

Aldicarb (CASRN 116-06-3)

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Aldicarb

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	11/01/1993
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/22/1988

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Aldicarb
CASRN — 116-06-3
Primary Synonym — Temik
Last Revised — 11/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an

elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Sweating as clinical sign of AChE inhibition	NOAEL: 0.01 mg/kg-day LOAEL: 0.025 mg/kg-day	10	1	1E-3 mg/kg-day
Acute Human Oral Exposure Study				
Rhone-Poulenc, 1992				
Clinical signs and symptoms of acetylcholinesterase inhibition including sweating, pinpoint pupils, leg weakness, and other effects	NOAEL: None LOAEL: (FEL) 0.1 mg/kg-day			
Acute Human Oral Exposure Study				
Union Carbide, 1971				
Nausea, diarrhea, and other signs and symptoms	NOAEL: None LOAEL: (FEL) 0.01 mg/kg-day			
Acute Human Oral				

Critical Effect	Experimental Doses*	UF	MF	RfD
Poisoning Episodes				
Goldman et al., 1990a,b; Hirsch et al., 1987				

*Conversion Factors and Assumptions — Oral doses administered in 200 ml orange juice ingested over 15 minutes with a light breakfast (study 1). Oral doses administered neat in 100 ml water. Dose administered affected 4 out of 4 exposed men (study 2). Oral doses estimated based on self reports of amount of commodities consumed, measured residue levels in commodities, and average body weights for given age and sex. Level listed is median of 41 cases (study 3).

I.A.2. Principal and Supporting Studies (Oral RfD)

Rhone-Poulenc Ag Company. 1992. A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. Inveresk Clinical Research Report No. 7786. MRID No. 423730-01. HED Doc. No. 0010459. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Union Carbide Corporation. 1971. R. Haines, J.B. Dernehl, and J.B. Block, supervising physicians. Ingestion of Aldicarb by Human Volunteers: A Controlled Study of the Effects of Aldicarb on Man. ALD-03-77-2215. February 11, 1971. MRID No. 00101911. HED Doc. No. 010450. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Goldman, L.R., M. Beller and R.J. Jackson. 1990a. Aldicarb food poisonings in California, 1985-1988: Toxicity estimates for humans. Arch. Environ. Health. 45(3): 141-147. HED Doc. No. 010451, 010455, 010458. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Goldman L.R., D.F. Smith, R.R. Neutra, et al. 1990b. Pesticide Food Poisoning from Contaminated Watermelons in California, 1985. Archives of Environmental Health. 45(4): 229-236.

Hirsch, G.H., B.T. Mori, G.B. Morgan, P.R. Bennett, and B.C. Williams. 1987. Report of Illnesses Caused by Aldicarb-Contaminated Cucumbers. Food Additives and Contaminants. 5(2): 155-60. HED Doc. No. 010455, 010458. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

The double blind, placebo controlled study included 38 men and 9 women, with 6 men and 5 women receiving both a dose and a placebo exposure (Rhone- Poulenc Ag Company, 1992). Men were exposed to doses of 0, 0.01, 0.025, 0.05, 0.06, or 0.075 mg/kg of aldicarb, while women received 0, 0.025, or 0.05 mg/kg. Subjects were given a light breakfast on the day of the study, including a drink of orange juice containing one of the doses of aldicarb or the placebo to be consumed over 15-30 minutes of the breakfast period. Subjects remained generally seated or recumbent for the first 4 hours after dosing. A number of biological parameters known to be affected by cholinesterase inhibitors were monitored before dosing, hourly for the first 6 hours after dosing, and at 24 hours after dosing. These measures included recording of signs and symptoms (e.g., sweating), measurements of pulse and blood pressure, evaluation of pulmonary functions (FEV-1 and FVC), saliva and urine output, pupil diameter measurements, and measurement of plasma and red blood cell cholinesterase activity. All study subjects were evaluated with respect to the above consequences after dosing with aldicarb or placebo. Emphasis was placed on the first 6 hours after exposure, because it is known that the effects and cholinesterase inhibition caused by aldicarb are acute and readily reversible. The major endpoints seen in the study and discussed as potentially treatment-related were effects on red blood cell and plasma cholinesterases, sweating, light-headedness, headaches, salivation, and supine diastolic blood pressure.

Aldicarb treatment of both males and females resulted in statistically significant inhibition of both red blood cell and plasma cholinesterase at all dose levels. Peak effects were noted at 1 hour after the dose, and the degree and duration of effect increased with increasing doses. One male in the 0.075 mg/kg group who had mistakenly received 0.06 mg/kg, developed diffuse and profuse sweating that began within 2 hours and abated within 6 hours of dosing. Two other treated males, one given 0.05 mg/kg and another given 0.025 mg/kg, developed localized and mild sweating with onset within the first 2 hours of dosing and abated within 6 hours of dosing. One male given 0.075 mg/kg reported that he was light-headed within 1 hour of dosing. Three men in the 0.01 mg/kg group reported headaches, two with onset within 6 hours of dosing, and one within 8 hours. This long time between dosing and onset is beyond the peak of cholinesterase inhibition and the other effects seen here and in both the Union Carbide study and the poisoning episodes. None of the females developed any clinical signs or symptoms consistent with cholinesterase inhibition or treatment.

Females given 0.05 mg/kg showed higher saliva output than controls, with marginal statistical significance. Observed changes in blood pressure were generally small in magnitude, limited to supine diastolic pressure, and statistically significant in some, but not other analyses. There were no treatment-related changes in standing or supine pulse, pupil size, or urine volume in either males or females. As expected, there were no changes in hematology and clinical chemistry parameters.

There were statistically significant increases in FVC in men at the 0.01 and 0.075 mg/kg doses, but these were not considered to be treatment-related based on a one way analysis of variance and on the observation that the statistically significant findings were likely a result of a drop in control values during the session.

A number of questions arose during the review of this study that made it more difficult to fully interpret the results. Some of these were related to incomplete reporting by the study authors. Others are simply limitations in the design and conduct of the study.

The paucity of clearly and statistically significant chemical-related effects other than inhibition of plasma and red blood cell cholinesterase activity, and the limitations noted, make a definitive judgment of toxic and non-toxic doses difficult. Effects noted tended not to demonstrate statistical significance, dose-response or dose effect relationships, or correspondence between males and females. Diffuse and profuse sweating in one man given 0.06 mg/kg was the most clearcut sign of toxicity; the appearance of localized sweating in one man at 0.05 and another at 0.025 mg/kg suggests some dose-related response, especially in light of the Union Carbide (1971) study, where all males receiving 0.1 mg/kg showed sweating. Some other effects consistent with cholinesterase inhibition were noted in the range of 0.025-0.075 mg/kg.

In conclusion, the NOAEL for this study was considered to be 0.01 mg/kg-day and the LOAEL is 0.025 mg/kg-day, based on the sweating seen in males. This NOAEL serves as the operational basis for the RfD derivation.

In another human study (Union Carbide Corporation, 1971), 12 adult male volunteers were weighed and assigned to different treatment groups based on nearly equal average weights. None of the subjects had known exposure to aldicarb or other cholinesterase inhibitors for a week prior to the study. Subjects were divided into three test groups (4/group) and administered aldicarb at 0.025, 0.05, or 0.1 mg/kg. A stock solution of 1 mg/ml of aldicarb was prepared by dissolving 0.2 g of analytical grade aldicarb in 200 ml of distilled water. Dosages were prepared by diluting the appropriate amount of aldicarb solution into 100 ml of distilled water, which was then ingested in one draft. Subjects were given their doses between 9:00 and 9:15 a.m. and engaged in normal business activities except during blood and urine sampling and clinical observations. Liquids were provided ad libitum during the post-exposure period. Observations were reported 1, 2, 3, 4, and 6 hours following the dose. These observations included measurement of pulse, blood pressure, observation of pupil size, and subjects' complaints.

All three groups experienced significant cholinesterase inhibition in whole blood, with the peak inhibition between 1-2 hours and almost complete recovery in 6 hours. The 0.1 mg/kg dose elicited clinical signs in all four subjects, predominantly sweating and leg weakness, while most subjects given the two lower doses had no signs or symptoms. At 0.025 mg/kg, one subject

reported apprehension. The method of analysis of cholinesterase in blood was valid and appropriate for this carbamate. The range of cholinesterase inhibition at this dose(0.025 mg/kg) was 30-57%.

Therefore, an FEL of 0.1 mg/kg-day can be established for this study based on clinical signs and symptoms of acetylcholinesterase inhibition including sweating, pinpoint pupils, leg weakness, and other effects.

Dosage estimates for 28 cases of alleged aldicarb poisoning were derived from average body weights by age and sex (from standard tables), self-reported symptoms and estimated consumption, and aldicarb sulfoxide residues from watermelons and cucumbers (Goldman et al., 1990a). Estimates for 13 additional cases were provided by Hirsch et al. (1987), also based on estimates of body weights and consumption, and measurements of residues of total aldicarb, believed to be primarily 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 description of cases used for estimates was limited in terms of onset, duration, and severity, and many of the reported symptoms of cholinesterase inhibition, (i.e., nausea, vomiting, and diarrhea) are nonspecific. The analytical methodology 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 due to these factors (i.e., some false positives and false negatives), may have occurred among the over 1000 reported cases of illness. Further, the use of sex and age averages for body weights and self-reported food consumption values are also subject to estimation errors, but these are expected to include both under and overestimates. Nevertheless, these effects were consistent with the expected syndrome, the analytical techniques were considered valid and these dosage estimates are regarded as reasonable general estimates of effects.

In conclusion, an FEL of 0.01 mg/kg-day can be established from these three studies based on nausea, diarrhea, and other signs and symptoms.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 10 is proposed based on the NOAEL in the Rhone- Poulenc human study to account for variation in sensitivity among persons in the population. Several considerations went into the choice of this uncertainty factor. Based on a relatively complete database for systemic toxicity, effects from repeated exposures have not been seen in laboratory animals at levels comparable to those seen in humans exposed acutely, and so would not support a lower RfD. While human data on the adverse consequences of repeated aldicarb exposure is lacking, available evidence both in experimental animals and in humans exposed to aldicarb suggest that neurobehavioral effects are short lived with no accumulation of effects over time.

Thus, the doses producing effects following repeated daily exposure are comparable to those following a single dose. Also, comparable degrees of cholinesterase inhibition are seen from the same dose levels, whether delivered in one acute dose or following subchronic or chronic dosing (Hazelton et al., 1988; Rhone-Poulenc, 1992). Since aldicarb does not appear to produce neurobehavioral effects at doses below those producing inhibition of cholinesterase, an acute human experimental study is expected to reasonably evaluate the potential neurobehavioral consequences of repeated human exposure. Compared with the controlled studies, the human poisoning episodes document effects in a group of individuals probably self-selected as a sensitive population and more heterogeneous than the healthy adults chosen for the controlled studies. The dosage estimates from these reports, however, were derived from estimates of the body weights of the people involved, based on tables of average weights for a given age and sex. They also were derived from self-reported estimates of the amount consumed. Thus, while these dosage estimates are based on reasonable estimates of body weight and amount of watermelon consumed for each population sample, they are not as precise as those derived in the controlled studies, where each subject was weighed and received a known dose. It is more reasonable to examine the distribution of estimated doses over which effects were reported, rather than to regard each individual estimate as precise. All the estimates for the 41 cases from the poisoning episodes are subsumed within this RfD. The proposed RfD provides for a margin of exposure of 10 from that recorded in the controlled studies or from the median poisoning estimate. It also subsumes the entire range over which effects have been reported in the poisoning episodes which empirically define, to some extent, the sensitivity of a more sensitive heterogeneous population.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

There is a rich database bearing on the toxicity of aldicarb. The compound is a potent cholinesterase inhibitor that rapidly induces adverse effects that are rapidly reversed. Chronic toxicity in laboratory animals is manifest at doses comparable to those that produce acute toxicity. Essentially all Hazards from aldicarb exposure are associated with cholinesterase inhibition (ChEI). Both human and laboratory animal data can be used to determine levels of aldicarb exposure that are probably not associated with significant risk. An overall view of the data indicates that various species show toxic effects at similar doses. Because of the availability of human studies, it is logical to place primary reliance on these studies in determining the RfD.

These four studies of humans provide the best information on the toxic effects of aldicarb: the recent experiment conducted on behalf of Rhone-Poulenc (1992), the Haines experimental study conducted by Union Carbide (1971), and the evaluations of some pesticide misuse poisoning incidents developed by Goldman and Hirsch (Goldman et al., 1990a,b; Hirsch et al., 1987). In developing the RfD, primary emphasis has been placed upon the Rhone-Poulenc study. The

Union Carbide study provides some correlative evidence of a frank effect level and sweating, while the poisoning incidents provides important general estimates of potential population sensitivity. The weight of the evidence from all of the available human data cited here were considered critical in the estimation of this reference dose. Each of these sources has limitations that raise concerns about sole reliance on any one as a basis for this estimate. However, it was considered equally important to consider use of all of the available evidence to estimate potential risks.

The Union Carbide study (1971) helps define a dose (0.1 mg/kg) that is clearly associated with adverse effects in humans. At least three of four subjects showed sweating, pupillary constriction, muscle weakness, and increased salivation, while fewer demonstrated slurred speech, malaise, nausea, gastrointestinal cramping, and vomiting. No confirmation of these signs was noted in groups receiving 0.05 or 0.025 mg/kg of aldicarb. Significant reductions in blood cholinesterase activity, which returned to normal within a few hours, was noted in all dosed individuals.

In the Rhone-Poulenc study (1992), where groups received doses of aldicarb between 0.01 and 0.075 mg/kg, there were less obvious indications of toxicity. Some male subjects manifested sweating, headache, or light-headedness that could have been due to aldicarb exposure. Only the sweating was a manifestation in common with the subjects in the Union Carbide study. The most obvious sign in the new study was the finding of diffuse and profuse sweating in one male who had received 0.06 mg/kg of aldicarb; the other two cases were males demonstrating localized sweating of the palms with or without sweating of the soles (0.05 and 0.025 mg/kg, respectively). One of the control males also developed sweating of the palms and forehead. Diffuse body sweating is a well characterized cholinergic sign, whereas localized sweating is mediated by sympathetic fibers that synapse at cholinergic ganglia and communicate with the sweat glands of the palms and soles by norepinephrine. Cholinesterase inhibition at the ganglia may sensitize these neurons to other potential stimuli, like emotional factors. At 0.1 mg/kg, all four of the treated males in the Union Carbide study demonstrated sweating, and two of them had sweating localized to the palms and forehead. As in the Union Carbide study (1971), dosed subjects in the Rhone-Poulenc study (1992) showed depressions in blood cholinesterase that generally began to recover within a few hours.

The relative drop in supine diastolic blood pressure during the first hour post-dosing in the Rhone-Poulenc (1992) study was significantly greater in the male 0.075 mg/kg group than in the controls when an unweighted analysis was performed but not when a weighted analysis was performed. Females in the 0.025 mg/kg group showed a decrease in the relative diastolic pressure at 1 hour post-dosing, which was significant in a weighted analysis but not in an unweighted analysis. Higher-dosed females (0.05 mg/kg) showed no significant differences. In contrast, the mean supine diastolic pressure of the male 0.05 mg/kg group in the Rhone-Poulenc

(1992) study was statistically significantly higher than that in the placebo group. There were no differences in the supine systolic pressures or the standing blood pressures in treated males and females. Also of interest is the absence of blood pressure changes in the males in the Union Carbide (1971) study who received doses of 0.025, 0.05, or 0.1 mg/kg of aldicarb.

As would be expected from ChEI, salivation was statistically significantly increased in the 0.05 mg/kg female dose group (highest dose tested in females) as compared with controls in the Rhone-Poulenc study. In contrast, males in the 0.01 and 0.05 mg/kg groups and the male who received 0.06 mg/kg showed a significant decrease in salivation; males receiving 0.075 mg/kg showed no difference from the placebo group. Increased salivation was noted in 3 of the 4 treated males in the Union Carbide study that received 0.1 mg/kg aldicarb, but not in those receiving 0.025 or 0.05 mg/kg. Headache was reported by three males in the 0.01 mg/kg dose group in the Rhone-Poulenc study (1992), but this symptom was not declared among males in any of the other groups or in any of the females. Headache was not reported in the males in the Union Carbide study.

In sum, there is very good information that 0.1 mg/kg of aldicarb is toxic to humans and produces multiple effects including such things as sweating, muscular weakness, and pinpoint pupils. Diffuse or localized sweating was noted in 4 of 4 subjects at 0.1 mg/kg and in one subject each who had received the 0.06, 0.05, and 0.025 mg/kg doses; no sweating was reported at 0.01 mg/kg. Other indications of a potential cholinergic response in these studies are less reliable: they occur at some doses but not at doses higher or doses lower; there is a failure across sexes to confirm the presence of effects or there is an opposite effect; there is no statistical significance and there is no dose response. These limitations apply to the evaluation of all the effects in these studies.

A reasoned course is to place major emphasis on sweating, the only sign of cholinergic response that was noted in both experimental studies. Therefore based on sweating, a LOAEL of 0.025 mg/kg and a NOAEL of 0.010 mg/kg were identified. These considerations include the bulk of other potential effects such as headaches that were noted in the Rhone-Poulenc study.

Recognizing that these judgments are based upon a limited number of observations in humans, an uncertainty factor of 10 is included to account for potential human variability. The estimates of potential exposure from five pesticide misuse poisoning incidents (Goldman et al., 1990a,b; Hirsch et al., 1987) were all higher than the proposed RfD. Based upon all of the data on humans from these sources, exposure to 0.001 mg/kg of aldicarb, the present RfD, is expected to be without significant adverse effect.

Two other general comments related to the population sensitivity and the nature and extent of effects should be noted. First, the broad range of exposure levels over which effects in humans have been seen in these studies (0.002-0.1 mg/kg) suggests that some portion of population

sensitivity is accounted for in the data. Second, the effects seen are acute, relatively small in magnitude in many cases, and of relatively low incidence at all but the highest dose levels.

Other Data Reviewed:

1) 1-Year Feeding - dog: Core grade supplementary (Rhone-Poulenc, 1988a; Rhone-Poulenc, 1991a).

Groups of beagle dogs (5/sex/dose) were administered Aldicarb, technical grade, in the diet for 52 weeks at doses of 0, 0.028, 0.054, 0.132, and 0.231 mg/kg-day for males and 0, 0.027, 0.055, 0.131, and 0.251 mg/kg-day for females. It was initially concluded that the lowest dose tested, 1 ppm (0.028 mg/kg-day) was a LOAEL for plasma cholinesterase inhibition in males and that the next higher dose level (0.055 mg/kg) and above produced signs consistent with cholinesterase inhibition, including diarrhea and mucoid and/or soft stool. According to the study report, group brain cholinesterase was significantly inhibited only at the highest dose in males compared with controls. A NOAEL for ChE inhibition in the study was not established. Review of an addendum submitted by the registrant (Rhone-Poulenc, 1991a) which provided additional pre-exposure data on clinical signs seen in the 1-year dog study, and after extensive statistical analyses by EPA, it was concluded that the available data and evaluations on clinical signs in dogs of diarrhea and soft and mucoid stool were insufficient to support the conclusion that this was an effect of treatment.

2) Subchronic Feeding - dog: (Rhone-Poulenc, 1991b).

This study established a clear NOAEL for plasma cholinesterase between 0.35 and 0.7 ppm in the diet (0.012-0.025 mg/kg) for dogs fed these levels in the diet for 5 weeks. No clinical signs were noted as effects of treatment. Levels of red blood cell cholinesterase inhibition may have been underestimated, however.

3) 2-Year Feeding - rat: Core grade supplementary (Union Carbide, 1966c).

Four groups of rats (20/sex/dose) were maintained on diets containing 0, 0.005, 0.025, 0.05, or 0.1 mg/kg-day of aldicarb for 2 years. Based upon measurements of food consumption; mortality and lifespan; incidence of infection; liver and kidney weights as percentage of body weight; body weight gain; hematology; incidence of neoplasms; incidence of pathological lesions; and brain, plasma, and erythrocyte cholinesterase levels, the animals were found not to differ significantly from controls for any of these parameters. Therefore, the NOAEL for systemic toxicity is greater than or equal to 0.1 mg/kg-day.

4) 2-Year Feeding (carcinogenicity) - rat: Core grade minimum (Union Carbide, 1972).

Groups of 20 Greenacres laboratory controlled flora rats of each sex were fed 0 or 0.3 mg/kg-day of aldicarb in the diet for 2 years. There were no differences from controls in mortality, growth, hematological characteristics, or other histological abnormalities. The NOAEL for systemic toxicity is therefore greater than or equal to 0.3 mg/kg-day.

5) 3-Generation Reproduction - rat: Core grade minimum (Union Carbide, 1974a).

Rats were fed aldicarb at dose levels of 0, 0.2, 0.3, or 0.7 mg/kg-day for 90 to 100 days and mated to produce the respective F1, F2, and F3 generations. All animals were maintained continuously on diets containing aldicarb. The F3 animals were histologically examined either at weaning or at 90 days of age. No reproductive effects were noted at any dose tested. Decreased body weight of F2 pups was observed at 0.7 mg/kg-day. Therefore, the NOAEL and LOAEL for fetotoxicity are 0.3 and 0.7 mg/kg-day, respectively.

6) 2-Generation Reproduction - rat: core grade minimum (Rhone Poulenc, 1991c).

Twenty-six males and females/dose were administered aldicarb at dose levels of 0, 0.1, 0.4, 0.7-9, and 1.4-1.7 mg/kg-day for 70 days prior to mating and then bred to obtain the F1A litters. These progeny were raised until weaning (day 21). The F0 rats were then bred producing the F1B litters. Aldicarb had no adverse effects on reproductive capacity during either mating. At 1.4-1.7 mg/kg-day dose, there were decrease pup weights and reduced pup viability observed at lactation day 4. At 0.7-0.9 mg/kg-day, in parents decreased body weights and decreased RBC and plasma cholinesterase levels were seen. The NOEL for parental systemic toxicity was 0.4 mg/kg-day and the fetotoxic NOEL was 0.7-0.9 mg/kg-day.

7) Developmental toxicity - rat: Core grade minimum (Union Carbide, 1966a).

Pregnant rats were administered aldicarb in the diet at dose levels of 0, 0.04, 0.2, and 1 mg/kg-day. The rats were further divided into three groups: Group 1 rats were fed aldicarb in the diet throughout pregnancy or until the pups were weaned; Group 2 rats were administered aldicarb from the day the vaginal plug first appeared through the seventh day; and Group 3 received aldicarb from days 5 through 15 of gestation. No congenital malformations were reported for any of the treated groups, and body weights of both the mothers and pups were normal. No significant effects were observed on fertility, gestation, viability of offspring, or lactation. Therefore, the NOAEL for systemic and developmental effects is equal to or greater than 1 mg/kg-day (HDT).

8) Developmental toxicity - rat: Core grade minimum (Rhone-Poulenc, 1988b).

Groups of CD rats were administered aldicarb by gavage at dose levels of 0, 0.125, 0.25 and 0.5 mg/kg-day. Effects on pregnant dams were found at 0.25 and 0.5 mg/kg-day and consisted of decreased body weight gain and food consumption. There were some maternal deaths at 0.5 mg/kg-day. The NOEL for maternal toxicity was 0.125 mg/kg-day. In offspring, at the 0.5 mg/kg-day dose level, there were significant increases in the dilation of the lateral ventricles of the brain, poor ossification of the sixth sternebra, and significant decreases in fetal body weight. In addition, ecchymosis (small hemorrhages) of the trunk were significantly increased ($p < 0.05$) at the 0.25 and 0.5 mg/kg-day dose levels. The incidence of this finding at the low-dose group was not statistically significant and was within the historical control range. The NOEL for developmental effects was 0.125 mg/kg-day.

9) Developmental toxicity - rabbit: Core grade guideline (Union Carbide, 1983).

Groups of pregnant Dutch Belted rabbits (16/group) were administered aldicarb by gavage at dose levels of 0, 0.1, 0.25, and 0.5 mg/kg-day from days 7 through 27 of gestation. On the first day of dosing (day 7), 8 animals/group were misdosed with 3 ml/kg instead of 1 ml/kg. Consequently, 5/8 rabbits died in the 0.5 mg/kg-day group. Remaining misdosed animals in all groups were sacrificed and replaced. Survival, other than noted above, was comparable among all groups. General observations for toxic signs were unremarkable, except for pale kidneys and hydroceles on the oviducts at doses greater than or equal to 0.25 mg/kg-day. There were compound-related decreases in body weight for dams at the two highest doses. Based on decreased body weight, pale kidneys, and hydroceles on the oviducts, the NOEL and LOEL for maternal toxicity are 0.25 and 0.5 mg/kg-day, respectively. The number of viable fetuses/doe was significantly reduced in all treatment groups, as was the total number of implantations/doe. Group mean post-implantation loss was significantly reduced in all treatment groups, as was the total number of implantations/doe. These observations (which were statistically significant only at the lowest dose tested) were considered to be due to the unusually large number of corpora lutea/dam and the low rate of pre-implantation loss in the control group, both of which contributed to a higher number of viable fetuses and implantations in the control group. The historical control data supported this conclusion. Therefore, the NOEL for fetotoxicity was 0.5 mg/kg-day, and the overall NOEL for developmental toxicity is 0.25 mg/kg-day.

10) 2-Year Feeding - dog: Core grade minimum (Union Carbide, 1966b).

Four groups of dogs (3/sex/dose) were fed aldicarb in the diet at dose levels of 0, 0.025, 0.05, and 0.1 mg/kg-day for 2 years. Based upon observations of body weight changes, appetite, mortality, histopathology, hematology, biochemistry, and terminal liver and kidney weights, there were no statistically significant effects found at any dose tested. Therefore, the NOAEL for systemic toxicity is greater than or equal to 0.1 mg/kg-day.

11) 3-Month Feeding - dog: Core grade minimum (Union Carbide, 1974b).

Dogs were fed aldicarb in the diet at dose levels of 0, 0.2, 0.3, and 0.7 mg/kg-day for 90 days. The only effects observed were the slightly decreased weight of the testes and the slightly increased weight of the adrenal glands in males at 0.7 mg/kg-day. Therefore, the NOAEL and LOAEL for systemic toxicity are 0.3 and 0.7 mg/kg-day, respectively.

12) 14-Day Feeding - dog: Core grade supplementary (Union Carbide, 1987).

One dog/sex/dose received aldicarb in the diet at dose levels of 0, 0.1, 0.3, 1, 3, and 10 ppm (Male: 0, 0.003, 0.008, 0.029, 0.08, and 0.269 mg/kg-day; Female: 0, 0.003, 0.008, 0.029, 0.114, and 0.294 mg/kg-day) for 2 weeks. Treatment-related effects were observed for inhibition of red blood cell (RBC) acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE) which occurred at or about 3 ppm. Three weekly pre-dose determinations for both RBC and plasma were utilized for comparison of an individual to its own baseline cholinesterase levels. Serial measurements performed every 2 hours for the first 8 hours post-dosing in Group 6 (10 ppm dose) clearly demonstrated inhibition of RBC AChE to 45% of normal and plasma BuChE to 34% of normal. Inhibition was not fully recovered at 8 hours. Based on plasma and RBC ChE inhibition, the NOAEL and LOAEL for systemic toxicity are 1 (0.029 mg/kg-day) and 3 ppm (Male: 0.08 mg/kg-day; Female: 0.114 mg/kg-day).

13) Immunotoxicity - humans: Fiore et al., 1988; Mirkin et al., 1990.

These two published studies suggest that data from women exposed to aldicarb in their drinking water indicated immunomodulatory effects on T Cell subsets. The second, followup study notes evidence of lymphocyte (CD8+ T- cell increases) in peripheral blood without clinical signs in five women. U.S. EPA, Office of Pesticide Programs reviews conclude that for a number of methodological, statistical, and other reasons, that immunological Hazards due to Aldicarb have not been demonstrated in these studies.

Data Gap(s): The Agency is preparing a Data Call In for aldicarb that is expected to call for further neurotoxicity studies, and a rat dominant lethal study.

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

The principal studies are given a medium to low confidence rating because none establish a definitive state of the science NOAEL for adverse effects and are limited in the ways described above. Their corroboration of one another in some ways provide additional support. The database consists of numerous studies and is given a medium confidence rating for completion due to the lack of definitive neurotoxicity studies for a chemical which is a potent neurotoxicant. Confidence in the RfD can be considered medium.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984, 1988, 1991

Agency Work Group Review — 12/02/1985, 02/05/1986, 05/15/1986, 06/20/1990, 07/25/1990, 09/22/1992, 10/15/1992

Verification Date — 10/15/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Aldicarb conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Aldicarb

CASRN — 116-06-3

Primary Synonym — Temik

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Aldicarb

CASRN — 116-06-3

Primary Synonym — Temik

Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as to human carcinogenicity.

Basis — Aldicarb was not found to induce statistically significant increases in tumor incidence in mice or rats in feeding studies or mice in a skin painting study. In the feeding studies there were, however, significant trends in pituitary tumors in female rats and fibrosarcomas in the male

mouse. This evidence, together with the fact that less than maximum tolerated doses were used, indicates that the available assays are inadequate to assess the carcinogenic potential of aldicarb.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. The NCI (1979) conducted a bioassay of aldicarb for possible carcinogenic effects in rats and mice. Fifty male and 50 female F344 rats and the same numbers of male and female B6C3F1 mice were administered doses of 2 or 6 ppm in the diet for 103 weeks. The animals were then observed for an additional 0 to 2 weeks before terminal sacrifice. Matched controls were composed of 25 untreated rats and 25 untreated mice of each sex. There was a dose-related trend in incidence of pituitary adenomas or carcinomas in the female rats for which the Cochran-Armitage test was statistically significant but the Fisher exact test was not significant. There were occurrences of pancreatic islet-cell adenomas in both treated male and female rats. The incidences were not statistically significant but were nonetheless regarded as compound-related by NCI since there were no pancreatic tumors in the concurrent controls. A dose-related trend in incidence of fibrosarcoma or sarcoma of the subcutaneous tissue was observed in treated male mice for which the Cochran-Armitage test was statistically significant. The Fisher exact test, however was not significant. NCI acknowledged that maximum tolerated doses were not achieved in this study, and it was concluded that none of the tumors could be clearly attributed to the administration of aldicarb.

In a 2-year feeding study, Weil and Carpenter (1965) administered 0.005, 0.025, 0.05 or 0.1 mg aldicarb/kg/day in the diet (0.1, 0.5, 1.0 or 2.0 ppm, assuming food consumption of 5% of body weight per day) to an unspecified strain of rats. The tumor incidences were not significantly greater than those of the control animals. Weil and Carpenter (1972) reported similar results in Greenacres Laboratory Controlled Flora rats fed 0.3 mg/kg/day (6 ppm) for 2 years. No adverse effects were observed due to the aldicarb administration.

Weil (1973) conducted a skin painting study using male C3H/HEJ mice. Female mice were not used for the study due to the high incidence of spontaneous mammary tumors. Mice were administered the aldicarb in the form of applications of 0.125% concentration to hair-free skin on the backs of the animals twice a week for up to 28 months or until death. When compared to controls (positive control group painted with cholanthrene), aldicarb was determined to be noncarcinogenic under the conditions of the experiment.

II.A.4. Supporting Data for Carcinogenicity

Ercegovich and Rashid (1973) found aldicarb to be weakly mutagenic in five strains of *Salmonella typhimurium* in the absence of liver microsomal enzymes.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1987

The 1987 Drinking Water Criteria Document for Aldicarb has received Agency peer and administrative review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 08/05/1987, 08/26/1987

Verification Date — 08/26/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Aldicarb conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Aldicarb

CASRN — 116-06-3

Primary Synonym — Temik

VI.A. Oral RfD References

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Hirsch G.H., B.T. Mori, G.B. Morgan, P.R. Bennett, and B.C. Williams. 1987. Report of Illnesses Caused by Aldicarb-Contaminated Cucumbers. *Food Add. Contam.* 5(2): 155-60.

Mirkin I.R., H.A. Anderson, L. Hanrahan, R. Hong, R. Golubjatnikov, and D. Belluck. 1990. Changes in T-Lymphocyte Distribution Associated with Ingestion of Aldicarb Contaminated Drinking Water: A Follow-up Study. *Environ. Res.* 51: 35-50.

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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Weil, C.S. 1973. Miscellaneous toxicity studies. Mellon Institute Report 35-41. EPA Pesticide Petition No. 3F1414.

Weil, C.S. and C.P. Carpenter. 1965. Two-year feeding of Compound 21149 in the diet of rats. Mellon Institute Report No. 28-123. EPA Pesticide Petition No. 9F0798.

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VII. Revision History

Substance Name — Aldicarb

CASRN — 116-06-3

Primary Synonym — Temik

Date	Section	Description
08/22/1988	II.	Carcinogen summary on-line
08/01/1990	I.A.	RfD withdrawn; new Oral RfD verified (in preparation)
07/01/1991	I.A.	Oral RfD summary replaced; RfD changed
11/01/1993	I.A.	Oral RfD summary replaced; new RfD
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Aldicarb

CASRN — 116-06-3

Primary Synonym — Temik

Last Revised — 01/31/1987

- 116-06-3
- Aldecarb
- Aldicarb

- Ambush
- Carbamyl
- Carbanolate
- ENT 27,093
- 2-Methyl-2-(Methylthio)Propanal, O-((Methylamino)Carbonyl) Oxime
- 2-Methyl-2-(Methylthio)Propionaldehyde O-(Methylcarbamoyl)Oxime
- NCI-C08640
- OMS 771
- Propanal, 2-Methyl-2-(Methylthio)-, O-((Methylamino)Carbonyl)Oxime
- Propionaldehyde, 2-Methyl-2-(Methylthio)-, O-(Methyl-carbamoyl)Oxime
- Sulfone aldoxycarb
- Temic
- Temik
- Temik 10 G
- Temik G 10
- Temik TSK
- UC 21149
- Union Carbide 21149
- Union Carbide UC-21149