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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 15, 1998

MEMORANDUM

SUBJECT: Aldicarb - Report of the Hazard Identification Assessment Review Committee.

FROM: William F. Sette, Ph.D., Toxicologist. *William F Sette*
Science Analysis Branch *9-15-98*
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, *K. Clark Swentzel 9/17/98*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Christina Swartz, Risk Assessor
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

PC Code: 098301

On July 23, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of Aldicarb, reassessed the Reference Dose (RfD) established in 1993 and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. At the July 23 meeting and in a subsequent meeting on August 25, The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to aldicarb as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

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Committee Members in Attendance

Members present on July 23 were: Clark Swentzel, Mike Metzger, William Burnam, John Redden, Karen Hamernik, Robert Fricke, Melba Morrow, Nancy Mc Carroll, and Karl Baetcke

Members *in absentia* were: Jess Rowland, Sue Makris

Also in attendance were Christina Swartz of RCAB (7/23 only), and Brenda Halbrook of SRB/SRRD (both meetings).

Members present on August 25 were: Clark Swentzel, William Burnam, John Redden, Robert Fricke, Karl Baetcke, Sue Makris, and Brenda Tarplee.

Members *in absentia* were: Jess Rowland, Mike Metzger, Karen Hamernik, and Melba Morrow.

Data was presented by William Sette of Science Analysis Branch.

Data Presentation
and
Report Presentation

William F Sette

William F. Sette, Ph. D.
Toxicologist

Report Concurrence:

Clark Swentzel

Clark Swentzel,
Committee Chairman

I. INTRODUCTION

On November 6, 1992, an SAP/SAB panel reviewed a set of scientific issues in connection with proposed reference doses for aldicarb and aldicarb sulfone, including EPA's proposed use of the human data on aldicarb, the studies's NOAELs, appropriate uncertainty factors, and the role of data from poisoning episodes. The Panel concurred with the use of the NOAEL and UF for aldicarb (U.S. EPA, 1992).

On January 23, 1996, the HED Toxic Endpoint Selection Committee selected the dose and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES document, 2/20/96).

The purpose of the HIARC meeting was to review all of the endpoints for risk assessments, to review the carcinogenicity data base, to review the data relevant to potential increased susceptibility of young organisms, and to consider any impact of more recent toxicity studies on these evaluations.

U.S. Environmental Protection Agency 1992. Report of a Joint Science Advisory Board (SAB) and FIFRA Scientific Advisory Panel (SAP) Meeting on A Set of Scientific Issues being considered by the Agency in connection with aldicarb and aldicarb sulfone. 11/25/92. 5 pp.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: Rhône-Poulenc Ag Company (sponsor). 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.: 42373001

Executive Summary: This double blind, placebo controlled acute oral human exposure study included 38 men and 9 women, with 6 men and 5 women receiving both a dose and a placebo exposure. 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 in orange juice with breakfast to be consumed over 15-30 minutes.

A number of biological parameters were monitored before dosing, hourly for the first 6 hours after dosing, and at 24 hours after dosing. These measures included signs and symptoms (e.g., sweating), pulse and blood pressure, pulmonary functions (FEV-1 and FVC), saliva and urine output, pupil diameter, and plasma and red blood cell cholinesterase activity.

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 cholinesterases at all dose levels. In males, mean plasma cholinesterase inhibition was 13%, 35%, 55%, and 70%, respectively 1 hour after dosing; in females, 49% and 68% (0.025 and 0.05 mg/kg). In males, RBC ChE inhibition was 3.8%, 12%, 29%, and 38%, respectively, also at 1 hour. For females, RBC ChE inhibition was 20% and 36% at the same time. While statistically significant, the

effects seen in men at 0.01 mg/kg, inhibition of plasma of 13% and of RBCs of 3.8% were not considered toxicologically significant. 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 came on within 2 hours and abated within 6 hours of dosing. Two other treated males, one given 0.050 mg/kg and another given 0.025 mg/kg, developed localized and mild sweating with onset within the first 2 hours of dosing which also abated within 6 hours of dosing. One male given 0.075 mg/kg reported that he was lightheaded within one 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 of 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 10 and 75 ug/kg dose, but these were not concluded to be treatment-related, based upon one way analysis of variance which was not statistically significant and upon the observation that the statistically significant findings were likely a result of a drop in control values during the session.

In conclusion, we considered the NOAEL for this study as 0.010 mg/kg and the LOAEL 0.025 mg/kg, based on the sweating seen in the men.

There are no guidelines for human studies, but this study was considered acceptable and, in conjunction with an earlier acute human study (Union Carbide, 1971; MRID No. 00101911) and 2 published studies of acute human poisoning episodes (Goldman et al., 1990; Hirsch, 1987) formed the basis of the EPA 1992 Reference Dose.

In another human study (Union Carbide, 1971) 12 adult male volunteers served as subjects. They 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, and 0.1 mg/kg-day. 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 was 30 to 57%.

Co-critical Studies

Goldman, L.R., M. Beller and R.J. Jackson. 1990. Aldicarb food poisonings in California, 1985-1988: Toxicity estimates for humans. Arch. Environ. Health. 45(3): 141-147.

Hirsch G.H., Mori B.T., Morgan G.B., Bennett P.R., and Williams B.C. 1987. "Report of Illnesses Caused by Aldicarb-Contaminated Cucumbers." Food Additives and Contaminants. 5:2, pp. 155-60.

Dosage estimates for 28 cases of alleged aldicarb poisoning were derived from age and sex average body weights (from standard tables), self-reported symptoms and estimated consumption, and aldicarb sulfoxide residues from watermelons and cucumbers (Goldman et al., 1990). 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, a first quartile of 0.006 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 non-specific. The analytical methodology was valid, although the limit of detection of 0.2 ppm (Goldman) was somewhat higher than in other reports. As a result, there may have been some misclassification errors due to these factors (i.e., some false positives and false negatives), 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 be both under- and over-estimates. 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.

Dose and Endpoint for Risk Assessment: NOAEL of 0.01 mg/kg/day established in the 1992 acute human exposure study. The LOAEL of 0.025 mg/kg/day was based on sweating.

Comments about Study/Endpoint: This dose/study was also used, in combination with the other human data cited above, to establish the chronic RfD. In addition, the NOAEL of 0.01 mg/kg following acute human exposures was also a NOAEL for blood ChEs in that study.

Based on a relatively complete data base for systemic toxicity, effects from repeated exposures have not been seen in animals at levels comparable to those seen in humans exposed acutely, and so would not support a lower RfD.

While we lack any human data on the adverse consequences of repeated aldicarb exposure, available evidence with aldicarb both in experimental animals and in humans suggest that neurobehavioral effects are short lived with essentially no indication of accumulation of

effects over time. Thus, the doses producing effects following repeated daily exposure are comparable to those following a single dose. Using inhibition of cholinesterase activity as a biomarker of exposure, one notes comparable degrees of inhibition from essentially the same dose whether delivered once or following subchronic or chronic dosing (See e.g., Hazelton, 1988; Rhone-Poulenc, 1992). Since aldicarb appears not to produce neurobehavioral effects at doses equivalent or below those producing inhibition of cholinesterase, an acute human experimental study is expected to reasonably evaluate the potential neurobehavioral consequences of repeated human exposure.

In comparison to the controlled studies, the human poisoning episodes note effects from a group of individuals more heterogeneous than the healthy adults chosen for the controlled studies and probably self-selected as a sensitive population. 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 may be reasonable body weights and amount of watermelon consumed for any given population sample, they are not precise individual cases as seen in the controlled studies, where each subject was weighed and received a precisely measured dose. It seems, then, more reasonable to examine the distribution of estimated doses over which effects were reported, rather than to regard each individual estimate as precise. For the 41 cases from the poisoning episodes, all of the estimates are subsumed within this RfD, with the median of 0.01 mg/kg, there is a margin of exposure of 10. Thus, the proposed RfD provides a margin of exposure of 10 from the controlled studies and 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.

Uncertainty Factor (UF): An MOE of 10 is considered adequate.

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

State: This Risk Assessment is required.

B. Chronic RfD

Study Selected: Same as acute dietary RfD. This study was used, in combination with the other human data cited above, to establish the chronic RfD.

MRID No.: 42373001

Executive Summary: See summary under acute dietary section.

Dose and Endpoint for Establishing RfD: 0.01 mg/kg/day; NOEL established in an acute human exposure study. The LOEL of 0.025 mg/kg/day was based on sweating, a cholinergic sign. The NOEL of 0.01 mg/kg was also an NOAEL for blood cholinesterase inhibition in this study.

Uncertainty Factor(s): 10

$$\text{Chronic RfD} = \frac{0.010 \text{ mg/kg/day}}{(10)} = 0.001 \text{ mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: See acute dietary RfD section.
This RfD was reviewed and approved by both the EPA RfD Committee and an SAP/SAB panel.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption (Study not yet available)

Dermal Absorption Factor: 100%

While a comparison of data in rats of an oral LD50 of 0.8 mg/kg (in water) with a dermal LD50 of 20 mg/kg (in water) suggests that there is much less than 100% dermal absorption, the Committee had low confidence in these and other summary data as a result of limited reporting and data reviews available and so concluded that a conservative estimate of 100% dermal absorption should be used for risk assessment. A summary of a new 21 day dermal toxicity study of a granular formulation has been submitted, but the complete report is not available.

2. Short-Term Dermal - (1-7 days)

Study Selected: Same as acute dietary RfD.

MRID No.: 42373001

Executive Summary: See acute dietary RfD section.

Dose and Endpoint for Risk Assessment: The NOEL of 0.01 mg/kg/day from the human study will be used as the basis for risk assessment with an acceptable MOE of 10.

Comments about Study/Endpoint: See acute dietary RfD section.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Same as acute dietary RfD.

MRID No.: 42373001

Executive Summary: See acute dietary RfD section.

Dose/Endpoint for Risk Assessment: The NOEL of 0.01 mg/kg/day from the human study will be used as the basis for risk assessment with an acceptable MOE of 10.

Comments about Study/Endpoint: See acute dietary RfD section.

This risk assessment is required:

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Same as acute dietary RfD.

MRID No.: 42373001

Executive Summary: See acute dietary RfD section.

Dose and Endpoint for Risk Assessment: The NOEL of 0.01 mg/kg/day from the human study will be used as the basis for risk assessment with an acceptable MOE of 10.

Comments about Study/Endpoint: See acute dietary RfD section.

This risk assessment is not required.

5. Inhalation Exposure (Any Time period)

Study Selected: Same as acute dietary RfD.

MRID No.: 42373001

Executive Summary: See acute dietary RfD section.

Dose/Endpoint for Risk Assessment: The NOEL of 0.01 mg/kg/day from the human study will be used as the basis for risk assessment with an acceptable MOE of 10.

Comments about Study/Endpoint: See acute dietary RfD section.

This risk assessment is not required. This assumes that neither granular formulation causes appreciable dust (a topic for which we have requested data in our dermal protocol review).

D. Recommendation for Aggregate (Food, Water, Dermal, and Inhalation) Exposure Risk Assessments

An oral NOEL was selected for calculating MOEs from oral, dermal, and inhalation exposures. Using appropriate absorption factors, the dermal and inhalation exposure levels should be converted to oral equivalent levels and combined.

For acute aggregate exposure risk assessment, combine the exposure values from food and water and compare this to the oral NOEL to calculate the MOE.

For short term, intermediate term, and chronic aggregate exposure risk assessments, combine the average exposure values from food and water together with the aggregate exposures from dermal and inhalation scenarios and compare the total to the appropriate oral NOEL to calculate the MOEs.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

For any occupational risk assessments, HIARC determined that an MOE of 10 is required to account for variability among humans in susceptibility.

III. MUTAGENICITY

1. Gene Mutation Assay

In a Chinese Hamster Ovary (CHO/HGPRT) mammalian cell forward gene mutation assay (MRID 00148168), duplicate cultures, both with and without S-9 activation, were exposed to aldicarb at doses of 1000, 2000, 3000, 4000, or 5000 ug/ml. Aldicarb was dissolved in DMSO. 200 ug/ml EMS -S9 and 100 ug/ml DMN +S9 were the positive control agents.

In a preliminary cytotoxicity assay, slight cytotoxicity was observed at 5000 ug/ml, with and without activation (74% and 81% initial survival, respectively). In the main study, aldicarb was marginally cytotoxic at 5000 ug/ml, with initial survivals of 94.3 and 85.8%, +/- S9 activation, respectively. Both positive controls induced marked increases in the total number of mutants and the mutation frequencies.

There was no evidence of a mutagenic effect at any aldicarb dose, with or without activation.

This study is classified core minimum and satisfies the guideline requirement for a gene mutation assay (84-2).

2. In vivo cytogenetics assay

In an *in vivo* cytogenetics assay (MRID 41661301, 41661302), groups of 15 ICR mice/sex/dose were gavaged with 0.1, 0.2, or 0.4 mg/kg of aldicarb and bone marrow cells harvested from 5 mice/sex/dose at 6, 18, or 30 hours after exposure. Control mice received either de-ionized water or cyclophosphamide (80 mg/kg).

Mortality and signs of toxicity (dyspnea, tremors) were observed in male and female mice at the 0.4 mg/kg dose. Cyclophosphamide produced pronounced cytotoxic and significant clastogenic responses in both male and female mice.

Aldicarb did not induce any significant increase in the frequency, percentage, or specific type of structural chromosomal aberrations in the bone marrow of treated mice.

This study is classified acceptable and satisfies the guideline requirement for a structural chromosomal aberration study.

3. Unscheduled DNA Synthesis

In an unscheduled DNA synthesis assay, primary hepatocytes from male Fischer 344 rats, (MRID 00142081) were exposed to 33.3, 100, 1000, 3333, and 10,000 ug/well for 24 hours, 3 cultures of 20 cells per dose. DMSO was the solvent. 2-AAF at 10-5M was the positive control.

Aldicarb exposure was cytotoxic at 10,000 ug/well. The AAF positive control induced a high net grain count/nucleus of 15.7 +/-2.9.

Aldicarb exposures failed to induce any significant changes in the nuclear labelling (mean net nuclear grain counts 0.4) and thus in unscheduled DNA synthesis.

This study is classified acceptable and satisfies the guideline requirement for other genotoxic effects.

4. Dominant Lethal Study

In a dominant lethal study (MRID 43575101), groups of 40 male CD (Sprague-Dawley) rats were fed dietary concentrations of 0, 7.5, 15, or 30 ppm (0.57, 1.11, or 2.28 mg/kg/day) aldicarb technical in the diet (98.7%) for 10 weeks. Males were mated at a 1:1 ratio with untreated females once weekly for 2 weeks. Satellite groups of 10 males/group, receiving 0 or 30 ppm (2.28 mg/kg/day) were sacrificed after 4 days of dosing; recovered plasma, red blood cell (RBC) and brain samples were assayed for cholinesterase (ChE) activity.

Compound toxicity at 30 ppm was manifested as significant body weight reductions (7-13%) throughout the study, early (weeks 1-2) decrements in body weight gain (66%) and food consumption (24%); fine motor tremors (13% of animals) and significant inhibition of plasma (89%), RBC (35%), and brain (30%) ChE activity.

The NOEL for ChE inhibition was not established since ChEI was not evaluated in the lower dose groups, but for other effects, the LOEL was 30 ppm.

There was, however, no evidence that aldicarb technical induced a dominant lethal effect in male germinal cells treated over the entire period of spermatogenesis.

The study was classified as acceptable and satisfies the data call in requirement for this study.

5. Conclusion

In summary, there are acceptable negative studies for all 3 required categories of mutagenic effects: gene mutations, chromosomal aberrations, and other genotoxic effects (here, unscheduled DNA synthesis). In addition, based on concern for clastogenic effects noted in the open literature (Dearfield, 1991), a dominant lethal study was required and this study was also found to be negative. Based on all of this evidence, there is no concern for mutagenicity for aldicarb.

IV. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 43045401

Executive Summary

In a 2 year combined chronic toxicity/carcinogenicity study (MRID 43045401), Aldicarb technical (99.7% a.i.) was administered in the diet to groups of 80 male and female Sprague-Dawley Crl:CD BR rats for either 52 or 104 weeks at dose levels of:

0	1	10	and 30 ppm
0	0.047	0.47	and 1.44 mg/kg in males; and
0	0.06	0.59	and 1.87 mg/kg in females.

At 30 ppm, male and female rats showed decreased group mean body weight (7-15%, for males, 5-10% for females) and body weight gain (23% decrease for males, 9% decrease for females for weeks 1-104). Ophthalmoscopic abnormalities were also evident at 30 ppm in the form of ectopic pupil and damage to the iris. Inhibition of red blood cell and plasma ChE was evident at the 30 ppm (40-50%) and 10 ppm dose levels (15-27%) for male and female rats at weeks 26, 52, 78, and 104. Brain ChEI was significantly inhibited at 30 ppm in females at weeks 52(12%) and 105 (8%). There was no consistent change in the level of ChE inhibition in blood across weeks 26-105, or in brain from week 52-105. There was suggestive evidence for a neurotoxic effect of aldicarb at 30 ppm in both sexes of rat, including tail paralysis, sciatic and tibial nerve degeneration, and coccygeal and tail muscle atrophy and degeneration, but the differences were not significantly different from control.

There was no evidence of carcinogenicity for aldicarb technical in this study.

Oncogenic NOEL > 1.44 -1.87 mg/kg.

The LOEL of 0.47 mg/kg (10 ppm) is based on inhibition of plasma and RBC cholinesterase in the range of 15-27%.

The chronic NOEL is 0.047 mg/kg.

This study is classified CORE Minimum and satisfies the guideline requirements for 83-5, Combined Chronic Toxicity and Carcinogenicity Study in Rats.

Discussion of Tumor Data: There was no evidence of carcinogenicity for aldicarb technical in this study.

Adequacy of the Dose Levels Tested: Dosing was considered adequate in both sexes based on treatment related inhibition of plasma, RBC, (40-50%) and brain cholinesterase (8-12%) as well

as decreased body weight gain (9-23%) at 30 ppm.

2. Carcinogenicity Studies in Mice

MRID Nos. 00044732, 00044733, 00044734

1. Executive Summary

In a mouse carcinogenicity study (MRID 00044732), aldicarb (99%) was administered in the diet to groups of 44 male and 44 female Charles River CD-1 mice at levels of 0, 0.1, 0.2, 0.4, or 0.7 mg/kg/day for 18 months. During the first 3 months, there were significantly increased incidences of mortality seen in the males at 0.4 and 0.7 mg/kg (0/44, 1/44, 4/44, 7/45*, 9/44*) and females at 0.2, 0.4, and 0.7 mg/kg (0/44, 1/44, 8/44* 9/47* 8/44*). This was attributed to undissolved crystals of aldicarb, and thus inconsistent and excessive dosing. In response, aldicarb was thereafter dissolved in acetone prior to mixing in the diet. After 90 days, no treatment related differences in mortality were seen at any time-point. Cumulative mortality for the whole study among males given 0.4 and 0.7 mg/kg was significantly increased at 41% for both dose groups. (survival for both sexes was 59% or greater). There were no effects on body weight or body weight gain. In males that survived to terminal sacrifice, there were significant increases in hepatomas in the 0.1 and 0.7 mg/kg, but not 0.2 or 0.4 mg/kg groups:

(1/37, 3%; 7/33*, 21%; 2/26, 8%; 6/30, 20%; 7/25*, 28% in increasing dose order).

When the animals sacrificed were included, only the increase at 0.7 mg/kg was statistically significant (8/33* vs 2/39 controls):

In males in the 0.7 mg/kg group, there were also significant increases in lymphoid neoplasias (0/39, 0/34, 4/30, 2/32, 7/33*). (<3%, <3%, 13%, 6%, 21%*). These were all due to mice that died on study (0/2, 0/1, 4/4, 2/2, 7/8). No other effects were seen.

This study is classified CORE Minimum and satisfies the data requirement for Guideline 83-2, a Carcinogenicity Study.

A second study using 50 CD1 male mice/dose and the same high dose of 0.7 mg/kg failed to detect any carcinogenic response (MRID 00044733).

2. Executive Summary

In a follow up 18 month mouse carcinogenicity study, groups of 50 male CD-1 mice were fed diets containing 0, 0.1, 0.3, or 0.7 mg/kg/day of aldicarb (99%; dissolved in acetone) (MRID 00044733). Three concurrent control groups were used: for one group (C), one mouse was killed each day one exposed mouse died; the other two groups were untreated (A, B). There were no differences in overall mortality between the dosed and control groups (0A, 30%; 0B, 12%; 0.1, 26%; 0.3, 24%; 0.7, 30%). There were no significant effects on body weight. There were no treatment related increases in any tumors in comparison to the control groups, except for lymphoid neoplasias in 0.1 and 0.7 mg/kg animals that died, but only when compared to group C, the day of death matched controls. (A, 5/11, 45%; B, 1/5, 20%; C, 0/18, <5.6%; 0.1, 6/10, 60%; 0.3, 2/5, 40%; 0.7, 3/7, 43%). In that group (C), no neoplasias were seen, while in the other controls, the incidences were greater and not significantly different from the treated groups.

The study authors rejected this group as non-random. These findings were also not dose dependent. It was concluded that the study was negative.

This study was rated minimum, despite use of one sex, but was obviously designed to replicate the findings of the first study and is considered valid for that purpose.

Adequacy of the Dose Levels Tested: In a preliminary range finding study, CD-1 mice were exposed to diets containing 0 -1.2 mg/kg/day for 7 days. Deaths were seen at 0.6 (1/10) and 1.2 mg/kg (4/10). Thus, the doses used in these dietary exposure studies (0.7-0.9 mg/kg), are in the lethal range and would be considered adequate.

In mice, there is also an NCI study from 1979. In the NCI study, B6C3F1 mice receiving aldicarb at 6 ppm (0.9 mg/kg) for 103 weeks did not differ from controls in occurrence of benign or malignant tumors, nor did gross microscopic examination of tumors reveal any difference between treated and control groups.

Discussion of Tumor Data:

Further analysis of the first study (MRID 00044734) concluded that the incidence of hepatomas and lymphoid neoplasias in the control groups were exceptionally low and that this lead to the apparent significant increase in the treated groups. The incidences of these lesions in the treated groups were comparable to their incidences in both control and treated groups in other studies. For the hepatomas, the incidence in the control groups in the follow up study (0A, 20%; 0B, 19% total) were not different from the incidence of 27% in the 0.7 mg/kg group in the first study, whose concurrent control was 5%. For the lymphoid hyperplasias, the incidence in the control groups in the follow up study (0A, 5/11, 45%; 0B, 1/5, 20%) were greater than the incidence in the 0.7 mg/kg group in the first study (21%); and comparable to the incidence in the 0.7 mg/kg group (43%), but lower than the lower dose 0.1 mg/kg group (60%) in the second study. In total, lesions varied considerably in their incidence in control groups, and were not dose dependent. (U.S. EPA, 1984. HED Doc No. 004022).

3. Classification of Carcinogenic Potential

In conclusion, there are acceptable guideline rat (MRID 43045401) and mouse carcinogenicity studies (MRID Nos. 00044732, 00044733, 00044734), and an NCI mouse carcinogenicity study that were considered acceptable and negative. There were also no mutagenicity concerns.

On the basis of these studies and analyses the HIARC concluded that the carcinogenicity data on aldicarb should be treated as providing data classifiable as:

Category E, Evidence of Non-Carcinogenicity for Humans.

V. FOPA CONSIDERATIONS

1. Adult and Developmental Neurotoxicity.

There are both acute and subchronic neurotoxicity studies in rats. For the acute study of young adults, the most sensitive endpoint is blood ChE inhibition (Acute LOEL = 0.05mg/kg for plasma ChEI). No neuropathological effects related to treatment were noted.

For the 90 day study, the LOEL was 0.05 mg/kg for pinpoint pupils in males at 13 weeks, and ChE inhibition in blood and brain in both sexes.

For both studies, the NOEL was < 0.05 mg/kg.

There is a developmental neurotoxicity study in which the maternal NOEL and offspring NOEL were the same. Maternal toxicity at 0.30 mg/kg/day included clinical signs of toxicity such as tremor, salivation, and lacrimation, blood ChE inhibition, and 17% reduced body weight gain during gestation.

The maternal LOEL is 0.10 mg/kg/day based on plasma ChEI of 40% on GD 7.

The maternal NOEL is 0.05 mg/kg/day.

The offspring LOEL is 0.10 mg/kg/day based on reduced body weights from birth through postweaning, and on decreased motor activity on day 17 in male pups.

The offspring NOEL is 0.05 mg/kg/day.

2. Developmental Toxicity

In the rat developmental toxicity study, the LOEL for maternal toxicity is 0.25 mg/kg, based on reduced body weight gain and food consumption.

The maternal toxicity NOEL was 0.125 mg/kg.

The LOEL for developmental toxicity was 0.25 mg/kg based on ecchymosis (discoloration) of the trunk. The developmental NOEL is 0.125 mg/kg.

In the rabbit developmental toxicity study, based on decreased body weight, pale kidneys, and hydroceles (fluid) on the oviducts, the LOEL for maternal toxicity is 0.25 mg/kg.

The NOEL for maternal toxicity in the rat was 0.1 mg/kg/day.

The NOEL for developmental toxicity in rabbits was considered to be 0.5 mg/kg/day, the highest dose tested.

3. Reproductive Toxicity

In the 2 generation reproduction study, the parental LOEL was 0.7 mg/kg (M)- 0.9 mg/kg (F) based on decreased body weight gains (>96%) in the F0 females during the first week of lactation of the first breeding; RBC ChE depression (11%) in F0 females at termination; and in plasma ChE depression (18%) in F1 males prior to breeding.

The parental NOEL was 0.4 mg/kg for both sexes.

The reproductive LOEL was 1.4 mg/kg (M)- 1.7 mg/kg (F) based on decreased pup body

weights (10%) in F1a females on days 14,21; in F1b males and females on days 14-21 (13-20%); and in F2a pups; and reduced viability in F1a pups (viability index 78% vs 94% in controls) on day 4 and F2b pups (56% viability vs 89% controls). Pups showed signs of debilitation as well: weak, thin, dehydration.

The reproductive NOEL was 0.7-0.9 mg/kg.

4. Additional information from the literature

Two studies from the open literature, one by Cambon et al. 1979, and the second an abstract from an EPA investigator (Moser, 1997) studied pups exposed either *in utero* (Cambon), or directly dosed as pups (Moser).

The study by Moser found a 2 fold difference in sensitivity between acute doses to pups at day 17 in comparison to adults on the maximum non-lethal dose and some difference (2-4 fold) in brain ChE inhibition in male pups.(pups more sensitive). Behavioral differences were not clear cut, and differed among measures.

A new and unpublished study conducted by Dr. Ginger Moser of ORD comparing the sensitivity of rats at 3 different ages to acute oral exposure to aldicarb. She looked at rats at post-natal day (PND) 17, PND 27, or PND 70 in terms of lethality, behavioral effects, and cholinesterase inhibition in both blood and brain.

Six-eight rat pups/group on postnatal day 17, 27, or 70 were gavaged with aldicarb at doses between 0.1 -1.0 mg/kg by the up and down method to determine the lethal dose range at those ages. Data from males and females were combined. The maximum non-lethal dose, called the maximum tolerated dose in this study or MTD was determined for those 3 ages and were as follows:

PND 17 pups: 0.18 mg/kg;

PND 27 pups: 0.25 mg/kg;

PND 70 pups: 0.36 mg/kg.

For the Cholinesterase Inhibition Data, 10 rats/sex/dose were assayed for levels of inhibition in the blood and brain. For day 17 and day 27 rats, both considered immature young rats, these data show:

for males, greater (up to 2 fold) inhibition in brain; little difference in blood measures;
for females, greater inhibition in brain (but less than effect in males), and little difference in blood measures. To illustrate, comparing levels of brain ChEI at 0.18 mg/kg,

Level of Brain ChEI 1 hour after 0.18 mg/kg of aldicarb

	Day 17 Pups	Day 27 rats
Males	70 +/- 8 % (s.e.)	45+/-3%
Females	52 +/- 8% (s.e.)	44+/-5%

The difference in males appears to be significant (means > 2 standard errors apart), while the changes in females do not, since the means are within one standard error of each other. Estimating (from a graph) a common level of inhibition and comparing doses for 50% yields 0.17 mg/kg for day 27 weanlings, and 0.10 mg/kg for day 17 pups.

For the adult measures of brain ChEI after acute exposures, we have 15% at 0.1, 50% at 0.5 mg/kg from the acute study (females). Moser found 55% brain ChEI at 0.3 mg/kg in 70 day old adults. In summary, then, ED50s for the rats would be as follows:

Day 17, 0.10 mg/kg; Day 27, 0.17 mg/kg; Day 70, 0.3 mg/kg (55%). The youngest rats are 3 times more sensitive than the adults.

Behavioral measures did not show consistent differences for the different age groups, however. In conclusion, there are small but reliable differences in sensitivity for this chemical both in terms of lethality and brain ChEI defined in this study.

The Cambon study provides limited suggestive data of the increased sensitivity of rat fetuses in brain and blood ChEI in comparison to the dams after acute exposure on day 18 of gestation to doses between 0.001 and 0.1 mg/kg. This study suggests a 10 fold difference in sensitivity between the adults and the fetus, but is limited by a number of factors which make it more difficult to interpret, including the use of an unusual solvent and vehicle (diethyloxide and corn oil), fasting of the animals, pooling of the fetal samples, findings of statistical significance from effects at levels not often seen, i.e., on the order of 10% in blood.

5. Determination of Susceptibility

Based on the guideline studies, then, there was no evidence of increased susceptibility in the developmental, reproduction, or neurotoxicity studies. But these studies did not include data comparing cholinesterase inhibition in young and adult animals.

There was some evidence for increased susceptibility in terms of lethal doses and brain cholinesterase inhibition noted in an unpublished EPA study and suggestive evidence for increased susceptibility of fetuses in cholinesterase inhibition from a study in the open literature.

6. Determination of the FQPA Safety Factor

The HIARC, on 8/25/98, concluded that it has concerns about the potential increased susceptibility of infants and children on the basis of increased lethal potency of young rats (Moser), and increased brain cholinesterase inhibition of young rats. Comparisons between measures of cholinesterase inhibition in young adult rats in the acute neurotoxicity study and the young rats (17 and/or 27 days old) in the Moser study support the notion of increased susceptibility.

As a result, HIARC recommended retention of an FQPA safety factor (3x was suggested, based chiefly on the magnitude of the differences seen between young and adult rats).

VI. HAZARD CHARACTERIZATION

Aldicarb is a carbamate chemical (2-methyl-2-(methylthio) propionaldehyde; CAS 116-06-3) registered as a systemic insecticide, acaricide, and nematicide.

There are several types of toxicity that have been reported to occur with exposure to Aldicarb, but the predominant hazards are the neurotoxic syndrome related to acetylcholinesterase (AChE) inhibition.

Aldicarb is rapidly absorbed, widely distributed, and rapidly excreted, with more than 90% excreted within 24 hours after either acute or repeated oral doses. It is metabolized primarily to Aldicarb Sulfoxide which appears rapidly and then much more slowly to Aldicarb sulfone; these 3 moieties (aldicarb, sulfoxide, and sulfone) may then be further metabolized to oximes and nitriles (See e.g., EPA 1984). Both the sulfoxide and sulfone are also potent cholinesterase inhibitors. Aldicarb sulfoxide (oral LD50 0.8 mg/kg; MRID Nos. 00080708, 00091241) is roughly as potent as Aldicarb (oral LD50 0.6-1.0 mg/kg; MRID Nos. 00053343, 00069916, 00057333), while Aldicarb sulfone is less potent (oral LD50 20 mg/kg; MRID No. 00053343).

Aldicarb is classified as Category I by EPA for its lethal potency following oral, dermal, or inhalation exposure, the most toxic category. It causes no eye irritation or dermal irritation after acute exposure to fatal levels. It has been reported to cause no dermal sensitization in guinea pigs. In summary, available data are adequate on acute lethal potency by the oral, dermal, or inhalation routes (81-1,2,3) all of which indicate its great potency (Category I); and data on irritation or sensitization (81-4,5,6) are adequate or waived based on their acute lethal potency.

Dose related inhibition of cholinesterases in plasma, red blood cells, or brain (animals only), accompanied at some doses by overt clinical signs of cholinesterase inhibition are seen in both humans and animals. In humans, effects include sweating and lightheadedness, leg weakness, nausea, vomiting and diarrhea. In animals, decreased strength, lacrimation, salivation, pinpoint pupils, and decreased activity were seen. In general, the LOELs following repeated exposures were similar to the LOELs following acute exposure, i.e., there is little evidence of cumulative toxicity from this rapidly acting chemical. No treatment related neuropathology was seen in any of the available acute, subchronic, or chronic toxicity studies in rats, mice, or dogs.

On the basis of several studies and analyses, which concluded that aldicarb exposures at adequate doses did not cause carcinogenicity in rats or mice, the HIARC concluded that the carcinogenicity data on aldicarb should be treated as providing data classifiable as: Category E, Evidence of Non-Carcinogenicity for Humans.

There are also no mutagenicity concerns for aldicarb, based on several studies.

There was no indication of increased susceptibility of offspring in rat or rabbit developmental toxicity studies, or in a rat developmental neurotoxicity study. The parental LOELs in all of these studies were the same or greater than the LOELs in the offspring; thus, there were no specific developmental or reproductive effects.

However, these studies did not provide comparative data on cholinesterase inhibition, which were assessed in 2 studies from other sources. One literature study reported greatly increased sensitivity of rat fetuses in brain and blood ChEI after acute exposure, but this study was considered limited and the data therefore only suggestive. An unpublished EPA study,

however, reported some evidence for increased susceptibility of young rats in terms of lethal doses and brain cholinesterase inhibition. On this basis, the HIARC concluded that it has concerns about the potential increased susceptibility of infants and children on the basis of increased lethal potency of aldicarb to young rats, and increased brain cholinesterase inhibition of young rats.

VII. DATA GAPS

- 21 day dermal toxicity study.

VIII. ACUTE TOXICITY

Acute Toxicity of Aldicarb

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00057333	LD ₅₀ = 0.8 mg/kg	I
81-2	Acute Dermal	00091241 00069916	LD ₅₀ = 20 mg/kg, wa- ter LD ₅₀ = 5 mg/kg, pro- pylene glycol	I
81-3	Acute Inhalation	00066916 00057333	LC ₅₀ < 0.007 mg/L	I
81-4	Primary Eye Irritation	00069916	No corneal irritation at fatal dose	N/A
81-5	Primary Skin Irritation	00069916	None at fatal levels	N/A
81-6	Dermal Sensitization	N/A	N/A	N/A
81-8	Acute Neurotoxicity	43442301	NOEL < 0.05 mg/kg	

IX SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL= 0.01 mg/kg UF = 10	Sweating, plasma, and RBC ChE inhibition.	Rhône-Poulenc, 1992
	Acute RfD = 0.001 mg/kg		
Chronic Dietary	NOEL = 0.01 mg/kg UF = 10	Same as acute dietary	Rhône-Poulenc, 1992
		Chronic RfD = 0.001 mg/kg/day	
Short-Term (Dermal)	NOEL= 0.01 mg/kg UF = 10	Assumed 100% dermal absorption. 21 day dermal study completed, but only summary submitted.	Rhône-Poulenc, 1992
Intermediate-Term (Dermal)	NOEL= 0.01 mg/kg UF = 10	Same as Short-Term Dermal	Rhône-Poulenc, 1992
Long-Term (Dermal)	NOEL= 0.01 mg/kg UF = 10	Same as Short-Term Dermal	Rhône-Poulenc, 1992
Short-Term (Inhalation)	NOEL= 0.01 mg/kg UF = 10	Assume no worker inhalation of only granular formulations.	Rhône-Poulenc, 1992
Intermediate Term (Inhalation)	NOEL=0.01 mg/kg UF =10	Same as Short-Term Inhalation	Rhône-Poulenc, 1992
Long Term (Inhalation)	NOEL= 0.01 mg/kg UF = 10	Same as Short-Term Inhalation	Rhône-Poulenc, 1992