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DRAFT

METHOMYL

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.

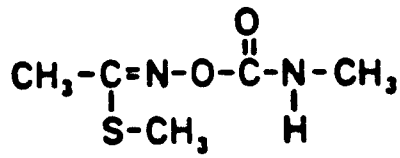
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as 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 th t 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. 16752-77-5

Structural Formula



S-Methyl-N[(methylcarbamoyl)oxy]-thioacetimidate

Synonyms

° Dupont Insecticide 1179; Dupont 1179; Insecticide 1,179; Insecticide 1179; IN 1179, Lannate; Mesomile; Nudrin; SD 14999; WL 18236 (Meister, 1983).

Uses

° Methomyl is a carbamate insecticide used to control a broad spectrum of insects in agricultural and ornamental crops (Meister, 1983).

Properties (Meister, 1983; Windholz et al., 1983; Cohen, 1984; CHEMLAB, 1985; and TDB, 1985)

Chemical Formula	$C_5H_{10}O_2N_2S$
Molecular Weight	162.20
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	78 to 79°C
Density (24°C)	1.29
Vapor Pressure (25°C)	5×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (25°C)	10,000 mg/L
Log Octanol/Water Partition Coefficient	-3.56
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

° Methomyl has been found in 2 of 446 surface water samples analyzed and in 25 of 1,023 ground water samples (STORET, 1987). Samples were collected at 110 surface water locations and 1,000 ground water locations, and methomyl was found in California, Georgia and Texas. The 85th percentile of all non-zero samples was 2 ug/L in surface water and 10 ug/L in ground water sources. The maximum concentration found in surface water was 2 ug/L and in ground water it was 10 ug/L.

Environmental Fate

- In laboratory and greenhouse studies, methomyl was more rapidly degraded in a sandy loam and a California soil than in silt loam soils, with 21, 31, and 44 to 48% of the applied methomyl remaining in the respective soils 42-45 days after treatment. The major degradation product was carbon dioxide, which accounted for 23 to 47% of the applied methomyl after 42 to 45 days. A minor degradation product, S-methyl-N-hydroxy-thioacetimidate (a possible hydrolysis product), was also found. Methomyl half-lives were less than 30 days in sandy loam soil, less than 42 days in California soil, and approximately 45 days in muck and silt loam soils. In a sterilized Flanagan silt loam soil, 89% of the methomyl remained 45 days after application, indicating that methomyl degradation in soil is primarily a microbial process (Harvey, 1977a,b).

- The nitrogen-fixing ability of some bacteria was severely reduced (by as much as 85%) when methomyl was applied at 20 to 160 ppm (Huang, 1978).

- In another study, methomyl (18 ppm) had no effect on fungal and bacterial population or on carbon dioxide production in either silt loam or fine sand soils (Peeples, 1977).

- No methomyl residues were detected in a muck soil 7 to 32 days after treatment (E.I. DuPont de Nemours and Co., 1971).

- The environmental fate of methomyl has also been the subject of several undated, unpublished reports (Harvey, undated a,b; Harvey and Pease; Han).

III. PHARMACOKINETICS

Absorption

- Single oral doses of 1-^{14}C-methomyl (purity not specified) were administered via gavage to female CD rats as a suspension in 1% aqueous methylcellulose. Ninety-five percent of the dose could be accounted for in excretory products or tissue residues, indicating virtual complete absorption from the gastrointestinal tract (Andrawes et al, 1976).

- Baron (1971) reported that in rats given a single oral dose of 5 mg/kg of 1-^{14}C-labeled methomyl (purity not specified), approximately 2% of the original label was excreted in the feces after 3 days, indicating essentially complete gastrointestinal absorption.

Distribution

- Baron (1971) fed a single oral dose of 1-^{14}C-labeled methomyl (5 mg/kg, purity not specified) to rats and analyzed 13 major tissues for residues at 1 and 3 days after dosing. Only 10% of the label was present in

tissues 24 hours after dosing, with no evidence of accumulation at any site. By this time, over 40% of the label had been excreted via the lung. At 3 days after dosing, tissue residues were essentially unchanged from day 1, suggesting incorporation of label into tissue components.

- Baron (1971) reported that feeding methomyl to a lactating cow at levels of 0.2 or 20 ppm in the diet (duration not specified) resulted in very low residues (less than 0.02 ppm) in the milk, meat, fat, liver and kidney.

Metabolism

- According to Baron (1971), in 72 hours approximately 15 to 23% of a 5-mg/kg oral dose of 1-^{14}C-labeled methomyl in rats could be accounted for as carbon dioxide, 33% as another metabolite in expired air, and 25% as metabolites in the urine.

- Harvey (1974) reported that in the rat, 1-^{14}C-labeled methomyl (dose and purity not specified) was metabolized to carbon dioxide (25%) or acetonitrile (50%) within 72 hours.

- Andrawes et al. (1976) reported that single oral doses of 4 mg/kg were rapidly metabolized in the rat. In exhaled air, carbon dioxide and acetonitrile were the major metabolites. In 24-hour urine samples, polar metabolites (80%) and acetonitrile (18%), both free and conjugated, were found with free methomyl, methy(o), the oxime and the sulfoxide oxime detected at low levels.

- Dorough (1977), in a series of studies with ^{14}C-labeled isomeric forms of methomyl, confirmed the report by Harvey (1974) of the excretion of labeled carbon dioxide and acetonitrile in the expired air of treated rats. In addition, nearly complete (79 to 84%) hydrolysis of the ester linkage was apparent within 6 hours, prior to the major formation of carbon dioxide and acetonitrile from methomyl. The author suggested the following pathway: partial isomerization of methomyl is followed by hydrolysis of the two isomeric forms to yield two isomeric oximes that then break down to carbon dioxide and acetonitrile at different rates. No additional metabolites were identified.

Excretion

- Baron (1971) stated that within 72 hours after receiving a single oral dose of 1-^{14}C-labeled methomyl, rats excreted 15 to 23% as carbon dioxide, 33% as other metabolites in the expired air and approximately 16 to 27% as methomyl and metabolites in the urine.

- Harvey (1974) reported that 75% of an oral dose of 1-^{14}C-labeled methomyl (dose and purity not specified) was excreted by rats within 72 hours, 50% as acetonitrile and 25% as carbon dioxide in the expired air. In contrast to other carbamates, sulfur-containing metabolites were not found in the urine.

° Andrawes et al. (1976) reported that single oral doses (4 mg/kg) of 1-^{14}C-labeled methomyl were rapidly excreted, with 32% of the dose recovered in urine, 19% in feces and 40% in exhaled air after 4 days.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

° Liddle et al. (1979) reported a case of methomyl poisoning in Jamaica, W.I., involving five men who had eaten a meal that included unleavened bread. Methomyl was discovered in an unlabeled plastic bag in a tin can, and had evidently been used as salt in preparation of the bread. Approximately 3 hours after the meal, the men were found critically ill, frothing at the mouth, twitching and trembling. Three were dead on arrival at the hospital. One of the two survivors showed generalized twitching and spasms, fasciculation, and respiratory impairment thought to be due to severe bronchiospasms. The other patient walked unaided and appeared generally normal. Both patients were given atropine intravenously, and the symptomatic patient recovered within 2 hours after treatment. Methomyl was confirmed in the stomach contents of each of the men who died, and analysis of the bread indicated that it contained 1.1% methomyl. It was stated that two of the victims had eaten about 75 to 100 g of bread each, or 0.82 to 1.1 g of methomyl. From these data it may be calculated that a dose of 12 to 15 mg/kg body weight can be fatal in humans.

° Araki et al. (1982) reported a case of a 31-year old woman who committed suicide, giving methomyl in drinks to herself and her two children. The 9-year-old elder son survived. In autopsies performed on the mother and the 6-year-old son, the mucous membranes of the stomach were blackish-brown, markedly edematous and congested. The lungs were heavy and congested. On the basis of measured stomach contents and tissue levels, it was estimated that the total doses taken were 2.75 g (55 mg/kg) by the mother and 0.26 g (13 mg/kg) by the child.

Long-term Exposure

° Morse and Baker (1979) reported on a survey of the health of workers in a plant that manufactured methomyl. The plant had also manufactured propanil, an herbicide manufactured from 3,4-dichloroaniline. The plant employed 111 workers in seven job categories. A complete work history, symptoms or history of poisoning, personal habits, and sources of other chemical exposure were obtained. Blood samples were collected from 100 of the 111 workers (96% males). Blood chemistries, blood counts, and cholinesterase (ChE) determinations were carried out. A routine urinalysis was also performed. Average employment at the plant was 2 years. Packaging workers had the highest rate of "methomyl" symptoms: small pupils (46%), nausea and vomiting (46%), blurred vision (46%) and increased salivation (27%). Biomedical

examination did not demonstrate significant effects, and acetylcholinesterase findings were normal. Other effects, such as chloracne, were reported but were considered related to propanil exposure.

Animals

Short-term Exposure

- The acute oral LD_{50} reported for methomyl in the fasted male and female rat ranged from 17 to 25 mg/kg (Bedo and Cieleszky, 1980; Dashiell and Kennedy, 1984; Kaplan and Sherman, 1977). The oral LD_{50} in the nonfasted rat was 40 mg/kg (Dashiell and Kennedy, 1984). Clinical signs in rats included chewing motions, profuse salivation, lacrimation, bulging eyes, fasciculations and tremors characteristic of ChE inhibition.

- The acute oral LD_{50} for methomyl in the mouse ranged from 27 to 55 mg/kg (Boulton et al., 1971; El-Sebae et al., 1979; Natoff and Reiff, 1973).

- The oral LD_{50} in hens was 28 mg/kg and in Japanese quail, 34 mg/kg. (Kaplan and Sherman, 1977).

- The 4-hour inhalation LC_{50} of methomyl in rats was 300 mg/m^3. Animals showed the typical signs of ChE inhibition, including salivation, lacrimation and tremors (ACGIH, 1984).

- Bedo and Cieleszky (1980) administered single oral doses of methomyl (purity not specified) by gavage to stock colony rats at dose levels of 0, 2, 3 or 10 mg/kg. The high dose (10 mg/kg) produced typical tremors in rats, and brain ChE levels were decreased. Mixed-function oxidase, glucose-6-phosphatase activity, glycogen, and vitamin A levels in the liver were unaffected. Apparently, dose levels of 2 or 3 mg/kg did not produce these effects.

- Woodside et al. (1978) fed methomyl (purity not specified) in the diet to male and female Wistar rats for 7 days at dose levels of 0, 5.0, 17 or 41 mg/kg/day in males and 0, 6.3, 15 or 39 mg/kg/day in females. Body weight gain was depressed at doses of 17 and 41 mg/kg/day in the males and at 15 and 39 mg/kg/day in the females. Liver and kidney weight were also depressed at 41 mg/kg/day in the male rat and at 15 and 39 mg/kg/day in the female rat. No effects were noted at the lowest doses. This study did not mention clinical signs of toxicity, and no measurements of plasma or brain ChE activity were reported. The No-Observed-Adverse-Effect-Level (NOAEL) identified in this study is 5.0 mg/kg/day.

- Bedo and Cieleszky (1980) fed methomyl (purity not specified) in the diet at levels of 0, 100, 400 or 800 ppm to young adult male and female stock colony rats for 10 days. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to 0, 5, 20 or 40 mg/kg/day. Brain ChE inhibition could not be detected at any dietary level. The only findings were increased mixed-function oxidase activity in the livers of female rats at 400 and 800 ppm. This study identified a NOAEL of 800 ppm (40 mg/kg/day).

° Kaplan and Sherman (1977) administered methomyl (90% pure) to six male Charles River-Cesarian Derived (ChR-CD) rats at 0 or 5.1 mg/kg/day, five times a week for 2 weeks. Following treatment, survival, clinical signs, ChE activity and histopathology were evaluated. All rats survived the dosing period. Clinical signs in treated rats included chewing motions, profuse salivation, lacrimation, bulging eyes, fasciculations and tremors characteristic of ChE inhibition. The authors reported that the signs became less pronounced after the first week of dosing, indicating some degree of adaptation. Plasma ChE was comparable to control levels, and no compound-related histopathologic effects were reported. A Lowest-Observed-Adverse-Effect-Level (LOAEL) of 5.1 mg/kg/day was identified from this study.

Dermal/Ocular Effects

° Kaplan and Sherman (1977) applied a 52.8% aqueous suspension of methomyl to the clipped, intact skin of six adult male albino rabbits and covered the area with an occlusive patch for a 24-hour period. The lethal dose was found to be greater than 5,000 mg/kg, the maximum feasible dose.

° McAlack (1973) reported a 10-day subacute exposure of rabbit skin to methomyl. Male albino rabbits, six per dosage group, were treated with 0, 50 or 100 mg/kg/day for 10 days. The compound was diluted in water (29% solution), placed on the skin and covered with an occlusive covering for 6 hours per day. No signs of ChE inhibition were noted in any of the animals.

° Ten rabbits survived 15 daily doses of 200 mg/kg/day of methomyl applied to intact skin. When the same dose of methomyl was applied to abraded skin, rabbits showed labored respiration, nasal discharge, salivation, excessive mastication, tremors, poor coordination, hypersensitivity and abdominal hypertonia. These effects occurred within 1 hour after dosing in most animals. One animal died after the first dose, and another died after the eighth application. These deaths appeared to be compound-related (Kaplan and Sherman, 1977).

Long-term Exposure

° Kaplan and Sherman (1977) reported a 90-day feeding study in ChR-CD rats (10/sex/group) given food containing methomyl (90% purity) at dietary levels of 0, 10, 50, 125 or 250 ppm active ingredient (a.i.). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 0.5, 2.5, 6.2 or 12.5 mg/kg/day. After 6 weeks, the 125-ppm dose was increased to 500 ppm (25 mg/kg/day) for the remainder of the study. Clinical signs, biochemical analyses (including plasma ChE) and urinalyses were not abnormal. In a few cases, lower hemoglobin valves were observed at one month in females receiving 50 ppm (2.5 ug/kg/day) and at two months in males receiving 250 ppm. At three months, the red cell count of female rats at 250 ppm was somewhat lower than controls, but still within normal limits. These findings were consistent with moderate increases of erythroid components observed histologically in the bone

marrow. Microscopic examination of all other tissues showed no consistent abnormalities. Based on these observations, this study identified a NOAEL of 50 ppm (2.5 mg/kg/day) and a LOAEL of 250 ppm (12.5 mg/kg/day).

- In a 90-day study using dogs, Kaplan and Sherman (1977) fed methomyl (90% pure) to four males and four females, 11 to 13 months of age, at dietary levels of 0, 50, 100 or 400 ppm a.i. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 1.25, 2.5 or 10 mg/kg/day. Hematological, biochemical and urine analyses were conducted at least three times on each dog prior to the study and then at 1, 2 and 3 months during the exposure period. Body weight was monitored weekly. At necropsy, organ weights were recorded, and over 30 tissues were prepared for histopathologic examination. No effects attributable to methomyl were found during or at the conclusion of the study. Based on these data, a NOAEL of 10 mg/kg/day was identified.

- Homan et al. (1978) reported a 13-week dietary study of methomyl (purity not specified) in F-344 rats. Dose levels were reported to be 0, 1, 3, 10.2, or 30.2 mg/kg/day for male rats, and 0, 1, 3, 9.9 or 29.8 mg/kg/day for female rats. There were no deaths or clinical signs of toxicity. The body weight gain of females (but not males) was significantly depressed at all dose levels from day 28 until completion of the study. Kidney weight to body weight ratios were significantly increased in female rats at the two highest dose levels. Red blood cell ChE activity was elevated at the high dose levels, but plasma and brain ChE levels were normal at all dose levels. Histopathological examination of 31 tissues from representative high-dose and control animals revealed no significant effects. Weights of brain, liver, kidney, spleen, heart, adrenals and testes were not altered. This study identified a NOAEL of 3 mg/kg/day and a LOAEL of 9.9 mg/kg/day.

- Bedo and Cieleszky (1980) reported a 90-day feeding study of methomyl in male and female rats receiving dietary levels of 100 or 200 ppm. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of 5 or 10 mg/kg/day. At 200 ppm, the female rats showed decreased brain ChE activity, decreased liver vitamin A content and elevated total serum lipids. This study identified a NOAEL of 100 ppm (5 mg/kg/day).

- Kaplan and Sherman (1977) reported a 22-month dietary feeding study in which Charles River-CD male and female rats were fed methomyl (90 or 100% pure) at dietary levels of 0, 50, 100, 200 or 400 ppm a.i. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 2.5, 5, 10 or 20 mg/kg/day. Mortality data were not reported. At autopsy, 9 of 13 males and 21 of 23 females at the 400-ppm level had kidney tubular hypertrophy and vacuolization of epithelial cells of the proximal convoluted tubules. Compound-related histological alterations were also seen in the spleens of female rats at the 200-ppm dose level. No effects were seen on ChE levels in plasma or

red blood cells. This study identified a LOAEL of 200 ppm (10 mg/kg/day) and a NOAEL of 100 ppm (5 mg/kg/day).

- Kaplan and Sherman (1977) performed a 2-year feeding study in beagle dogs (four/sex/dose). Methomyl (90 or 100% pure) was supplied at dietary levels of 0, 50, 100, 400 or 1,000 ppm a.i. Assuming that 1 ppm in the diet of dogs is equivalent to 0.025 mg/kg/day (Lehman, 1959), this corresponds to doses of about 1.25, 2.5, 10 or 25 mg/kg/day. Hematological, biochemical (including plasma- and red-blood-cell ChE activity) and urinanalyses were conducted once on each dog prior to the start of the study, at 3, 6, 12, 18 months during the exposure period and at 24-month sacrifice. At 1 year, one male and one female per dose group were sacrificed for histopathological examination. One female dog at the 1,000-ppm dose level died after 8 weeks in the study, and a replacement dog died after 18 days. Death was preceded by convulsive seizures and coma. These deaths appear to be compound-related. Two male dogs in the 1,000-ppm dose group showed clinical signs during week 13, including tremors, salivation, incoordination and circling movements. Hematological studies revealed slight-to-moderate anemia in five dogs (1,000-ppm dose group) at 3 months, which persisted in one dog to sacrifice. No compound-related signs or effects were noted with respect to appetite, body weight changes, biochemical studies (including ChE) and urinanalyses. Dose-related histopathological changes were seen in kidney and spleen of animals receiving 400 and 1,000 ppm. Changes were also seen in livers and bone marrow of animals receiving 1,000 ppm. Pigment deposition was noted in the epithelial cells of the proximal convoluted tubules of the kidney in males at 400 and 1,000 ppm and in females at 1,000 ppm. A minimal-to-slight increase in bile duct proliferation and a slight increase in bone marrow activity was seen in animals receiving 1,000 ppm. The authors concluded that histological results indicated a NOAEL of 100 ppm (2.5 mg/kg/day). Minimal histopathological changes seen in the kidneys and spleen of animals receiving 400 ppm (10 mg/kg/day), identified this level as the LOAEL.

- Hazelton Laboratories (1981) reported a 2-year study of methomyl (purity not specified) in mice. Male and female CD-1 mice (80/sex/dose) were fed methomyl in the diet at dose levels of 0, 50, 100, or 800 ppm for 104 weeks. Assuming 1 ppm in the diet to be equivalent to 0.15 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 7.5, 15 or 120 mg/kg/day. Survival was significantly reduced (no details provided) in both males and females at the 800-ppm dose level by week 26. The 800 ppm dose level was reduced to 400 ppm (1.0 mg/kg/day) at week 28 and then further reduced to 200 ppm (30 mg/kg/day) at week 39. At week 39, the 100 ppm was decreased to 75 ppm (11.2 mg/kg/day). Survival was depressed in all groups of treated males at 104 weeks. No compound-related histopathological changes were noted in tissues of animals necropsied at 104 weeks. A LOAEL of 50 ppm (7.5 mg/kg/day; the lowest dose tested) may be identified based on decreased survival.

Reproductive Effects

- Male and female weanling Charles River-CD rats were fed methomyl (90% pure) at dietary levels of 0, 50, or 100 ppm a.i. for 3 months.

Assuming that 1 ppm in the diet of weanling rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to about 0, 2.5 or 5 mg/kg/day. Ten males and twenty females from each group were bred and continued on the diet through three generations. No adverse effects were reported on reproduction or lactation, and no pathologic changes were found in the weanling pups of the F_{3b} generation (Kaplan and Sherman, 1977). A NOAEL of 5 mg/kg/day was identified from the highest dose tested.

Developmental Effects

- New Zealand White rabbits, five per group, were dosed with 0, 2, 6 or 16 mg/kg of methomyl (98.7% pure) on days 7 through 19 of gestation. One animal died at the 16 mg/kg dose level, exhibiting characteristic signs of ChE inhibition, including tremors, excitability, salivation and convulsions. No adverse effects were observed at any dose level on embryo viability or on the frequency of soft-tissue or skeletal malformations (Feussner et al., 1983). This study identified a maternal NOAEL of 6 mg/kg and a teratogenic NOAEL of 16 mg/kg/day, the highest dose tested.

- Kaplan and Sherman (1977) fed methomyl (90% pure) to pregnant New Zealand White rabbits on days 8 to 16 of gestation at dietary levels of 0, 50 or 100 ppm active ingredient. Assuming that 1 ppm in the diet of rabbits is equivalant to 0.03 mg/kg/day (Lehman, 1959), this corresponds to doses of about 0, 1.5 or 3 mg/kg/day. One-third of the fetuses were stained with Alizarin Red S and cleared for skeletal examination. Since no soft tissue or skeletal abnormalities were observed at any dose level tested, a NOAEL of 3 mg/kg/day was identified.

Mutagenicity

- Methomyl has been reported to be negative in the Ames test utilizing Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 without metabolic activation (Blevins et al., 1977; Moriya et al., 1983). Waters et al. (1980) reported methomyl as negative with and without metabolic activation in strains TA 100, TA 1535, TA 1537 and TA 1538.

Carcinogenicity

- Kaplan and Sherman (1977) fed ChR-CD rats (35/sex/dose) methomyl (90% pure) in the diet at levels of 0, 50, 100, 200 or 400 ppm active ingredient for 22 months. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these doses correspond to about 0, 2.5, 5, 10 or 20 mg/kg/day. Gross and histological examination revealed no increased tumor incidence in either male or female rats.

- Hazelton Laboratories (1981) reported the results of a 2-year study of methomyl (purity not specified) in CD-1 mice (80/sex/dose). Initial dose levels were 0, 50, 100, or 800 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman, 1959), these

doses correspond to 0, 7.5, 15 or 120 mg/kg/day. Because of early mortality, the 800-ppm dose was reduced to 400 ppm (60 mg/kg/day) at week 28, and then to 200 ppm (30 mg/kg/day) at week 39. At week 29, the 100-ppm dose was reduced to 75 ppm (11.2 mg/kg/day). Histological examination at necropsy did not reveal any treatment-related effects on tumor incidence.

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:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

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 found in the available literature was suitable for determination of the One-day HA value for methomyl. It is, therefore, recommended that the Drinking Water Equivalent Level (DWEL), adjusted for a child, (0.25 mg/L) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The health effects associated with acute and subchronic exposure to methomyl are primarily associated with cholinesterase (ChE) inhibition. Symptoms of ChE inhibition have been shown in rats at doses (via gavage) as low as 5.1 mg/kg/day for 2 weeks (Kaplan and Sherman, 1977). Methomyl incorporated into the diet may have less dramatic effects; no ChE effects were observed in rats exposed subchronically to methomyl at dietary levels of 100 ppm (5 mg/kg/day)(Kaplan and Sherman, 1977; Bedo and Cieleszky, 1980). Animal studies may be misleading in assessment of human toxicity. No controlled human studies have been performed, but human fatalities from methomyl ingestion after a single exposure to an estimated dose of 12 mg/kg in bread or 13 mg/kg in drinks have been reported (Liddle et al., 1979; Araki et al., 1982).

Because the timing and nature of administration can profoundly affect the expression of methomyl toxicity, and little margin of safety can be expected between doses that are fatal and those that cause little or no acute toxicity, the available studies were judged to be inadequate for the basis of the Ten-day HA value. Therefore, it is recommeded that the DWEL, adjusted for a 10-kg child (0.25 mg/L), be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The onset of subchronic or chronic methomyl toxicity appears to occur at doses similar to those that cause acute toxicity. Kidney toxicity (increased kidney weight and hypertrophy) in acute, subchronic and chronic conditions has been reported at doses of 15, 9.9 and 10 mg/kg/day, respectively (Woodside et al., 1978; Homan et al., 1978; Kaplan and Sherman, 1977). Acute ChE inhibition in rats exposed to methomyl via gavage has been reported to occur at doses as low as 5.1 mg/kg/day, and human fatalities from methomyl ingestion of approximately 12 mg/kg in bread and 13 mg/kg in drinks have been reported (Liddle et al, 1979; Araki et al., 1982).

Little margin of safety can be expected between doses of methomyl that are fatal and those that cause little or no longer-term toxicity. Therefore, it is recommended that the DWEL adjusted for the child (0.25 mg/L) be used at this time as a conservative estimate of the Longer-term HA value.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Chronic exposure to methomyl in the diet induces renal toxicity in rats and dogs. Rats exposed to 900 ppm (20 mg/kg/day) for 22 months exhibited

kidney tubular hypertrophy and vacuolation of the eptithelial cells, and dogs exposed to 400 ppm (10 mg/kg/day) for 2 years exhibited swelling and increased pigmentation of the epithelial cells of the proximal tubules (Kaplan and Sherman, 1977). Effects on the kidney (increased weight) have also been observed in rats exposed to 9.9 mg/kg/day in the diet for 13 weeks (Homan et al., 1978). The NOAEL of 2.5 mg/kg/day identified from the dog study is a conservative estimate of the NOAEL and serves as the basis for the Lifetime HA.

In the Kaplan and Sherman (1977) study, beagle dogs (4/sex/dose) were exposed to 50, 100, 400 or 1,000 ppm methomyl in the diet for 2 years (1.25, 2.5, 10 and 25 mg/kg/day). Dogs receiving 1.25 or 2.5 mg/kg/day showed no evidence of toxic effects. Those receiving 10 mg/kg/day exhibited histopathological changes in the kidney and spleen. In addition to these effects, animals receiving the highest dose also exhibited symptoms of central nervous system (CNS) toxicity, as well as liver and bone marrow effects.

Using a NOAEL of 2.5 mg/kg/day, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(2.5 \text{ mg/kg/day})}{(100)} = 0.025 \text{ mg/kg/day}$$

where:

2.5 mg/kg/day = NOAEL, based on absence of effects on blood chemistry (including ChE activity), hematology, urinalysis, histopathology or body weight in dogs exposed 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)

$$DWEL = \frac{(0.025 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.875 \text{ mg/L (875 ug/L)}$$

where:

0.025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

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

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

$$DWEL_{child} = \frac{(0.025 \text{ mg/kg/day}) (10 \text{kg})}{(1 \text{ L/day})} = 0.25 \text{ mg/L (250 ug/L)}$$

where:

0.025 mg/kg/day = RfD

10 kg = assumed body weight of a child

1 L/day = assumed daily water consumption of child

Step 3: Determination of a Lifetime Health Advisory

Lifetime HA = (0.875 mg/L) (20%) = 0.175 mg/L (175 ug/L)

where:

0.875 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Two-year carcinogenicity studies in rats and mice (Kaplan and Sherman, 1977; Hazelton Laboratories, 1981) have not revealed any evidence of carcinogenicity.
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of methomyl.
- Applying the criteria described in EPA's final guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), methomyl is classified in Group D: not classifiable as to human carcinogenicity. This group is used for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The National Academy of Sciences (NAS, 1983) has a Suggested-No-Adverse-Response-Level (SNARL) of 0.175 mg/L, which was calculated using an uncertainty factor of 100 and a NOAEL of 2.5 mg/kg/day identified in the 2-year dog study by Kaplan and Sherman (1977).
- Residue tolerances have been established for methomyl in or on raw agricultural commodities (U.S. EPA, 1985). These tolerances are based on an ADI value of 0.025 mg/kg/day, based on a NOAEL of 2.5 mg/kg/day in dogs and an uncertainty factor of 100. Residues range from 0.1 (negligible) to 40 ppm.
- The World Health Organization identified a Temporary ADI of 0.01 mg/kg/day (Vettorazzi and Van den Hurk, 1985).
- ACGIH (1984) has adopted a threshold limit value (TLV) of 0.2 mg/m^3 as a time-weighted average exposure for an 8-hour day.

VII. ANALYTICAL METHODS

- Analysis of methomyl is by a high-performance liquid chromatographic (HPLC) procedure used for the determination of N-methyl carbamoyloximes and N-methylcarbamates in drinking water (U.S. EPA, 1984). In this method, the water sample is filtered and a 400-uL aliquot is injected into a reverse-phase HPLC column. Compounds are separated by gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methyl amine formed during hydrolysis is reacted with o-phthalaldehyde to form a fluorescent derivative that is detected using a fluorescence detector. The method detection limit for methomyl has been estimated to be approximately 0.7 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) adsorption will remove methomyl from water. Whittaker (1980) experimentally determined adsorption isotherms for methomyl solutions on GAC.

- Whittaker (1980) reported the results of GAC columns operating under benchscale conditions. At a flow rate of 0.8 gpm/sq ft and empty bed contact time of 6 minutes, methomyl breakthrough (when effluent concentration equals 10% of influent concentration) occurred after 124 bed volumes (BV). When a bi-solute methomyl-metribuzin solution was passed over the same column, methomyl breakthrough occurred after 55 BV.

- Treatment technologies for the removal of methomyl from water are available and have been reported to be effective (Whittaker, 1980). However, the selection of individual or combinations of technologies must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

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