/kg/day was identified. This value is supported by a 90-day rat study (Ozer, 1966) which also identified a NOAEL of 10 mg/kg/day, a 2-year feeding study in dogs by Holsing (1969b) which identified a NOAEL of 15 mg/kg/day, and an 84-week mouse study (Jessup et al., 1982) which identified a NOAEL of 8 mg/kg/day for males and 9 mg/kg/day for females.

Using the NOAEL of 10 mg/kg/day, the Lifetime HA for carboxin 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 effects on appearance, behavior, body weight, mortality, hematology, blood chemistry, urinalysis, gross pathology or histopathology in rats exposed to carboxin in the diet for 2 years.

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%) = 0.7 mg/L (700 ug/L)

where:

3.5 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Jessup et al. (1982) reported a possible compound-related increase in pulmonary adenoma/alveolar-bronchiolar adenoma frequency in male CD-1 mice that received carboxin in the diet at 751 mg/kg/day.

- Holsing (1969a) fed Charles River rats carboxin at dietary levels up to 30 mg/kg/day for 2 years, and detected no compound-related histopathologic changes. This study is limited, however, by the following factors: inadequate numbers of animals were used; survival was generally poor and, therefore, late-developing lesions may not have been detected; all tissues from all animals were not examined microscopically; and there was no adjustment in dietary levels of carboxin to account for growth of the test animals.

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

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), carboxin is classified in Group D: not classified. This category is for substances with inadequate human and animal evidence of carcinogenicity or for which no data are available.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- No existing criteria or standards for oral exposure to carboxin were located.

- The U.S. EPA (OPP) has proposed an Acceptable Daily Intake (ADI) of 0.4 mg/kg/day, based on a NOAEL of 200 ppm established in a 2-year rat feeding study and an uncertainty factor of 100 (U.S. EPA, 1981).

- The U.S. EPA has established residue tolerances for carboxin in or on raw agricultural commodities that range from 0.01 to 0.5 ppm (CFR, 1979).

VII. ANALYTICAL METHODS

- Analysis of carboxin 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 carboxin 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

- No information regarding treatment techniques to remove carboxin from contaminated waters is currently available.

IX. REFERENCES

Brusick, D.J., and R.J. Weir.* 1977. Mutagenicity evaluation of D-735. CBI Project No. 1683. Final Report 53727. Unpublished study. MRID 00053727.

Brusick, D., and C. Rabenold.* 1982. Mutagenicity evaluation of technical grade Vitavax in the Ames Salmonella microsome plate test. CBI Project No. 20988. Final Report. Unpublished study. MRID 00132453.

Byeon, W., H.H. Hyun and S.Y. Lee.* 1978. Mutagenicity of pesticides in the Salmonella/microsomal enzyme activation system. Korean J. of Microbiol. 14:128-134. MRID 00061590.

Chin, W.T., L.E. Dannals and N. Kucharczyk.* 1972. Environmental Fate studies on Vitavax. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:093515-A.) MRID 00002935.

Chin, W.T., G.M. Stone and A.E. Smith.* 1969. Fate of D735 in soil. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:091420.) MRID 00003041.

Chin, W.T., G.M. Stone and A.E. Smith.* 1970a. Degradation of carboxin (Vitavax) in water and soil. J. Agric. Food Chem. 18(4):731-732. MRID 05002176.

Chin, W.T., G.M. Stone, A.E. Smith and B. von Schmeling.* 1970b. Fate of carboxin in soil, plants, and animals. In: Proc. Fifth British Insecticide and Fungicide Conf., Nov. 17-20, 1969, Brighton, England. Vol. 2. pp. 322-327. MRID 05004996.

CFR. 1979. Code of Federal Regulations. 40 CFR 180.301. July 1, 1979. p. 527.

Dannals, L.E., C.R. Campbell and R.A. Cardona.* 1976. Environmental fate studies on Vitavax. Status report II on PR 70-15. Includes three updated methods. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:223866-A.) MRID 00003114.

Dzialo, D.G., and J.A. Lacadie.* 1978. Aerobic soil study of ^{14}C-Vitavax in sandy soil: Project no. 7746-1. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:236662-F.) MRID 00003225.

Dzialo, D.G., J.A. Lacadie, and R.A. Cardona.* 1978. Anaerobic soil metabolism of ^{14}C-Vitavax in sandy soil. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:236662-G.) MRID 00003226.

Holsing, G.C.* 1968a. Summary: Repeated dermal (Leary design) - rabbits. Project No. 798-148. Unpublished study. MRID 00021626.

Holsing, G.C.* 1968b. Three-generation reproduction study - rats. Final Report. Project No. 798-104. Unpublished study. MRID 00003032.

Holsing, G.C.* 1969a. 24-Month dietary administration - albino rats. Final Report. Project No. 798-102. Unpublished study. MRID 00003031.

Holsing, G.C.* 1969b. Two-year dietary administration - dogs. Final Report. Project No. 798-103. Unpublished study. MRID 00003030.

Jessup, D., G. Gunderson and R. Gail.* 1982. Lifetime carcinogenicity study in mice (Vitavax): 399-002a. Unpublished study. MRID 00114139.

Knickerbocker, M.* 1977. Teratologic evaluation of Vitavax technical in Sprague-Dawley rats. Unpublished study. MRID 00003102.

Lacadie, J.A., D.R. Gerecke and R.A. Cardona.* 1978. Vitavax ^{14}C laboratory column leaching study in clay loam: Project no. 7758. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:236662-H.) MRID 00003227.

Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Assoc. Food Drug Off. U.S. Q. Bull.

Matthews, R.J.* 1973. Acute LD_{50} rats, oral. Final Report. Unpublished study. MRID 00003012.

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

Myhr, B., and M. McKeon.* 1982. Evaluation of Vitavax technical grade in the primary rat hepatocyte unscheduled DNA synthesis assay. CBI Project No. 20991. Unpublished study. MRID 00132454.

Nandan, D., and D.S. Wagle. 1980. Metabolic effects of carboxin in rats. Symp. Environ. Pollut. Toxicol. pp. 305-312.

Ozer, B.L.* 1966. Report: Subacute (90 day) feeding studies with D-735 in rats. Unpublished study. MRID 00003063.

PIMS. 1980. Pesticide Incident Monitoring System. Summary of reported incidents involving carboxin. Report No. 383. Health Effects Branch, Hazard Evaluation Division, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C. October 1980.

Reagan, E., and P. Becci.* 1983. Acute oral LD_{50} assay in mice: (Vitavax Technical): FDRL Study No. 7581A. Unpublished study. MRID 00128469.

RTECS. 1985. Registry of Toxic Effects of Chemical Substances. National Institute for Occupational Safety and Health. National Library of Medicine Online File.

Schardein, J.L., and K.A. Laughlin.* 1981. Teratology study in rabbits: 399--042. Unpublished study. MRID 00086054.

Smilo, A.R., J.A. Lacadie and B. Cardona.* 1977. Photochemical fate of Vitavax in solution. (Unpublished study submitted by Uniroyal Chemical, Bethany, Conn. CDL:231932-C.) MRID 00003088.

Spare, W.* 1979. Report: Vitavax microbial metabolism in soil and its effect on microbes. (Unpublished study prepared by Biospherics, Inc., in cooperation with United States Testing Co., Inc., submitted by Uniroyal Chemical, Bethany, Conn. CDL:098029-A.) MRID 00005540.

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

U.S. EPA. 1981. U.S. Environmental Protection Agency. Carboxin. Pesticide Registration Standard. Office of Pesticides and Toxic Substances, Washington, DC.

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

U.S. EPA. 1986b. U.S. Environmental Protection Agency. U.S. EPA Method #1 - Determination of Nitrogen and Phosphorus Containing Pesticides in Ground Water by GC/NPD, January 1986 draft. Available from U.S. EPA's Environmental Monitoring and Support Laboratory, Cincinnati, OH.

Waring, R.N. 1973. The metabolism of Vitavax by rats and rabbits. Xenobiotica. 3:65-71.

Windholz, M., S. Budavari, R.F. Blumetti and E.S. Otterbein, eds. 1983. The Merck Index, 10th ed. Rahway, NJ: Merck and Co., Inc.

Wo, C., and R. Shapiro.* 1983. EPA acute oral toxicity. Report No. T-3449. Unpublished study. MRID 00143944.

Worthing, C. R. 1983. The Pesticide Manual. British Crop Protection Council.

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