ALDICARB, ALDICARB SULFOXIDE AND ALDICARB SULFONE

1995

Drinking Water Health Advisory

Health and Ecological Criteria Division
Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
Washington, DC 20460

I. INTRODUCTION

0 The Health Advisory (HA) Program, sponsored by the Office of Water (OW), 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 individual's lifetime) and lifetime exposures based on data describing noncarcinogenic endpoints 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.

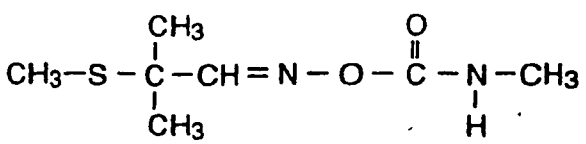
This Health Advisory (HA) is based on the revision of the 1987 drinking water HA document for these contaminants. The quantification of toxicological effects in this HA is based on the available new information on these chemicals up to 1994, including the November 1992 revised RfDs.

II. GENERAL INFORMATION AND PROPERTIES

CAS Nos. Aldicarb – 116-06-3
Aldicarb sulfoxide – 1646-87-3
Aldicarb sulfone – 1646-88-4

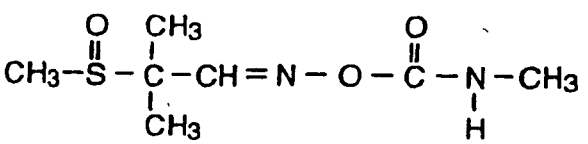
Structural Formulas

Aldicarb:



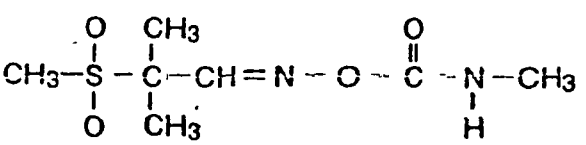
2-Methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime

Aldicarb Sulfoxide:



2-Methyl-2-(methylsulfinyl)propionaldehyde O-(methylcarbamoyl)oxime

Aldicarb Sulfone:



2-methyl-2-(methylsulfonyl)propionaldehyde O-(methylcarbamoyl)oxime

Synonyms

- Aldicarb: Temik
- Aldicarb sulfoxide: Temik sulfide
- Aldicarb sulfone: Aldoxicarb, Standak

Uses

- Pesticide (insecticide, nematocide, acaracide)

Properties (Registrant's unpublished data; FAO/WHO, 1980; Knaak et al., 1966; Kuhr and Dorough, 1976; Lemley and Zhong, 1983; Martin and Worthing, 1977)

	Aldicarb	Aldicarb Sulfoxide	Aldicarb Sulfone
Chemical Formula	$C_7H_{14}O_2N_2S$	$C_7H_{14}O_3N_2S$	$C_7H_{14}O_4N_2S$
Molecular Weight	190.3	206.06	222.1
Physical State	White crystals	Crystalline	Crystalline
Boiling Point (°C)	Decomposes above 100°C	–	–
Melting Point (°C)	100	108-110	132-133
Density	–	–	–
Vapor Pressure (mm Hg)	0.05 (20°C)	–	–
Specific Gravity	1.195 (25°C)	–	–
Water Solubility (g/L)	0.6 (room temp.)	330	10 (20°C)
Log Octanol/ Water Partition Coefficient	–	–	–
Taste Threshold (Water)	–	–	–
Odor Threshold (Water)	–	–	–
Odor Threshold (Air)	Odorless to light sulfur smell	–	–

Occurrence

Water

- Aldicarb will be released to the environment from its manufacture and use as a systemic pesticide, acaricide, and nematocide (Howard, 1991; Budavari, 1989).

- In a data base that describes the extent of ground-water contamination by aldicarb in the U.S., aldicarb was detected in 19 of 25 States. A total of 12 States reported levels above 10 µg/L of which 10 had concentrations above 30 µg/L and three had concentrations greater than 100 µg/L (Howard, 1991).

- In the U.S. EPA's National Survey of Pesticides in Drinking Water Wells (National Pesticide Survey), aldicarb was not found in 566 community water system wells and 783 rural domestic drinking water wells, with a minimum reporting limit of 0.71 µg/L. Based on the precision of the survey, U.S. EPA estimates that the maximum number of wells that may contain aldicarb nationwide is 750 (0.8%) community water supply wells and 83,100 (0.8%) rural domestic wells based on a 95% upper-bound confidence level (U.S. EPA, 1990).

- Based on a review of the literature, Cohen et al. (1984) found that typical aldicarb levels detected in well water from 13 States ranged from 1-50 μg/L.

- According to Miller et al. (1990), the California Department of Food and Agriculture's well inventory data base reported that aldicarb was undetected in 520 samples (456 wells) from 25 California counties. Aldicarb's degradation products, aldicarb sulfoxide and aldicarb sulfone, were detected in 7 wells and 8 wells, respectively, out of 67 wells sampled in 14 counties. Concentrations ranged from 0.18-1.02 μg/L for aldicarb sulfone and from 0.21-1.97 μg/L for aldicarb sulfoxide.

- Klaseus et al. (1988) reported that in a cooperative survey between the Minnesota Department of Health and the Minnesota Department of Agriculture, aldicarb was found in 2 wells (5 samples) from 100 private wells and was undetected in 400 public wells sampled. Detections ranged from 0.50-30.6 μg/L with a median of 9.0 μg/L. The detection limit was 0.5 μg/L.

- Jones and Beck (1984) reportedly found aldicarb in 10 of 39 surface water samples and 3 of 53 ground-water samples from six Florida citrus groves. Concentrations ranged from <1-4 μg/L in surface water samples and all three ground-water samples contained 1 μg/L.

- In a 1981 New York Department of Health survey of State drinking water, aldicarb was undetected in 80 finished water samples from 69 community water systems. The detection limit was 1 μg/L (Close et al., 1982).

- In a 1984 statewide survey of Wisconsin well waters, aldicarb was detected in 201 of 1,258 wells. A total of 70 wells contained concentrations in excess of 10 μg/L. The detection limit was approximately 1 μg/L (Krill, 1986).

Food

- In the FDA's pesticide residues monitoring program, samples of domestic (499 samples) and imported (770 samples) fruits and vegetables were analyzed for aldicarb residues during the period from October 1, 1988 to September 30, 1989. Specifically, samples included potatoes (137), peppers (116), watermelon (86), cantaloupe (72), pineapples (50), and bananas (40). A total of four samples contained aldicarb at or above the detection limit of 1 ppm, all of which were samples of domestic potatoes. Concentrations reportedly ranged from 30-150 ppm (U.S. FDA, 1990).

- Based on FDA Total Diet Survey sampling results from the period April 1982 to April 1985, the daily dietary intake of aldicarb for eight different age-sex groups were calculated to be as follows: Infants (6-11 months) 0.002 μg/day, toddlers (2 years) 0.006 μg/day, females (14-16 years) 0.009 μg/day, males (14-16 years) 0.008 μg/day, females (25-30 years) 0.008 μg/day, males (25-30 years) 0.011 μg/day, females (60-65 years) 0.014 μg/day, and males (60-65 years) 0.018 μg/day (Gunderson, 1986).

Air

- No data were available concerning aldicarb levels in air. However, it is anticipated that levels in ambient air may be negligible due to its low vapor pressure.

Environmental Fate

- If released to soil, aldicarb is expected to be degraded both biologically and chemically, being subject to oxidation and hydrolysis. It is expected to be mobile in soil and has been found to be susceptible to leaching. Vaporization from soils will vary with soil moisture, evaporating more rapidly from dry soils (Howard, 1991). In a laboratory study by (Bull et al., 1970 as cited in Howard, 1991), 8.2% and 16.7% of aldicarb applied to wet and dry sand (25°C), respectively, was lost over a 24-hour period.

- The adsorption coefficient (K_{oc}) for aldicarb was measured in several studies with values ranging from 8.2-37 (Howard, 1991). Kenaga (1980) estimated a similar value of 32. Based on these K_{oc} values, aldicarb should not adsorb significantly to soil.

- In soils where oxidation and hydrolysis rates are slow compared to the leaching rates, aldicarb will be leached into ground water. The susceptibility of aldicarb to leaching is supported by monitoring results which indicate the presence of aldicarb in the ground waters of many States (Howard, 1991; Cohen et al., 1984).

- The hydrolysis of aldicarb in soil is catalyzed by both acids and bases. The rate of hydrolysis was found to vary with pH in some experiments with half-lives as low as 0.4-3.2 days (at 25°C) for a pH range of 4.5-4.9 and as much as 23 days (at 15°C) for a pH of 7.2. In another study, however, rates varied only slightly in the pH range of 4-10 with half-lives found to be approximately 0.67 days (Howard, 1991).

- Aldicarb is oxidized in soil to the sulfoxide and sulfone by chemical processes and is probably mediated biologically in some cases. It has been reported that 8-20% of the aldicarb added to soil is oxidized immediately to the sulfone, presumably by chemical oxidation, followed by slower oxidation rates. The overall oxidation half-life for

aldicarb in soil varies from 1.7-12 days (pH 1-10), but remains fairly constant over the pH range of 4.4-10. The lowest oxidation half-lives have been reported for greenhouse soil, sandy loam, and Palmyrian soil, ranging from less than 1 day to several days, while in clay loam and peaty sand half-lives of about 1 week were measured. In surface soils, oxidation occurs more rapidly than in subsurface soils and fertilization may result in increased oxidation rates (Howard, 1991).

- Depending on the soil type, hydrolysis of aldicarb may occur at a faster or slower rate than oxidation. Results from field studies have found aldicarb half-lives ranging from several days to several months. In fields previously treated with aldicarb, degradation rates were found to be more rapid (Howard, 1991).

- In water, aldicarb is not expected to adsorb significantly to bottom sediments or suspended particles based on its low K_{oc} value. Experimental results indicate that it will be subject to hydrolysis with rates varying with pH and temperature. At pH 7.5 or lower and temperatures of 15°C or lower, aldicarb is relatively stable to hydrolysis. The half-life at pH 7.5 and 15°C is 1,900 days and 3,240 days at pH 5.5 and 15°C. The lowest measured hydrolysis half-life was 131 days at a pH of 4 and a temperature of 20°C. Based on an estimated Henry's Constant of 4.17×10^{-9} atm-m^3/mole, volatilization from water should not be an important fate process. The volatilization half-life for aldicarb in lake and pond water was determined to be 5 days (Howard, 1991; Cohen et al., 1984).

- Degradation of aldicarb in ground water occurs at a slow rate. Under aerobic conditions, it does not degrade unless a relatively high pH exists (pH 8.5). In anaerobic studies, reported half-lives in ground water were between 62-1,300 days at a pH range of 7.7-8.3. Experimental results have shown that aldicarb sulfoxide is reduced to aldicarb in ground water under aerobic conditions and under anaerobic conditions when glucose is added (Howard, 1991). No studies on biodegradation in natural waters were found.

- Aldicarb has been shown to photolyze when irradiated at 254 nanometers in acetonitrile. No information was found, however, concerning photolysis of aldicarb in the environment (Howard, 1991).

- In the atmosphere, aldicarb may be partially adsorbed onto particulates in air based on a relatively low vapor pressure of 1×10^{-4} mm Hg. Aldicarb, which is not adsorbed onto air particulates, will be susceptible to vapor phase reactions with hydroxyl radicals, with an estimated half-life of 0.24 days (Howard, 1991).

- Aldicarb is not expected to bioconcentrate on aquatic organisms based on reported bioconcentration factors (BCF) of 42 and 4. Kenaga (1980) calculated the BCF to be 4 from the water solubility of aldicarb, while Garten and Trabalka (1983 as cited in Howard, 1991) measured a BCF of 42 in a microcosm study for a single species of fish.

III. PHARMACOKINETICS

Aldicarb:

Absorption

- Aldicarb is readily and almost completely absorbed through the gut in a variety of mammalian and non-mammalian species (Knaak et al., 1966; Andrawes et al., 1967; Dorough and Ivie, 1968; Dorough et al., 1970; Hicks et al., 1972; Cambon et al., 1979).

- Dermal absorption of aldicarb has been demonstrated in rabbits (Kuhr and Dorough, 1976; Martin and Worthing, 1977; West and Carpenter, 1966) and rats (Gaines, 1969) and would be expected to occur in unprotected humans in manufacturing and field application settings. West and Carpenter (1966) have shown that dermal absorption of aldicarb by rabbits is facilitated by the use of oil or an organic solvent as the application vehicle.

Distribution

- Aldicarb was distributed widely in the tissues of Holstein cows when administered in feed at 0.6 or 1.2 ppm (Dorough et al., 1970). Highest residues were found in the liver. When aldicarb was administered at 0.12 ppm in this study, residues were detected only in the liver. Aldicarb residues have also been found in cow's milk (Dorough and Ivie, 1968).

- In rats administered aldicarb orally, residues were found in all 13 tissue types analyzed. Hepatic residue levels were similar to those of many other tissues (Andrawes et al., 1967).

- Aldicarb (in a 1:1 molar ratio of the parent compound to the sulfone) administered orally to laying hens in a single dose for 21 consecutive days resulted in patterns of distribution that were similar for both exposure durations. The liver and kidneys were the main target organs (Hicks et al., 1972). Residues also were present in both the yolks and whites of the eggs laid by these hens.

Metabolism

- The metabolism of aldicarb involves both hydrolysis of the carbamate ester and oxidation of the sulfur to the sulfoxide and sulfone derivatives. All three of these compounds are active cholinesterase (ChE) inhibitors (Andrawes et al., 1967; Bull et al., 1967).

- Metabolic end products of aldicarb detected in both the milk and urine of a cow included the sulfoxides and sulfones of the parent compound. An oxime and a nitrile, as well as a number of unknown metabolites, were also detected (Dorough and Ivie, 1968).

Excretion

- Elimination of aldicarb and its metabolites occurs primarily via the urine, as demonstrated in rats (Knaak et al., 1966), cows (Dorough and Ivie, 1968) and chickens (Hicks et al., 1972).

- Excretion of aldicarb as CO_2 via the lungs has been demonstrated to be a minor route in rats (Knaak et al., 1966).

- Excretion of aldicarb is relatively rapid with reported 24-hour elimination values in rats and cows of approximately 80 to 90% of the administered dose (Knaak et al., 1966; Dorough and Ivie, 1968).

Aldicarb Sulfoxide:

Absorption

- Aldicarb sulfoxide is readily and almost completely absorbed through the gut in a variety of mammalian and non-mammalian species (Knaak et al., 1966; Andrawes et al., 1967; Dorough and Ivie, 1968; Dorough et al., 1970; Hicks et al., 1972; Cambon et al., 1979). Administration of oral doses of radiolabeled aldicarb sulfoxide to female rats resulted in 80-90% excretion of the radiolabel in the urine and 2-5% excretion in the feces within the first 24 hours (Andrawes et al., 1967).

- Dermal absorption of aldicarb sulfoxide by laboratory animals is highly dependent on the methodology employed, particularly the application vehicle. Studies by West and Carpenter (1966) have shown that aldicarb and its metabolites are absorbed when applied to the skin of rabbits; however, the rate and extent of absorption vary greatly. Aldicarb sulfoxide which is considerably more water soluble than aldicarb, the parent compound, is not well absorbed into the skin from aqueous solutions.

Distribution

- Information regarding the distribution of aldicarb sulfoxide is limited to studies in which tissue levels of the aldicarb and its metabolites were measured following administration of the parent compound (Cambon et al., 1979; Andrawes et al., 1967; Hicks et al., 1972). These studies have provided information on the general distribution pattern of radioactive label with no indication that any particular tissue or group of tissues was selectively sequestering aldicarb sulfoxide.

Distribution

- Information on distribution patterns of aldicarb sulfone is limited to studies in which tissue levels of aldicarb and its metabolites were measured following administration of the parent compound (Cambon et al., 1979; Andrawes et al., 1967; Hicks et al., 1972). As stated previously, these studies have provided information on the distribution pattern of the radioactive label with no indication that any particular tissue or group of tissues was selectively sequestering aldicarb sulfone. As previously described, when aldicarb and/or aldicarb sulfone was orally administered to hens in either a single dose or for 21 consecutive days, the pattern of distribution was similar for either duration of exposure. Liver and kidney were found to contain the highest level of residues (Hicks et al., 1972).

Metabolism

- Incubation of aldicarb sulfone with microsomes, with or without $NADPH_2$ (reduced nicotinamide adenine dinucleotide phosphate), was found to partially destroy the sulfone derivative (Oonnithan and Casida, 1967).

Excretion

- Aldicarb sulfone is eliminated primarily through the urine as demonstrated in rats (Knaak et al., 1966), cows (Dorough and Ivie, 1968) and chickens (Hicks et al., 1972).

IV. HEALTH EFFECTS

Humans

Aldicarb:

Short-term Exposure

- In two related incidents in 1978 and 1979, ingestion of cucumbers presumed to contain aldicarb at about 7 to 11 ppm resulted in complaints of diarrhea, abdominal pain, vomiting, nausea, excessive perspiration, dyspnea, muscle fasciculation, blurred vision, headaches, convulsions and/or temporary loss of limb function in a total of fourteen residents of a Nebraska town (CDC, 1979; Goes et al., 1980). Symptoms occurred 15 minutes to 2.25 hours after food consumption and continued for approximately 4 to 12 hours.

- Goldman et al. (1990a,b) reviewed information available on four outbreaks of food poisoning allegedly involving aldicarb-contaminated cucumbers or watermelon in California between 1985 and 1988. Dosage estimates for 28 of over 1000 reported cases were derived from average body weights by age and sex (from standard tables), self reported symptoms and estimated consumption, and analyzed aldicarb sulfoxide residues from watermelons. Estimates for 13 additional cases were

provided by Hirsch et al. (1987) also based on estimates of body weights and consumption, and residues (in cucumbers) of total aldicarb believed to be primarily the sulfoxide. This total population (N = 41) had a median of 0.01 mg/kg (for total aldicarb), a first quartile of 0.06 mg/kg and a third quartile of 0.029 mg/kg. The dosage range later calculated by Sette (1990) was 0.002-0.086 mg/kg for the Goldman study. The studies have some limitations since the description of the cases (self-reported) was limited in terms of onset, duration, and severity and many of the symptoms (nausea, vomiting, and diarrhea) are nonspecific. However, the cases analyzed by Goldman (1990a,b) were defined as onset within 2 hours of ingestion which would be related to the expected peak of cholinesterase inhibition. The analytical methodology to determine aldicarb sulfone residues was valid although the limit of detection of 0.2 ppm (Goldman et al. 1990b) was somewhat higher than in other reports. As a result, some misclassification errors may have occurred. The use of sex and age averages for body weights and self-reported food consumption values are also subject to estimation errors (both underestimates and overestimates). Nevertheless the dosage estimates are regareded as reasonable general estimates of effects. The LOAEL is 0.01 mg/kg; for the most sensitive population the LOAEL may be lower (0.002 mg/kg).

- Industrial exposure by a man bagging aldicarb for 1 day resulted in nausea, dizziness, depression, weakness, tightness of chest muscles, and decreases in plasma and red blood cell ChE activity (Sexton, 1966). The symptoms lasted more than 6 hours, but the subject returned to work the following day without symptoms.

- A California farm worker was found dead from chest injuries about 2 hours after he had begun loading aldicarb (formulated as Temik 15G) into a hopper. A residue analysis of his remains indicated that aldicarb, aldicarb sulfoxide and aldicarb sulfone were present in samples of his blood, liver, kidney and skin (hand, abdomen and thigh). The skin of the hand had the highest concentration of aldicarb (0.492 ppm), while the kidney had the greatest concentrations of the sulfoxide and sulfone metabolites (0.261 and 0.422 ppm, respectively). Little or none of the parent compound was found in the blood, liver or kidney (Lee and Ransdell, 1984). The results of the toxicological analysis suggest that pesticide intoxication played at least a contributory role in his death.

- Union Carbide Corporation (1971) conducted a study using human volunteers (4 males/dosage level) who received aldicarb (99.2% a.i.) in a single dose (administered in 100 mL of distilled water) at 0.025, 0.05 or 0.10 mg/kg. Each man's own blood ChE levels (based on blood samples taken one hour prior to dosing) served as the control for post-dosing ChE activity. Blood ChE activity was decreased in every test subject at 1 and 2 hours post-exposure, with individual decreases ranging from 20 to 80% in the high-dosage group, 37 to 67% in the 0.05 mg/kg group and 30 to 57% in the 0.025 mg/kg group. There were no clear dose-related trends in ChE inhibition. Recovery was almost complete (75%) by 6 hours after dosing, with more complete recovery

seen in the lower dose groups. All subjects that received 0.10 mg/kg showed clinical effects within 1 to 2 hours with the most common complaints being leg weakness, constriction of the pupils, sweating, salivation, slurred speech, nausea, and malaise. One subject at 0.05 mg/kg had a runny nose and another at 0.025 mg/kg had a "panic attack." The relationship of either of these observations to the aldicarb dosing is not clear. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 0.025 mg/kg can be identified from this study for inhibition of blood ChE.

- Rhône-Poulenc (1992) conducted a double-blind placebo controlled oral dosing study with aldicarb (99.0% a.i.)including 38 men and 9 women. Subjects received a light breakfast and single doses of orange juice containing aldicarb to be consumed over a period of 15-30 minutes. The doses of aldicarb were 0.01, 0.025, 0.050, and 0.075 mg/kg body weight in groups of 8 males (only 4 males at the highest dose) and 0.025 and 0.050 mg/kg body weight in groups of 4 females; 16 control males and 6 control females were included. Subjects remained seated or supine for the first 4 hours after dosing. Subjects were observed and signs and symptoms (e.g., sweating) were recorded hourly for the first 6 hours and at 24 hours. Supine diastolic blood pressure, ECG and pulse rate, pulmonary functions (FEV-1 and FVC), saliva and urine output, and pupil diameter were measured at pretest, hourly for 6 hours and at 24 hours. Red blood cell and plasma cholinesterase activities were determined at pretest, 1, 2, 3, 4, 5, and 6 hours. Hematology and clinical chemistry parameters were evaluated at screening, pretest, and at 24 hours. Erythrocyte and plasma cholinesterase activities were depressed at all dose levels with peak depressions occurring at 1 hour and the degree and duration of the effect increased with increasing doses. Inhibition of ChE activities was greater in females than in males but lasted longer in males. At 1 hour post-dosing, red blood cell AChE was depressed 3.8%, 12%, 29%, and 38% compared to pretest activity in males receiving 0.01, 0.025, 0.050, or 0.075 mg/kg and were depressed 20% and 36% in females at 0.025 or 0.050 mg/kg aldicarb, respectively. One hour after dosing, mean plasma cholinesterase activity was depressed 13%, 35%, 55%, and 70% in males at 0.010, 0.025, 0.050, or 0.075 mg/kg and depressed 49% and 68% in females at 0.025 or 0.050 mg/kg, respectively. One male in the 0.075 mg/kg group who had mistakenly received 0.06 mg/kg developed diffuse and profuse sweating that began at about 2 hours and abated within 6 hours of dosing; no other males in the 0.075 mg/kg-group experienced sweating. Two other treated males, one given 0.05 mg/kg and another given 0.025 mg/kg, experienced localized and mild sweating with onset at 2 hours and abatement within 6 hours. One male receiving 0.075 mg/kg reported that he was light-headed within an hour of dosing and 2 men in the 0.01 mg/kg-group reported headaches within 6 hours of dosing. None of the females developed any clinical signs or symptoms consistent with cholinesterase inhibition. U.S. EPA (1992d) assessed the sweating in the male receiving 0.06 mg/kg to be definitely compound related and the mild sweating in other males to be a possible effect of treatment. A small decrease in supine diastolic blood pressure, in general greater in the high-dose males and females

than in other groups, was observed but was not clearly related to dosing. Females at 0.05 mg/kg showed a higher saliva output than controls which was marginally significant. No consistent treatment-related effects on ECG or pulse rate were seen and no effects on clinical laboratory parameters or on lung function tests or pupil diameters were observed in treated groups. The NOAEL is considered to be 0.01 mg/kg, and the LOAEL is 0.025 mg/kg aldicarb based on sweating observed in treated males.

Immunological Effects

Fiore et al. (1986) and Mirkin et al. (1990) investigated the effects of exposure to aldicarb in drinking water on immunological parameters in women living in the same country in Wisconsin. Appropriate controls had no detectable levels of aldicarb in their drinking water. Data in the first study and the followup study indicated immunomodulatory effects on T cell subsets, but no obvious adverse effects.

- In the Fiore et al. (1986) study, the approximate aldicarb dose in 23 exposed subjects was 0.005 to 0.803 μg/kg/day. [The mean adicarb ingestion level as reanalyzed by Mirkin et al. (1990) was 0.087 μg/kg/day]. Several in vivo and in vitro immunological tests did not reveal any differences between exposed and non-exposed groups (levels of various immunoglobulins, differential leukocyte counts, antibody titers after immunization with tetanus booster in vitro antigenic/mitogenic stimulation assays, and lymphocyte proliferation assays). An increase in the T-8 cell population was observed.

- In the Mirkin et al. (1990) followup, the aldicarb dose in 5 exposed subjects was 0.001-0.066 μg/kg/day. An increase in blood levels of IgG but not IgA or IgM was seen and the total numbers of CD2+ and CD8+ lymphocytes (same as T-8 cells) was increased. The CD 8+ population of T cells was 90% higher than in nonexposed women and there was a significant correlation between the level of aldicarb ingestion and the elevated parameters. The elevation of the T cell subset was not accompanied by any clinical signs in either study. Immunological hazards due to aldicarb are not considered to have been demonstrated in these studies (U.S. EPA, 1993)

Aldicarb Sulfoxide:

- Aldicarb sulfoxide has been identified as residues in watermelons and cucumbers that were implicated in human food poisoning incidents (Goldman et al. (1990a,b).

Aldicarb Sulfone:

- No information was located regarding human health effects resulting from direct exposure to aldicarb sulfone.

Animals

Aldicarb:

Short-term Exposure

- NAS (1977) stated that the acute toxicity of aldicarb is probably one of the greatest of any widely used pesticide.

- Reported oral LD_{50} values for aldicarb administered to rats in corn or peanut oil range from about 0.65 to 1 mg/kg (Weiden et al., 1965; Gaines, 1969). Females appear to be more sensitive than males. The oral LD_{50} in mice is 0.3 to 0.5 mg/kg (Black et al., 1973).

- Oral LD_{50} values for aldicarb were higher when using a vehicle other than corn or peanut oil. Weil (1973) reported an oral LD_{50} of 7.07 mg/kg/day in rats administered aldicarb as dry granules. Carpenter and Smyth (1965) reported an LD_{50} of 6.2 mg/kg in rats administered aldicarb in drinking water.

- The principal toxic effect of aldicarb in rats has been shown to be ChE inhibition (Weil and Carpenter, 1963; Nycum and Carpenter, 1968; Weil, 1969).

- Feeding studies of short duration (7 to 15 days) have demonstrated statistically significant decreases in ChE activity in rats at aldicarb dosage levels of 1 mg/kg/day (the approximate LD_{50} in rats) (Nycum and Carpenter, 1970) and at 2.5 mg/kg/day in chickens (Schlinke, 1970). The latter dosage also resulted in some lethality in test animals.

- Hazleton Laboratories (1987a) conducted a two-week, range-finding study in which beagle dogs (one/sex/dosage group) were administered aldicarb (99.5% a.i.) in their diet at 0, 0.1, 0.3, 1, 3 or 10 ppm (corresponding to dosage levels of approximately 0, 0.003, 0.008, 0.029, 0.08M/0.114F, and 0.269M/0.294F). The only effects reported were inhibition of plasma and erythrocyte ChE at about 3 ppm and above, corresponding to a LOAEL of 0.08-0.114 mg/kg/day. The study design and data presentation are not sufficient to clearly identify a No-Observed-Adverse-Effect Level (NOAEL) for this study.

- Hazleton Laboratories (1991) conducted a 5-week study in dogs (6/sex/dosage group) that received aldicarb (99.7% a.i.) in their diet at 0, 0.35, 0.7, or 2.0 ppm (corresponding to dosage levels of approximately 0.01, 0.02, or 0.57 mg/kg/day). Blood cholinesterase (ChE) activities were determined 2 hours after the 2-hour feeding period; brain cholinesterase activity was analyzed. No effect on ChE activity was observed in dosed females. In 1/6 males receiving 0.7 ppm, a marginal inhibition of plasma ChE was observed when compared to the pretest value (inhibition was defined as greater than 20% depression compared to the zero-day value); no effect on red blood

cell (RBC) ChE activity was seen at 0.7 ppm. In the 2 ppm group of males, a mean reduction of 30% in plasma ChE activity was observed at both 2 weeks (6/6 dogs) and 5 weeks (4/6 dogs). RBC ChE activity was affected in 1/6 dogs at 2 weeks and 3/6 dogs at 5 weeks (mean reduction 30%). The LOAEL for ChE inhibition in males is 2 ppm (0.057 mg/kg/day) and the NOAEL is 0.7 ppm (0.02 mg/kg/day). Effects on gut motility were not considered related to dosing (U.S. EPA, 1991b).

Long-term Exposure

- In a 1-year feeding study conducted by Hazleton Laboratories (1988), beagle dogs (5/sex/dose) were administered aldicarb (99.7% a.i.) in their diets at 0, 1, 2, 5, or 10 ppm (corresponding to doses of approximately 0.028, 0.054, 0.132, and 0.231 mg/kg/day for males and 0.027, 0.055, 0.132, and 0.251 mg/kg/day in females). Significant decreases in plasma cholinesterase (ChE) activity were seen in males at all treatment levels throughout the duration of the study. In females, transitory decreases in plasma ChE activity were seen at 2 ppm and above. Red blood cell ChE activity was transiently decreased in males (5 ppm) and females (5 ppm and 10 ppm), but the activity was comparable to controls at the 52-week test period. Brain ChE activity was decreased only in males at 10 ppm. An increased incidence of soft stool and mucoid stool in treated male dogs was reported. However, considering the predose incidence rates and variations in groups, this was not considered evidence of a treatment related effect. The data are flawed because of differences in reporting clinical signs, failure to compare incidence for individual dogs at pretest with that during dosing and inappropriate timing of observations to detect cholinergic effects expected to occur within 2 hours of dosing (U.S. EPA, 1992a). Dogs were checked for clinical signs only once daily. Therefore, a NOAEL cannot be determined. The LOAEL for effects on ChE activity was 0.028 mg/kg/day.

- Aldicarb administered for 2 years in the diets of rats or dogs at dosage levels up to 0.1 mg/kg/day resulted in no significant increases in adverse effects based on a variety of toxicologic end points (Weil and Carpenter, 1965, 1966a). In another 2-year study, levels of up to 0.3 mg/kg/day resulted in no adverse effects in rats (Weil, 1975).

Dermal/Ocular Effects

- Dermal LD_{50} values (24-hour) were 2.5 mg/kg for female rats, 3 mg/kg for male rats (Gaines, 1969) and 5 mg/kg for rabbits (Weiden et al., 1965).

- The results of dermal sensitization tests in guinea pigs were also reported to be negative (Pozzani and Carpenter, 1968). No other details are available.

- Hazleton Laboratories (1987a) conducted ophthalmologic examinations of beagle dogs exposed to aldicarb (technical) in their diet at dosage levels of 0.003 to 0.294 mg/kg/day. No adverse effects were reported.

Immunological Effects

- Olson et al. (1987) conducted a series of four experiments to determine the effects of very low concentrations of aldicarb in drinking water on certain immune parameters in two outbred strains of mice. In a 14-day study, Swiss-Webster mice (5/group) received aldicarb at 0, 10, 100 or 1,000 ppg in drinking water (corresponding to daily dosages of approximately 0, 0.0013, 0.013 and 0.13 mg/kg/day). On day 10, mice were challenged with an injection of sheep erythrocytes (SRBCs). In plaque-forming cell (PFC) assays to determine the number of specific anti-SRBC antibody secreting plasma cells, an inverse dose-response relationship was seen with the most dramatic and only statistically significant decrease occurring in the low dosage group (10 ppb). The number of PFCs per 10^6 spleen lymphocytes was also decreased only in the 10 ppb group.

- In another experiment in this series, CF-1 mice (10/group) were given drinking water with aldicarb at 0, 1, 10, 100 or 1,000 ppb (corresponding to approximately 0, 0.0002, 0.002, 0.02 and 0.2 mg/kg/day) for 44 days with SRBC challenge at 30 days (Olson et al., 1987). Significant decreases in the number of PFCs per spleen and per 10^6 spleen lymphocytes were seen only at the lowest level of exposure (1 ppb). Again, an inverse dose-response relationship was evident. Analysis of plasma hemolysin titers (antibodies produced in response to SRBCs) also showed an inverse dose-response relationship with the 1 ppb group having the lowest titer (62% of the control value).

- Similar results were reported for two additional 34-day experiments using Swiss-Webster and CF-1 mice (each with 10 mice/dosage group) at the same drinking water concentrations and estimated dosage levels as for the 44-day study described above (Olson et al., 1987). In addition, the study using CF-1 mice also measured chemiluminescence (CHLM), which is considered to be a correlate of phagocytic killing capability because it measures the respiratory burst in the phagocytic cell when phagocytosis occurs. CHLM measurements on peripheral blood cells indicated nonsignificant reductions of the CHLM response at the three lower dosages and a 16% enhancement over the controls at the highest level (1,000 ppb). The CHLM measurements in the peritoneal exudate cells (PECs) showed a clear and significant inverse dose-response with inhibition of this parameter to 63% of the control level at 1 ppb to 87% elevation over the control level at 1,000 ppb. Although the significance of the inverse dose-response relationship for any of these experiments is not understood, these studies provide evidence that immunomodulatory effects can occur in two strains of mice at extremely low levels of aldicarb in drinking water as low as 0.0013 mg/kg/day for 10 days for Swiss Webster mice and as low as 0.0002 mg/kg/day for 30 days in Swiss Webster and CF-1 mice.

- Thomas et al. (1990) did not observe adverse effects on the immune systems of $B6C3F_1$ mice exposed to aldicarb in drinking water at 0, 1, 10 or 100 ppb for 34 days (corresponding to dosage levels of

0,0.00032, 0.0031 and 0.033 mg/kg/day). Following aldicarb exposure, no effects were observed on the ability of splenic natural killer cells to lyse YAC-1 lymphoma cells and the ability of sensitized T-lymphocytes to lyse P815 ($H\text{-}2^d$) mastocytoma tumor cells. No differences were seen in the percentages or absolute numbers of spleen lymphocyte subpopulations of T-cells, T-suppressor cells, T-helper cells or B-cells. The NOAEL for these effects was 0.033 mg/kg/day.

Reproductive Effects

- No reproductive effects have been demonstrated to result from the administration of aldicarb to rats at levels up to 0.7 mg/kg/day in a 3-generation study (Weil and Carpenter 1966c). However, based on a decreased body weight of F_2 pups in this study, a fetotoxic LOAEL was identified as 0.7 mg/kg/day, and the NOAEL is 0.3 mg/kg/day.

- A two generation reproduction study in rats was conducted at dietary levels that provided 0. 0.1. 0.4. 0.7-0.9, or 1.4-1.7 mg (aldicarb (99.7% a.i.)/kg/day (Rhone-Poulenc, 1991). Males and females (26/sex/group) were fed treated diets for 70 days prior to mating and continuously throughout the study. F_0 females were bred twice; the second mating was 2 weeks after weaning the F_{1a} pups. The F_1 generations were similarly mated to produce 2 litters. Aldicarb had no apparent effect at any mating based on precoital interval, pregnancy rate, gestational index and length, and there was a lack of abnormalities in delivery. Body weight gains were decreased during the growth phase for F_0 males at 1.4-1.7 mg/kg/day; and for F_0 and F_1 females, weight gains were decreased during growth, gestation, and lactation at the two highest doses. Plasma and erythrocyte cholinesterase activities were decreased 21%-30% in both males and females receiving 1.4-1.7 mg/kg/day. The pup viability index at day 4 was decreased at the highest dose for both the first and second litters in both generation. At 1.4-1.7 mg/kg/day, body weights were significantly lower than controls during lactation in the F_{1a}, F_{1b}, and F_{2a} pups. The parental systemic LOAEL was 0.7-0.9 mg/kg/day based on decreased body weights and the NOAEL is 0.4 mg/kg/day. The reproductive LOAEL is 1.4-1.7 mg/kg/day based on decreased pup wights and decreased pup viability at day 4 of lactation; the NOAEL is 0.7-0.9 mg/kg/day.

Developmental Effects

- No developmental effects have been demonstrated to result from the administration of aldicarb to rabbits (IRDC, 1983) or rats (Weil and Carpenter 1964; Tyl and Neeper-Bradley, 1988).

- IRDC (1983) evaluated the developmental effects of aldicarb (99.5% a.i.) administered by gavage to Dutch-Belted rabbits (16/dosage group) at 0, 0.1, 0.25 or 0.5 mg/kg/day on gestation days 7 through 27. At the two higher dosage levels, body weight was decreased and pale kidneys and hydroceles on the oviducts were seen. The numbers of implantations and viable fetuses per dam were reduced in all treatment

groups. However, these decreases (only significant at the lowest dose) were not considered compound related and were due to the unusually large number of corpora lutea/dam and the low rate of preimplantation loss in the control group; historical data supported this conclusion (U.S. EPA, 1992e). No compound-related effects were seen on mean fetal body weight, sex ratio or incidence of visceral or skeletal malformations. The LOAEL for this study is 0.1 mg/kg/day for fetal viability and implantation loss. The NOAEL for this study (maternal toxicity) is 0.1 mg/kg/day.

- Weil and Carpenter (1964) fed aldicarb (99.7% a.i.) to pregnant rats either from gestation days 1-7, 5-15, or throughout pregnancy and weaning at dietary levels to provide an intake of 0, 0.04, 0.2, or 1 mg/kg/day. No congenital malformations were reported for any group. Maternal and fetal body weights were not affected and there were no effects on implantation, gestation, lactation, or pup viability. The NOAEL for systemic and developmental effects was equal to or greater than 1 mg/kg/day.

- Tyl and Neeper-Bradley (1988) investigated the developmental toxicity of aldicarb (99.5% a.i.) administered by gavage to rats (25/dosage group) at 0, 0.125, 0.25 or 0.5 mg/kg/day on gestation days 6 through 15. Three dams in the high dosage group died on day 7 of gestation and others in this group developed hypoactivity, tremors, urine stains, audible respiration, lacrimation, nasal and ocular crusting and loose feces. Significant reductions in body weight gain and decreased levels of food consumption were observed at the two higher dosage levels. In the fetuses, mean body weight was decreased at the high dose. Increases in the incidence of ecchymosis (small hemorrhages of the skin) of the trunk were seen at the mid and high doses. Also at the high dose, there was an increased incidence of lateral ventricle dilation with tissue depression and poor ossification of the sixth sternebra. Although fetuses at the 0.125 mg/kg/day dose displayed some ecchymosis, the incidence (on a litter basis) was within the range of laboratory historical controls (U.S. EPA, 1991a). The NOAEL for this study is, therefore, 0.125 mg/kg/day, and the LOAEL for effects on maternal weight gain and ecchymosis of the fetus is 0.25 mg/kg/day.

- No adverse effects on milk production were observed in studies of lactating cows (Dorough and Ivie, 1968; Dorough et al., 1970).

- Statistically significant inhibition of ChE activity has been demonstrated in the liver, brain and blood of rat fetuses when their mothers were administered aldicarb by gastric intubation on day 18 of gestation (Cambon et al., 1979). These changes were seen at doses of 0.001 mg/kg and above and were manifested within 5 minutes of the administration of 0.1 mg/kg. This study, because of its design, does not demonstrate any adverse developmental or fetotoxic effects. It does demonstrate that aldicarb rapidly crosses the placenta and the data reflect a potential effect on ChE activity in the fetus.

Mutagenicity

- Aldicarb has not been conclusively demonstrated to be mutagenic in Ames assays or in a dominant lethal mutagenicity test in rats (Ercegovich and Rashed, 1973; Weil and Carpenter, 1974; Godek et al., 1980).

Carcinogenicity

- Aldicarb does not significantly increase the incidence of tumors in mice or rats in feeding studies (Weil and Carpenter, 1965; NCI, 1979). Bioassays with aldicarb in which rats and mice were fed either 2 or 6 ppm in the diet for 103 weeks, revealed no treatment-related tumors (NCI, 1979). It was concluded that under the conditions of the bioassay, technical grade (99+%) aldicarb was not carcinogenic to F344 rats or B6C3F$_1$ mice of either sex. A 2-year feeding study reported by Weil and Carpenter (1965) also showed no statistically significant increase in tumors over controls when rats were administered aldicarb in the diet at concentrations equivalent to dosage levels of 0.005, 0.025, 0.05 or 0.1 mg/kg/day. However, the maximum tolerated dose (MTD) was not reached in these studies. Weil (1975) similarly reported no adverse effects in rats fed aldicarb at 0.3 mg/kg/day for 2 years; however, data from this study are questionable because the experimental protocol was not designed to assess the oncogenicity of this chemical.

- In a skin-painting study, Weil and Carpenter (1966b) found that aldicarb was noncarcinogenic in male C3H/H3J mice under the conditions of the experiment.

- Intraperitoneally administered aldicarb did not exhibit transforming or tumorigenic activity in a host-mediated assay using pregnant hamsters and nude (athymic) mice (Quarles et al., 1979).

Aldicarb Sulfoxide:

Short-term Exposure

- Oral LD_{50} values for aldicarb sulfoxide administered in corn oil to male rats range from 0.45-1.1 mg/kg (Weil and Carpenter, 1970; Nycum and Carpenter, 1968; West and Carpenter, 1966).

- In rabbits, an acute dermal LD_{50} value of 20 mg/kg was determined for aldicarb sulfoxide in aqueous solutions (West and Carpenter, 1966).

- The principal toxic effect of aldicarb sulfoxide (and the parent compound, aldicarb) in rats is ChE inhibition (Weil and Carpenter, 1963; Nycum and Carpenter, 1968; Weil, 1969).

- Nycum and Carpenter (1970) fed rats (5/sex/dosage group) aldicarb sulfoxide at 0, 0.4 or 0.8 mg/kg/day for 7 consecutive days. Evaluation criteria included plasma, erythrocyte and brain ChE

activity, body weight changes, relative liver and kidney weights and mortality. Male rats treated with 0.8 mg/kg/day had statistically significant decreases in erythrocyte ChE activity and in body weight. No effects were seen in females or males that received 0.4 mg/kg/day; this is identified as the NOAEL for this study. The LOAEL was 0.8 mg/kg/day.

- A NOAEL of 0.12 mg/kg/day has been determined for a 1:1 mixture of aldicarb products (sulfone and sulfoxide), based on data reported by Mirro et al. (1982) and DePass et al. (1985) who administered these compounds in the drinking water of young adult rats (10/sex/dosage group) for 29 days at a total concentration of 0, 0.075, 0.3, 1.2, 4.8, or 19.2 ppm. Based on water consumption, the dosage levels were approximately 0, 0.0074, 0.03, 0.12, 0.47 and 1.67 mg/kg/day for males and 0, 0.0098, 0.035, 0.14, 0.54 and 1.94 mg/kg/day for females. Body weight and water consumption were significantly reduced for males and females at the high dose level (19.2 ppm). Significant decreases in plasma and erythrocyte ChE activity were seen at 4.8 ppm in males and at 19.2 ppm in females. Female rats at 19.2 ppm also displayed significant reductions in brain ChE activity.

Long-term Exposure

- Aldicarb sulfoxide was administered at levels to provide an intake of 0, 0.125, 0.25, 0.5 or 1.0 mg/kg/day in the diet to rats for 6 months (15/sex/dosage group) for 6 months (Weil and Carpenter, 1968a). All animals were evaluated for relative ChE levels, liver and kidney weights and body weights. Only ChE activity was significantly altered. Plasma ChE activity was significantly inhibited in males and females that received 0.5 and 1.0 mg/kg/day and in males that received 0.125 and 0.25 mg/kg/day. The inhibition of plasma ChE activity at 0.125 mg/kg/day in males was noted at 3 months but not at 6 months. Erythrocyte ChE activity was inhibited at doses of 0.25 mg/kg/day and above following both 3 and 6 months of exposure in males and females. Brain ChE activity was significantly lower in females fed 1.0 and 0.5 mg/kg aldicarb sulfoxide for 6 months. A NOAEL of 0.125 mg/kg/day and a LOAEL of 0.25 mg/kg/day can be identified from this study based on brain ChE inhibition.

- In a second set of experiments by Weil and Carpenter (1968a), used the same dosage levels of aldicarb sulfoxide as above for 3 months, groups of rats (15/sex/dosage group) were either sacrificed immediately after the cessation of feeding or were placed on a control diet for a 1-day recovery period. Rapid recovery of inhibited ChE activity was observed at all but the highest dosage level.

- A 3-month feeding study with dogs that received aldicarb sulfoxide at dosage levels of 0, 0.0625, 0.125, 0.25 or 0.5 mg/kg/day was also conducted by Weil and Carpenter (1968a). None of the dogs died and no treatment-related effects were observed in body weight, organ weight,

pathology or clinical chemistry. The only effect observed was a slight decrease in plasma ChE activity at 0.5 mg/kg. This decrease was seen only after 1 month and not at 3 months of exposure. A NOAEL of 0.25 mg/kg/day and a LOAEL of 0.5 mg/kg/day can be identified from this study.

- In a 2-year study, Weil and Carpenter (1972) maintained rats (20/sex/dosage group) on diets containing aldicarb sulfoxide at 0.3 or 0.6 mg/kg/day or a 1:1 mixture of sulfoxide and sulfone (0.6 and 1.2 mg/kg/day). A control group on a basal diet was also maintained under identical conditions. Additional groups of 16 rats/sex/dosage group were maintained in parallel for serial sacrifice to determine interim organ weights and histological effects. The only treatment-related effect was reduced body weight and depression of plasma ChE activity in male rats at the high dose of the sulfoxide-sulfone mixture.

Dermal/Ocular Effects

- No information has been located on dermal or ocular effects resulting from exposure to aldicarb sulfoxide.

Reproductive Effects

- No reproductive studies on aldicarb sulfoxide have been located in the available literature. However, as with other effects, it is assumed that the reproductive effects of this compound would be similar to those of the parent compound.

Developmental Effects

- No studies of the developmental effects of aldicarb sulfoxide have been located in the available literature. However, Wilkenson et al. (1983) have speculated that due to the increased polarity of this compound, it would be less likely than aldicarb itself to cross the placenta. Therefore, it would be conservative to assume that the NOAEL identified for the developmental effects of the parent compound, aldicarb, would also be a NOAEL for aldicarb sulfoxide.

Mutagenicity

- No studies were located in the available literature that assess the mutagenic potential of aldicarb sulfoxide in somatic cells or germinal cells. Evaluations of the parent compound (aldicarb) have indicated that it is nonmutagenic (Blevins et al., 1977; Weil and Carpenter, 1974; Dunkel and Simmon, 1980; Ercegovich and Rashid, 1973). As with other effects, it is assumed that the mutagenic potential of aldicarb sulfoxide would be similar to that of the parent compound.

Carcinogenicity

- Neither aldicarb nor its sulfoxide metabolite significantly increase the incidence of tumors in mice or rats in feeding studies (Weil and Carpenter, 1965, 1972; NCI, 1979). A 2-year feeding study reported by Weil and Carpenter (1972) did not result in a statistically significant increase in tumors in the exposed group over the control group when rats were fed aldicarb sulfoxide or a 1:1 mixture of aldicarb sulfoxide and sulfone at concentrations equivalent to dosage levels of 0.3 and 0.6 or 0.6 and 1.2 mg/kg/day, respectively. The most frequent types of tumors in both controls and in treated rats were adenomas of the pituitary and thyroid; however, the overall incidence rate and type of tumor was similar in all groups. The existing data base is considered inadequate to evaluate the potential for human carcinogenicity by any of these compounds.

Aldicarb Sulfone:

Short-term Exposure

- Aldicarb sulfone is considerably less toxic via the oral route of exposure in rats than is aldicarb or aldicarb sulfoxide. An oral LD_{50} of 20-25 mg/kg has been reported for the sulfone in male rats (Weil and Carpenter, 1970; Nycum and Carpenter, 1968; West and Carpenter, 1966). However, in rabbits, acute dermal LD_{50} values of 20 mg/kg were determined for both aldicarb sulfoxide and aldicarb sulfone in aqueous solutions (West and Carpenter, 1966). Weil et al. (1974) reported that the acute dermal LD_{50} for male rabbits was 194 mg/kg.

- The principal toxic effect of aldicarb sulfone in rats has been shown to be ChE inhibition (Weil and Carpenter, 1963; Nycum and Carpenter, 1968; Weil, 1969).

- Nycum and Carpenter (1970) fed aldicarb sulfone at 0, 0.4, 1.0, 2.5, 5.0 or 20.0 mg/kg/day for 7 consecutive days to rats (5/sex/dosage group). Animals were evaluated on the following criteria: plasma, erythrocyte and brain ChE activity, body weight changes, relative liver and kidney weight and mortality. No effects were observed in male rats fed up to 2.5 mg/kg/day, while at 5.0 mg/kg/day, there was a significant decrease in plasma and erythrocyte ChE activity. In females, brain ChE activity was significantly decreased at 2.5 mg/kg/day and above. At the highest dose (20 mg/kg/day), there was a significant decrease in body weight and in plasma, erythrocyte and brain ChE activity for all animals. No effects were observed in those animals given the lowest dose (0.4 mg/kg/day) (Nycum and Carpenter, 1970).

- As described previously, a NOAEL of 0.12 mg/kg/day has been determined for a mixture of aldicarb oxidation products, based on data reported by Mirro et al. (1982) and DePass et al. (1985) who administered aldicarb sulfone and sulfoxide in a 1:1 ratio in the drinking water of rats for 29 days.

Long-term Exposure

- In a series of experiments in rats, Weil and Carpenter (1968b) administered aldicarb sulfone (99.7% pure, 0.24 sulfoxide) at levels of 0, 0.2, 0.6, 1.8, 5.4 or 16.2 mg/kg/day in the diet (15/sex/dosage group) for 3 or 6 months. After 3 months, groups were sacrificed immediately after feeding diet for a 1-day recovery period. All animals were evaluated for relative ChE levels, liver and kidney weights and body weights. A transient but significant body weight reduction was seen at the highest dose (16.2 mg/kg/day) but not at the lower dose levels. ChE (plasma, erythrocyte and brain) activity was significantly inhibited in both sexes at doses of 1.8 mg/kg/day and above after both 3 and 6 months on the diet. In all cases, the greatest inhibition of ChE activity was seen in the plasma, followed by erythrocytes and then brain. In the recovery period, ChE activity returned to control levels in all groups except those receiving the highest dosage level. The NOAEL for brain ChE inhibition after 6 months of dietary exposure was 0.6 mg/kg/day.

- A 3-month feeding study with dogs that received aldicarb sulfone (99.76% a.i., 0.24% sulfoxide) at levels of 0, 0.2, 0.6, 1.8 or 5.4 mg/kg/day was also conducted by Weil and Carpenter (1968b). Early in the study body weight was slightly reduced at 5.4 mg/kg/day. No mortality was observed and no treatment-related effects were observed in organ weight, pathology or clinical chemistry. After three months, brain cholinesterase activity was reduced at doses above 0.2 mg/kg/day (0.6, 1.8, or 5.4 mg/kg/day). Since animals were not fed for up to 24 hours prior to cholinesterase determinations, the values do not reflect peak ChE activity depression which is known to occur within 2 hours of dosing and is then partially or fully reversed. Red blood cell ChE activity on the average was not significantly different from controls in all dosed groups. The LOAEL for systemic toxicity is 5.4 mg/kg/day based on weight decrement and the NOAEL is 1.8 mg/kg/day. The NOAEL for depression of brain ChE activity is 0.2 mg/kg/day.

- Hazleton Laboratories (1987b) conducted a 1-year feeding study in beagle dogs that were administered aldicarb sulfone (99% a.i.)in their diets at 0, 5, 25 or 100 ppm (corresponding to dosage levels of approximately 0, 0.11, 0.58-0.61 and 2.21-2.30 mg/kg/day). Brain cholinesterase (ChE) activity at study termination was significantly depressed in high-dose males (24%) and mid- and high-dose females (19-23%) when compared to controls. Red blood cell cholinesterase activity was also significantly depressed in high-dose groups of both sexes (25-36%) and in mid-dose females (up to 22%). Plasma cholinesterase was inhibited 20-80% in dosed males and 40-72% in mid- and high-dose females. At the lowest dose, no inhibition of plasma ChE was observed in females, but a marginal decrease (25%) was seen in males. Decreased spleen weights were seen in mid- and high-dose females and decreased thyroid/parathyroid weights in high-dose females. In high-dose males, livers had slight centrilobular venous thickening and hyalinization and interlobular fibrosis. The LOAEL for

systemic toxicity based on brain ChE decrease is 25 ppm (0.58 mg/kg/day), and the NOAEL is 5 ppm (0.11 mg/kg/day).

- In a 2-year study, Weil and Carpenter (1972) maintained rats (20/sex/dosage group) on diets containing aldicarb sulfone (99.76% a.i. and 0.24% sulfoxide) at 0.6 or 1.2 mg/kg/day. No treatment-related effects were reported at either dosage level.

Dermal/Ocular Effects

- Hazleton Laboratories (1987b) found no treatment-related ophthalmic abnormalities in dogs that received aldicarb sulfone in their diet at levels corresponding to 0.11 to 2.30 mg/kg/day for 1 year.

- Myers et al. (1975) did not find aldicarb sulfone to be a primary eye irritant in rabbits or a primary dermal irritant in rats.

- Aldicarb sulfone was not a dermal sensitizer in guinea pigs (Conroy and Carpenter, 1977).

Reproductive Effects

- Aldicarb sulfone (a.i. 99.76% and 0.24% sulfoxide) was administered to Harlan-Wistar rats for 3 generations (one litter/generation) at dietary levels to provide an intake of 0, 0.6, 2.4 or 9.6 mg/kg/day Woodside et al. 1977). Males at 9.6 mg/kg/day had reduced body weights and both sexes at this dose had cholinesterase activity inhibition. Reduced pup survival and marginal effects on lactation were observed at the 9.6 mg/kg/day-dose. The LOAELs for reproductive effects and systemic toxicity are 9.6 mg/kg/day and the NOAELs are 2.4 mg/kg/day.

Developmental Effects

- In a separate study, Woodside et al (1977) administered aldicarb sulfone (a.i. 99.76% and 0.24% sulfoxide) by oral gavage to female Wistar rats at levels of 0, 0.6, 2.4, or 9.6 mg/kg/day. Different groups were dosed from gestation days 1-12, 7-9, or 6-15. Diarrhea was observed in females at the 9.6 mg/kg/day-dose. No developmental effects or anomalies were seen in pups. Wilkenson et al. (1983) noted that because of the increased polarity of aldicarb sulfone as compared to the parent compound, this chemical would be less likely to cross the placenta. Therefore, it would be conservative to assume that the NOAEL identified for the developmental effects of the parent compound, aldicarb, would also be a NOAEL for aldicarb sulfone.

Mutagenicity

- Aldicarb sulfone was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 with or without S9 at levels between 50 and 10,000 µg/plate (Godek et al., 1980). Aldicarb sulfone

was not clastogenic nor did it cause chromosome aberrations in cultured CHO cells activated with rat liver homogenate and tested at sulfone levels of 50, 250, or 500 μg/mL (Pharmacon, 1984). Evaluations of the parent compound, aldicarb, have indicated that it is nonmutagenic (Blevins et al., 1977; Weil and Carpenter, 1974; Dunkel and Simmon, 1980; Ercegovich and Rashid, 1973). As with other effects, it is assumed that the mutagenic potential of aldicarb sulfone would be similar to that of the parent compound.

Carcinogenicity

- Neither aldicarb nor its sulfone metabolite have been demonstrated to significantly increase the incidence of tumors in mice or rats in feeding studies (Weil and Carpenter, 1965, 1972; NCI, 1979). A 2-year feeding study reported by Weil and Carpenter (1972) did not result in a statistically significant increase in tumors over controls when rats were fed aldicarb sulfonate dosage levels equivalent to 0.3, 0.6 or 2.4 mg/kg/day. The most frequent types of tumors in both control and treated rats were adenomas of the pituitary and thyroid. However, the overall incidence rate and type of tumor was similar in all groups. The overall data base is considered inadequate to evaluate the potential for human carcinogenicity from aldicarb sulfone.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (up to 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:

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

where:

NOAEL = No-Observed-Adverse-Effect Level (the exposure dose in mg/kg bw/day).

LOAEL = Lowest-Observed-Adverse-Effect Level (the exposure dose in mg/kg bw/day).

BW = assumed body weight of protected individual (10-kg for child or 70-kg for adult).

UF(s) = uncertainty factors, based upon quality and nature of data (10, 100, 1,000, or 10,000) in accordance with NAS/EPA guidelines.

____ L/day = assumed water consumption (1 L/day for child or 2 L/day for adult).

The available data suggest that the appearance of cholinergic symptoms indicative of ChE inhibition is the most sensitive indicator of the effects of exposure to aldicarb and its metabolites. Because these effects are rapidly reversible, the same NOAEL or LOAEL can be used as the basis for the derivation of acceptable levels of exposure over virtually any duration. In addition, the Health Advisories values calculated in this document are appropriate for use in circumstances in which the sulfoxide and/or sulfone may be the substance(s) present in a drinking water sample. By establishing Health Advisories based upon data from valid studies with the most potent of the three substances, there is greater assurance that the guidance is protective of human health. This approach has been employed because it may not be possible to specifically characterize the residue present using some analytical techniques.

The studies upon which the Health Advisories values and Reference Dose (RfD) for aldicarb are based are the acute experimental human study by Rhône-Poulenc (1992), a similar study in humans by Haines (Union Carbide, 1971) and analysis of data from human food poisoning incidences by Goldman et al. (1990a,b) and Hirsch et al. (1987). The human studies are supported by the 1-year study by Hazleton Laboratories (1988) in beagle dogs.

Aldicarb:

In the human study by Rhône-Poulenc (1992), groups of male subjects received a single oral dose of 0, 0.01, 0.025, 0.050, or 0.075 mg/kg aldicarb over a period of 15-30 minutes and females received 0, 0.025, or 0.050 mg/kg similarly. A number of biological parameters known to be affected by cholinesterase inhibitors were monitored before dosing, hourly for 6 hours, and at 24 hours. The major endpoints that were considered treatment related were effects on plasma and erythrocyte cholinesterase activity at all dose levels in both sexes, sweating (profuse in one high-dose male receiving 0.06 mg/kg), light-headedness, headaches, salivation, and a slight decrease in supine diastolic blood pressure. No important clinical signs or symptoms consistent with cholinesterase inhibition developed in females. One female at 0.05 mg/kg (highest dose tested) had a higher saliva output than controls that was marginally significant. Sweating in the male that received 0.06 mg/kg developed at about 2 hours and abated by 6 hours; localized mild sweating was experienced in one male receiving 0.05 mg/kg and in one male receiving 0.025 mg/kg. Sweating was not observed in 3 other males in the high-dose group that received 0.075 mg/kg, but one male in this group reported light-headedness one hour after dosing. No consistent effects were seen on supine or standing diastolic blood pressure; and there were no effects on ECG, pulse rate, pupil diameter, or lung function test. RBC acetylcholinesterase activity was depressed 12-38% in males at doses between 0.025-0.075 mg/kg and depressed 20% and 36% in females at doses of 0.025 or 0.050 mg/kg. Plasma cholinesterase activity was depressed in a dose-related manner in dosed males (13-70%) and depressed 49% and 68% in females at 25 or 50 μg/kg. Cholinesterase activities reached peak depression at 1 hour and were reversed by 6 hours. The NOAEL was considered to be 0.01 mg/kg and the NOAEL 0.025 mg/kg based on sweating in treated males.

In the Haines study (union Carbide, 1971), male volunteers (4/dosage level)

received aldicarb as a single dose of 0.025, 0.05 or 0.10 mg/kg dissolved in 100 mL of distilled water. Each man's own blood ChE levels (based on blood samples taken 1 hour prior to dosing) served as the control for post-dosing ChE activity. Blood ChE activity was decreased in every test subject at 1 and 2 hours post-exposure, with decreases ranging from 20 to 80% at 0.1 mg/kg, 37 to 67% at 0.05 mg/kg and 30 to 57% at 0.025 mg/kg. There were no clear dose-related trends in ChE inhibition. Recovery was almost complete (75%) by 6 hours after dosing, with more complete recovery in the lower dose groups. All four subjects that received 0.10 mg/kg showed clinical effects with the most common complaints being leg weakness, constriction of the pupils and sweating. One subject in each of the two lower dosage groups had clinical symptoms (a runny nose and anxiety) that were not clearly related to aldicarb administration. The method of analysis of ChE activity in blood was considered valid and appropriate. Based on significant inhibition of whole blood ChE observed at all dose levels, the LOAEL for this study is 0.025 mg/kg (the lowest dose tested). The range of ChE inhibition at this dose was 30 to 57%. A NOAEL was not established for this study.

In the Goldman et al. (1990a,b) studies, information was reviewed on four outbreaks of food poisoning involving aldicarb or aldicarb sulfoxide-contaminated watermelons in California between 1985 and 1988. An additional study Hirsch et al., 1977) reported food poisonings from aldicarb contaminated cucumbers. Dosages were estimated for 28 persons (Goldman et al., 1990a,b) and 13 additional persons (Hirsch et al., 1977) who reported nausea, vomiting and diarrhea (nonspecific symptoms of ChE inhibition). The median dosage for 41 persons was 0.01 mg/kg (total aldicarb). The range of dosages were later recalculated by Sette (1990) as 0.002-0.086 mg/kg. Limitations in these studies include the use of hypothetical rather than actual weights to estimate dosage levels, self-classification of symptoms, and the use of analytical methodology with a limit of detection of 0.2 ppm to measure aldicarb sulfoxide (a higher limit than that used in other studies). Despite the limitations discussed above, this study is viewed as presenting valid evidence of clinical effects at aldicarb levels as low as 0.002 mg/kg in a sensitive human population. The symptoms reported by individuals exposed to fruits and vegetables with detectable aldicarb residues were consistent with the syndrome expected in cases of ChE inhibition. The analytical technique was a valid method for estimating aldicarb residues in fresh produce and estimates of cucumber and watermelon consumption were plausible and displayed limited variability. There was also a reasonable correlation of dosage estimates with ChE inhibition symptoms. These dosage estimates are, accordingly, regarded as acceptable approximations of aldicarb potency.

The critical study for deriving a reference dose (RfD) and Health Advisories is the Rhône-Poulenc 1992 study. Although longer-term studies are not available in human volunteers, both animal and human data support the finding that neurobehavioral changes are short lived, and there is no accumulation of effects over time. Using cholinesterase inhibition as a biomarker of potential neurotoxic or behavioral effects in animal studies, there is a comparable degree of cholinesterase inhibition at the same doses in acute, subchronic, and chronic studies and no neurotoxic signs are seen at dose levels below those causing cholinesterase inhibition. Therefore, the

effects of an acute human study are equivalent to those that would be observed after repeated human exposure. The peak of cholinesterase inhibition in human studies occurs within 2 hours of dosing and inhibition is reversed by 6 hours. The observed effects of aldicarb in animal studies are similarly rapidly reversed. The reversal is supported by pharmacokinetic studies demonstrating rapid absorption, metabolism, and excretion of aldicarb.

In the study by Haines, blood cholinesterase activity inhibition was observed within 1-2 hours and almost completely recovered by 6 hours in groups of 4 males administered 0.025, 0.05, or 0.1 mg/kg of aldicarb as a single oral dose. The highest dose elicited clinical signs in all four subjects, predominantly sweating and leg weakness, while most subjects at the two lower doses had no signs or symptoms. This study helps define a dose (0.1 mg/kg) that is clearly associated with adverse effects in humans. The study by Goldman et al. (1990) on alleged aldicarb poisoning identified a median effect dose of 0.01 mg/kg. The range of doses causing clinical effects (0.002-0.086 mg/kg) may reflect individual variation with the 0.002 mg/kg dose applicable to the most sensitive population. However, the estimated dose for this population was much less precise than the two controlled populations in the Rhône-Poulenc and Haines studies; the symptoms were non-specific for ChE; and blood cholinesterase levels were not measured. Both the Haines study and the Goldman study add weight of evidence to the Rhône-Poulenc study.

Based on the fact that the acute and chronic symptoms of ChE inhibition are the same, the One-day and Ten-day HAs for aldicarb can be calculated from the Rhône-Poulenc (1992) study with a NOAEL of 0.01 mg/kg/day. Therefore, the Lifetime HA of 7 μg/L will be used as the One-day HA for aldicarb.

Aldicarb Sulfoxide:

The One-day HA for a 10-kg child exposed to aldicarb sulfoxide is the same value as the One-day HA for aldicarb, 7 μg/L.

Aldicarb Sulfone:

Due to the data gaps in the toxicity profile of aldicarb sulfone and due to the absence of acute human data on the sulfone, the One-day HA for a 10-kg child exposed to aldicarb, 7 μg/L, will also be used for the sulfone.

Ten-day Health Advisory

Aldicarb:

The Lifetime HA for the 10-kg child will be used as the Ten-day HA (7 μg/L) for aldicarb.

Aldicarb Sulfoxide and Aldicarb Sulfone:

The Ten-day HA for a 10-kg child exposed to aldicarb sulfoxide or aldicarb sulfone is the same value as the Ten-day HA for aldicarb, 7 μg/L.

Longer-term Health Advisory

Aldicarb:

Since the chronic and acute effects of aldicarb are the same, the Longer-term HA values for a 10-kg child and a 70-kg adult are the same as the Lifetime HA of 7 μg/L as calculated below:

Aldicarb Sulfoxide:

The Longer-term HA values for aldicarb sulfoxide for the 10-kg child and the 70-kg adult are the same as the Lifetime HA value of 7 μg/L for aldicarb sulfoxide.

Aldicarb Sulfone:

The Longer-term HA values for aldicarb sulfone for the 10-kg child and the 70-kg adult are the same as the Lifetime HA value of 7 μg/L for aldicarb sulfone.

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. If the contaminant is classified as a known, probable or possible carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. For human (A) or probable human (B) carcinogens, a Lifetime HA is not recommended. For possible human carcinogens (C), an additional 10-fold safety factor is used to calculate the Lifetime HA. The risk manager must balance this assessment of carcinogenic potential and the quality of the data against the likelihood of occurrence and significance of health effects related to noncarcinogenic end points of toxicity. To assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the

range of 1 in 10,000 to 1 in 1,000,000 for the 70-kg adult drinking 2 L of water/day are provided in the Evaluation of Carcinogenic Potential section.

Aldicarb

The Lifetime Health Advisory and RfD are based on the acute human study by Rhône-Poulenc (1992) and as discussed above supported by the study of acute human exposure by Haines (Union Carbide Corporation, 1971) and analysis of data for human food poisonings (Golman et al., 1990a,b; Hirsch et al., 1987). The effects of aldicarb are readily reversible in humans and animals. A large data base in animals shows that a comparable inhibition of cholinesterase is found at the same doses in acute, subchronic, and chronic studies and that inhibition and recovery of cholinesterase activity parallels the clinical neurotoxic/neurobehavioral signs. Therefore, it is concluded that the same NOAELs or LOAELs for neurotoxic signs can be used as the basis for the calculation of acceptable levels of exposure over virtually any duration of exposure. The RfD for Aldicarb has been verified by the Agency in October, 1992 and peer reviewed by the SAP/SAB Committee in November, 1992 (U.S. EPA, 1992b).

Using a NOAEL of 0.01 mg/kg/day, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.01 \text{ mg/kg/day})}{(10)} = 0.001 \text{ mg/kg/day}$$

where:

0.01 mg/kg/day =
NOAEL, based on sweating (a cholinergic sign) in human volunteers (Rhône-Poulenc, 1992).

10 =
uncertainty factor (UF), chosen in accordance with NAS/EPA guidelines for use of human data to account for variation in sensitivity among persons in the population.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.001 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.035 \text{ mg/L} \quad (\text{rounded to } 35\ \mu\text{g/L})$$

where:

0.001 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 HA

Lifetime HA = (0.035 mg/L) (20%) = 0.007 mg/L (rounded to 7 $\mu g/L$)

where:

0.035 mg/L =
DWEL

20% =
assumed contribution of drinking water to total exposure to aldicarb and its metabolites.

Aldicarb Sulfoxide:

The Lifetime HA for aldicarb sulfoxide is the same as the Lifetime HA for aldicarb, 7 µg/L.

Aldicarb Sulfone:

The Lifetime HA for aldicarb sulfone is the same as the Lifetime HA for aldicarb, 7 µg/L. However, this value is based on data from the one year dog feeding study by Hagleton (1987b) and further supported by the data base and the human study (Rhone-Poulenc, 1992) for aldicarb.

In the Hazleton Laboratories (1987b) 1-year dietary study of aldicarb sulfone in dogs, a NOAEL of 0.11 mg/kg/day was identified for cholinesterase inhibition. At higher levels (0.58 mg/kg/day and above), levels of plasma, erythrocyte and brain cholinesterase activity were inhibited. Although human data were not available on aldicarb sulfone, and although data gaps were noted for reproductive and developmental effects, and there was the lack of an adequate rat chronic study, the available information on the parent compound is sufficient to support the data base for this metabolite. Therefore, the dog study was selected for calculation of the Lifetime HA. Aldicarb sulfoxide has also been demonstrated to be rapidly degraded and eliminated in animal studies (Andrawes et al., 1967). Therefore, the same NOAEL or LOAEL can be used as the basis for the calculation of acceptable levels of exposure over virtually any duration. The RfD for aldicarb sulfone has been verified by the Agency in September, 1992 and peer reviewed by the SAP/SAB Committee in November, 1992 (U.S. EPA, 1992c).

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.11 \text{ mg/kg/day})}{(100)} = 0\ 001 \text{ mg/kg/day}$$

where:

0.11 mg/kg/day = NOAEL, based on Brain ChE activity inhibition in dogs (Hazleton Laboratories, 1987b).

100 = uncertainty factor (UF), chosen in accordance with NAS/EPA guidelines to account for interspecies and intraspecies differences when a NOAEL from an animal study is used.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.001\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.035\ mg/L$$ (rounded to 35 µg/L)

where:

0.001 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 HA

Lifetime HA = (0.035 mg/L) (20%) = 0.007 mg/L (rounded to 7 µg/L)

where:

0.035 mg/L = DWEL

20% = assumed contribution of drinking water to total exposure to aldicarb and its metabolites.

Health Advisory Values for Mixture of the Aldicarbs

Because the mechanism of neurotoxicity of aldicarb, aldicarb sulfoxide and aldicarb sulfone is the same, the presence of these contaminants in mixture is additive. Therefore, the HA values for the mixture is also 0.007 mg/l.

Evaluation of Carcinogenic Potential

Aldicarb:

- Although aldicarb was noncarcinogenic under all conditions tested, the

MTD was not reached in the chronic feeding studies in rats (Weil and Carpenter, 1965; NCI, 1979) or mice (NCI, 1979).

- The International Agency for Research on Cancer (IARC) has not classified aldicarb in terms of its carcinogenic potential.

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

Aldicarb Sulfoxide and Aldicarb Sulfone:

- The carcinogenic potential for both aldicarb sulfoxide and aldicarb sulfone has not been assessed.

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

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

Aldicarb:

- The FAO/WHO proposed ADIs for total aldicarb residues of 0-0.001 mg/kg/day in 1979 and 0-0.005 mg/kg/day in 1982 (FAO/WHO, 1979, 1982).

- An MCLG of 0.001 mg/L was established for aldicarb by EPA's Office of Water on July 1, 1991. Based on practical quantitation limits (PLQs), an MCL of 0.003 mg/L has been set (U.S. EPA, 1991). In response to the registrant's appeal of the MCL, this regulation was stayed in May 1992 until additional new data were evaluated.

- Tolerances for aldicarb residues in agricultural commodities ranging from 0.002 to 1 ppm have been set by USDA (USDA, 1990).

Aldicarb Sulfoxide and Aldicarb Sulfone:

- An MCLG of 0.001 mg/L was established for aldicarb sulfoxide by EPA's Office of Water on July 1, 1991. Based on PLQs, an MCL of 0.004 mg/L has been set. An MCLG of 0.002 mg/L was established for aldicarb sulfone by EPA's Office of Water on July 1, 1991. This level has also been established as the MCL (U.S. EPA, 1991c). In response to the registrant's appeal of these MCLs, this regulation was stayed in May 1992 until additional new data were evaluated.

VI. ANALYTICAL METHODS

Aldicarb:

- Analysis of aldicarb and its metabolites, the sulfoxide and sulfone, is by a high performance liquid chromatographic 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 µL aliquot is injected into a reverse phase HPLC column. Separation of compounds is achieved using gradient elution chromatography. After elution from the HPLC column, the compounds are hydrolyzed with sodium hydroxide. The methylamine formed during hydrolysis is reacted with o-phthalaldehyde (OPA) to form a fluorescent derivative which is detected using a fluorescence detector (detection limit = 1.3 µg/L for aldicarb).

- Krause (1985a,b) reported a liquid chromatographic (LC) multiresidue method for determining residues of carbamate insecticides, including aldicarb, its sulfoxide and its sulfone. In this method, methanol and a mechanical ultrasonic homogenizer are used to extract carbamates. Water soluble and nonpolar material are separated by liquid-liquid partitioning. Estimated limits of quantitation are 0.01 ppm.

Aldicarb Sulfoxide:

- The analytical methodologies described above for aldicarb and its metabolites are the only known methodologies appropriate for aldicarb sulfoxide.

Aldicarb Sulfone:

- The analytical methodologies described above for aldicarb and its metabolites are the only known methodologies appropriate for aldicarb sulfone.

VIII. TREATMENT TECHNOLOGIES

Aldicarb:

- Techniques which have been used to remove aldicarb from water are carbon adsorption and filtration. Since aldicarb is converted to aldicarb sulfoxide and sulfone, all three compounds must be considered when evaluating the efficiency of any decontamination technique.

- Granular activated carbon (GAC) was used in two studies of aldicarb removal from contaminated water (Union Carbide, 1979; ESE, 1984). Both studies utilized home water treatment units rather than large-scale water treatment systems. Union Carbide tested the Hytest Model HF-1 water softener in which the ion exchange ion was replaced with 38.5 lb Filtrasorb 400 (Calgon GAC). The unit was operated at a flow rate of 3 gal/min. Water spiked with 200 ppb or 1,000 ppb of a mixture of

aldicarb, aldicarb sulfoxide and aldicarb sulfone in a 10:45:45 ratio was treated. Under these conditions, the total aldicarb residue level was reduced by 99% to 1 ppb for the treatment of 13,500 gallons of water with 200 ppb of residues and 41,500 gallons with 1,000 ppb total residues. No breakthrough of aldicarb occurred. When the study was terminated, the carbon had adsorbed 9 mg aldicarb residue per gram. This value can be compared with an equilibrium loading value of 21 mg per gram of carbon at 16°C determined using 200 ppb aldicarb residues. In the second study, ESE (1984) did a field study in Suffolk County, NY. Nineteen units using type CW 12 x 40 mesh carbon were tested. After 38 months of use, breakthrough of aldicarb occurred to levels over 7 μg/L in eight units tested. The range of usage values can be attributed to the fact that the natural well samples contained a variety of adsorbable substances in addition to aldicarb.

- Chlorination also appears to offer the potential for aldicarb removal (Union Carbide, 1979). The company reported that 1.0 ppm free chlorine caused a shift in the ratio of aldicarb, its sulfoxide and its sulfone so that all residues were converted to the sulfoxide within 5 minutes of chlorine exposure. Normal conversion of aldicarb to aldicarb sulfone did not appear to be affected. On standing, the sulfoxide and sulfone decomposed. The decomposition products were not identified.

- Aeration or air stripping which is commonly used to remove synthetic organic chemicals is not considered to be a good technique for the removal of aldicarb (ESE, 1984). This is because aldicarb has a low Henry's Law Constant (2.32×10^{-4} atm).

Aldicarb Sulfoxide:

- Treatment technologies described above for aldicarb and its metabolites are the only technologies known to be appropriate for aldicarb sulfoxide.

Aldicarb Sulfone:

- Treatment technologies described above for aldicarb and its metabolites are the only technologies known to be appropriate for aldicarb sulfone.

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