Supplement to Document# 010459 and DER for MRID No.: 42373001 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)proprionaldehyde-0-(methylcarbamoyl) oxime.

CITATION: A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. Inveresk Clinical Research Ltd., Edinburgh, Scotland. Report No. 7786. June 15, 1992.

SPONSOR: Rhône-Poulenc, Secteur Agro, 14-20 Rue Pierre Baizet 69009, Lyon, France

EXECUTIVE SUMMARY: A 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 (MRID No. 42373001; HED Doc. No. 010459). 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 (RBC) cholinesterase (ChE) 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. Mean plasma and RBC cholinesterase inhibition 1 hour after dosing are shown in the table below. 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 men, 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 1g/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 0.010 and 0.075 mg/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.

The LOAEL = 0.025 mg/kg/day, based on sweating seen in men and (blood cholinesterase inhibition).

The NOAEL = 0.01 mg/kg/day.

While there are no guidelines for human studies, this double blind study in healthy humans was considered acceptable for evaluating potential effects from acute oral exposures to Aldicarb.

Table 1. Mean Cholinesterase Inhibition 1 hour after exposure.

Dose (mg/kg)	0.01	0.025	0.5	0.75
Plasma				
Males	13%	35%	55%	70%
Females		49%	68%	
Red Blood Cells				
Males	3.8%	12%	29%	38%
Females		20%	36%	