



1-25-99



Aldicarb Technical

Acute Oral Toxicity Study in Humans

8PP

Supplement to Document# 010450-DER for MRID No. 00101911: Acute Oral Toxicity Study in Humans. This supplement provides a new Executive Summary and an additional data table to upgrade the original DER.

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DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity Study in Humans

OPPTS Number: None

OPP Guideline Number: None

PC CODE: 098301

TOX CHEM Number: 011A

TEST MATERIAL: Aldicarb technical

CHEMICAL NAME: 2-methyl-2-(methylthio)propionaldehyde-0-(methylcarbamoyl) oxime.

CITATION: Ingestion of Aldicarb by Human Volunteers: A Controlled Study of the Effects of Aldicarb on Man. Union Carbide Corporation Study No. ALD-03-77-2215. February 11, 1971

SPONSOR: Union Carbide Corporation.

EXECUTIVE SUMMARY: In this acute oral neurotoxicity study in human volunteers, (MRID No. 00101911; HED Doc. Nos. 007601, 010450), 12 adult male volunteers were divided into three test groups (4/group) and administered oral doses of aldicarb at 0.025, 0.05, or 0.1 mg/kg. Dosages were prepared by diluting the appropriate amount of a stock solution of 1mg/ml of aldicarb solution (distilled water) 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. Blood measures of cholinesterase (ChE) inhibition were made 18 hours and 1 hour before exposure, as well as 1,2,4, and 6 hours after exposure. Analysis was by the radiometric method. Urine samples were taken between 1-8 hours after exposure to measure the total amount of carbamate in the urine. 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.

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.

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 range of peak inhibition for each group was: 0.1 mg/kg, 32-80%; 0.05 mg/kg, 53-67%; 0.025 mg/kg, 34-57%). The method of analysis of cholinesterase in blood was considered valid and appropriate for this carbamate. Total carbamate (mg) excreted in the urine was dose related, but the % of the dose excreted in the urine, 5-10%, was relatively invariant with dose.

In conclusion, there was no NOEL for cholinesterase inhibition, i.e., NOEL < 0.025 mg/kg and a NOEL for clinical signs was indeterminate.

The LOEL < 0.025 mg/kg/day, based on clinical signs and whole blood cholinesterase inhibition and the NOEL < 0.025 mg/kg/day.

Summary Table of % of whole blood Cholinesterase Inhibition between 1-6 hours after exposure in relation to one hour prior to exposure

Hrs	+1	+2	+4	+6		+1	+2	+4	+6		+1	+2	+4	+6
Case					Case					Case				
1	32%	20%	+26%	+44%	5	60%	51%	27%	21%	9	46%	42%	25%	9%
2	38%	60%	26%	+6%	6	60%	61%	15%	16%	10	57%	55%	27%	24%
3	69%	75%	56%	35%	7	67%	37%	8%	2%	11	50%	32%	+5%	5%
4	69%	80%	32%	15%	8	42%	53%	9%	0%	12	34%	30%	8%	3%

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Secondary reviewer:

010450

DATA EVALUATION REPORT

C10450

STUDY TYPE: Acute Oral Toxicity Study in Humans

TOX. CHEM NO: 011A

TEST MATERIAL: Aldicarb

SYNONYMS: Temik, 2-methyl-2-(methylthio) propionaldehyde O-(methylcarbamoyl) oxime.

STUDY NUMBER: ALD-03-77-2215

SPONSOR: Union Carbide Corporation

TESTING FACILITY: Union Carbide Corporation

TITLE OF REPORT: Ingestion of Aldicarb by Human Volunteers: A Controlled Study of the Effects of Aldicarb on Man

AUTHOR(S): R. Haines; C.U. Dernehl, J.B. Block, supervising physicians

REPORT ISSUED: February 11, 1971

CONCLUSIONS:

All 3 groups experienced significant cholinesterase inhibition in the whole blood, with the peak inhibition between 1-2 hours and almost complete recovery in 6 hours.

0.10 mg/Kg elicited clinical signs in all 4 subjects receiving this dose, while most subjects given the 2 lower doses had no signs or symptoms. The 0.025 mg/Kg dose may have caused apprehension in one subject.

The method of analysis of cholinesterase inhibition in blood was valid and appropriate for this carbamate.

There was no NOEL for cholinesterase inhibition and a NOEL for clinical signs also is indeterminate.

A. MATERIALS:

1. Test compound: analytical grade of Aldicarb, Purity 99.2 %.
2. Test Subjects

Twelve adult male volunteers served as subjects. They were weighed and assigned to different treatment groups based on "nearly equal average weights". None had known exposure to aldicarb or other cholinesterase inhibitors for a week prior to the study.

B. STUDY DESIGN:

1. Subjects were assigned to the following test groups:

	Dose Level (mg/Kg)	# of Subjects
Low (LDT)	0.025	4
Mid (MDT)	0.050	4
High (HDT)	0.10	4

Dose preparation

0.2 g of analytical grade Aldicarb were dissolved in 200 ml of distilled water to produce a solution of 1mg/ml. Dosages were prepared by diluting the appropriate amount of aldicarb solution into 100 ml of distilled water, which was then ingested in one draft.

C. METHODS AND RESULTS:

Subjects were given their dose between 9:00 and 9:15 AM on December 4, 1970 and engaged in normal business activities except for the time of blood and urine sampling and clinical observations. Liquids were provided ad libitum during the post-exposure period.

1. Observations:

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 complaints of the subjects.

Results

A summary table was made from the symptoms reported and is shown below. All subjects in the 0.10 mg/Kg group showed effects, with the most frequent complaints leg weakness, pupillary constriction, and sweating in all subjects. All effects had disappeared within 6 hours of dosing, with the peak effect 2 hours after the dose.

The only effect reported in the 0.05 mg/Kg group was a runny nose in one subject after one hour of exposure.

One subject in the 0.025 mg/Kg group reported apprehension for several hours after exposure, which was discounted by the authors in the following sentence. "This man became apprehensive and developed a mild panic reaction [symptoms undescribed] when the high dose group reported symptoms immediately preceding his examination at hour 1. Aside from cardiac consciousness, he had no symptoms." They report his apprehensiveness as "almost completely gone" 4 hours after exposure.

DOSE GROUP

SIGNS AND SYMPTOMS	0.10 MG/KG				0.05 MG/KG				0.25 MG/KG			
	1	2	3	4	5	6	7	8	9	10	11	12
MALAISE	X	X										
LEG WEAKNESS	X	X	X	X								
ARM WEAKNESS	X		X									
PUPIL CONSTRICTION	X	X	X	X								
GI CRAMPS, PAIN	X											
GASPING	X											
SWEATING	X	X	X	X								
NAUSEA	X		X									
VOMITING	X											
SLURRED SPEECH			X	X								
SALIVATION			X	X	X							
RUNNY NOSE							X					
APPREHENSIVE												X

2. Blood Cholinesterase measurements

Duplicate blood samples of 10 ul were taken 18 hours and 1 hour before exposure, and 1, 2, 4, and 6 hours after dosing from all subjects.

Cholinesterase measurements were made by a radiometric procedure. Three samples were obtained from each donor; two for samples and one for reference. Preparation of the 3 slides were completed within 3 minutes after the blood was taken. The fraction of obtained substrate was calculated from the mean counts of sample and reference slides, after correction for background. Cholinesterase activities are expressed in units of micromoles of acetylcholine hydrolyzed/hour per milliliter of whole hemolyzed undiluted blood. Each observed hydrolysis rate reported was corrected for temperature recorded at the time of sampling.

Results

The summary table below shows the change in cholinesterase one and

2 hours after the dose, when the clinical signs were most significant and when the peak inhibition was seen.

[Che: -1 hour to +1, +2 hours]

0.10 mg/Kg Group

HOURS	+1	+2
Case 1	-32%	-20%
2	-38%	-60%
3	-69%	-75%
4	-69%	-80%

0.05 mg/Kg Group

	+1	+2
5	-60%	-51%
6	-60%	-61%
7	-67%	-37%
8	-42%	-53%

0.025 mg/Kg Group

	+1	+2
9	-46%	-42%
10	-57%	-55%
11	-50%	-32%
12	-34%	-30%

In all cases, peak inhibition occurred after one or two hours following exposure; at the lowest dose, some recovery was seen at 2 hours for all four subjects; at the high dose, there was greater inhibition at 2 hours for 3 of 4 subjects; the middle dose saw 2 subjects with greater and 2 with lesser inhibition after 2 hours than at one hour.

We performed a statistical analysis of this data in an appendix to the study report (Appendix B, attached). When the data were analyzed comparing the means using the one hour pre-exposure measures as controls, there were no differences between the dose groups; when calculated in comparison to the maximum pre-exposure values, i.e. 18 hours pre-dose, the 2 higher doses were different from the low dose at one hour, and the 2 lower doses were different from the high dose at 2 and 4 hours. At 6 hours, all values were similar. Peak percentages of pre-maximum dose levels showed maximum inhibition at 2 hours for the high dose and at one hour for the lower 2 doses.

3. Urinalysis

Urine samples were collected as untreated controls "for the analyses of carbamates in urine obtained in the postexposure period." Total urine voided was taken 1, 2, 4, 6, and 8 hours after dosing. Spot samples were taken 12 and 24 hours after dosing. Samples were stored in polyethylene bottles. The samples were analyzed by extraction of aldicarb with chloroform, oxidation with peracetic acid to aldicarb sulfone and measurement of the total residue as a single peak by injection into a gas chromatograph with a flame photometric detector equipped with a sulfur specific filter.

Results

The amount of carbamate in the urine over the 8 hours after the dose was between 5 and 10% and seemed to be independent of the dose given, while the total carbamate excreted in that time period was clearly dose related.

D. DISCUSSION

It is clear that all 3 groups experienced significant cholinesterase inhibition in the whole blood, with the peak inhibition between 1-2 hours and recovery not complete in 6 hours, but mostly, e.g. 75% or greater, and with more complete recovery for the lower dose groups.

It is also clear that 0.10 mg/Kg affected all 4 subjects receiving this dose, and that most subjects given the 2 lower doses had no signs or symptoms. The single subject given 0.05 mg/Kg who experienced a runny nose at one time point would seem to not have shown sufficient effects to be considered truly affected. The subject, however, given 0.025 mg/Kg and described as experiencing apprehension and a panic attack, attributed by the authors to a reaction to hearing the report of his high dose colleagues's symptoms, is more problematic. The failure to obtain report of effects independent of one another is a flaw in the conduct of the study; however, an argument can be made that apprehension and malaise may be experienced as similar and an undescribed panic reaction as including some sweating, both signs seen in other high dose subjects. Further this apprehension was described as lasting at least 4 hours, consistent with the reports of malaise and less often associated with panic reactions which tend to be much more brief and intense. It would seem from this line of argument more easy to believe that this subject was affected than to accept the assertion that the cause of his signs was the testimony of his colleagues. From Dorland's, the following definitions: Malaise: a vague feeling of bodily discomfort; Apprehension: anticipatory fear or anxiety; Anxiety: a feeling of apprehension, uncertainty, and fear without apparent stimulus, and associated with physiological changes (tachycardia, sweating, tremor, etc.) I conclude that the 0.025 mg/Kg dose may have caused this effect.