Toxicology

Toxicological data for aldicarb are summarized in the first part of this chapter, followed by an abstract of pertinent data on formulations. From the standpoint of practical use, only the toxicity of the formulations should be considered in evaluating applicator, environmental impact and benefit and risk hazards.

Table 22. Acute toxicity data for aldicarb.

Species	LD_{50}* (mg/kg body wt)	Administration Vehicle and Comments
Peroral		
Rat, male	0.9	
Rat, female	1.0	
Guinea pig	1.0	
Chicken	9.5	0.1% solution in corn oil
Mice	0.4	
Cat	1.3	
Rabbit	1.3	
Cow	1.0	Gelatin capsule (with
Calf	1.0	TEMIK 10G)
Sheep	5.0	
Dermal		
Rabbit	> 5.0	24-hour covered, as 5% solution in propylene glycol
	12.5	24-hour, covered, in dimethylphthalate solution
Rat	7.0	
Parenteral		
Rat	0.5	Intravenous, as 0.1% concentration in 0.85% NaCl solution
Rat	0.4	Intraperitoneal, as 0.03% concentration in polyethylene glycol
Inhalation		
Rat, mouse, guinea pig	200 mg/m³ (complete mortality)	Respirable size, dust killed all animals, each species, in 5 minutes
Rat	Saturated vapor (no mortality)	Generated at 50°C: 8-hour exposure
Rat	7.6 mg/m³ (67% mortality)	Aerosol grade, 8-hour exposure

*Active ingredient basis

Toxicology of Aldicarb

Primary Acute Toxicity

Peroral, dermal, parenteral and inhalation toxicity of aldicarb has been determined on several animal species (Table 22).

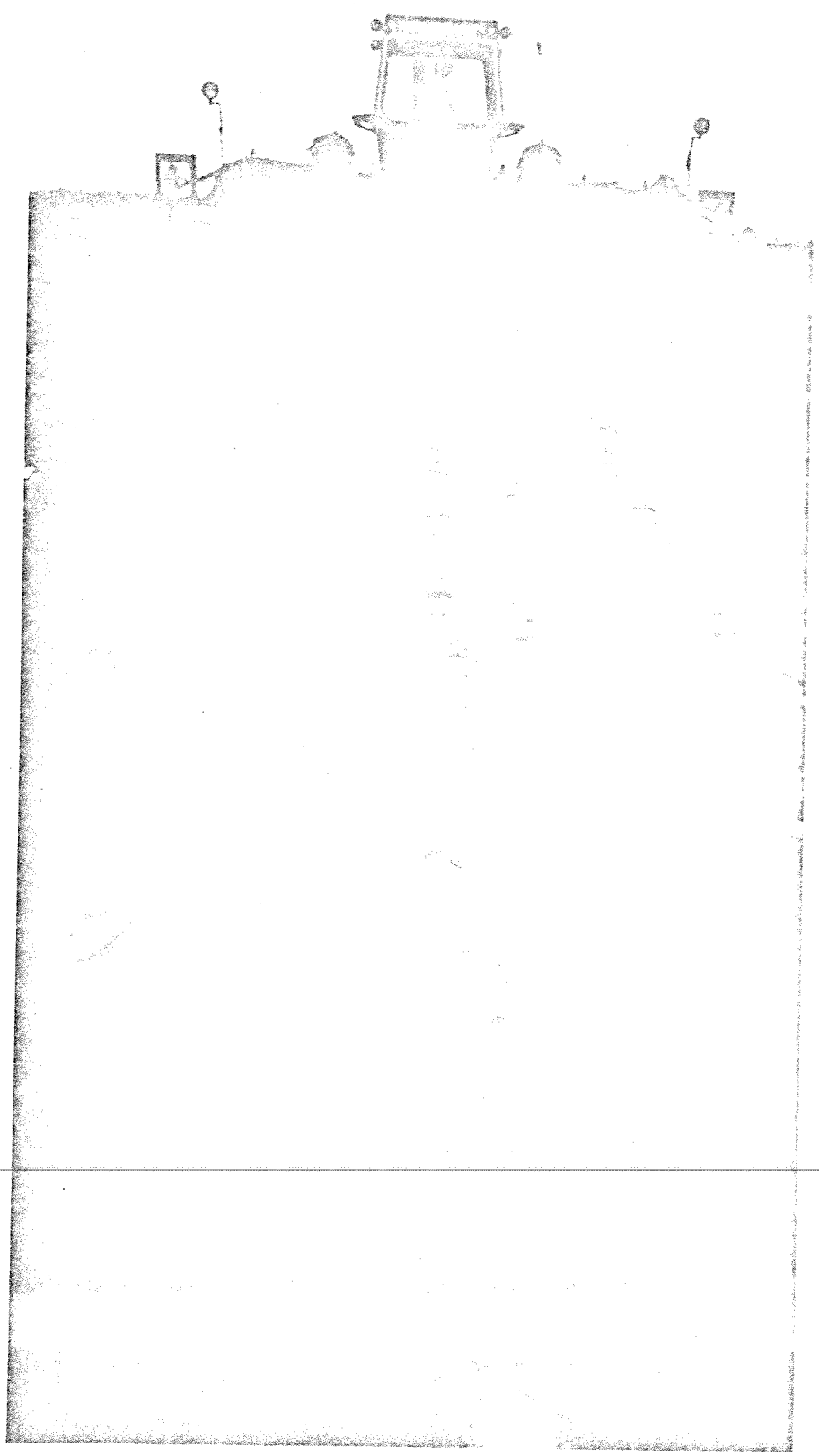
Skin Sensitization and Irritation. None of 22 male albino guinea pigs was sensitized to aldicarb when subjected to a modified intradermal Landsteiner test. In 24-hour covered dermal tests on rabbits, there were no cases of irritation from aldicarb.

Eye Irritation. Concentrated suspensions of aldicarb (5% to 25%) instilled in the rabbit eye resulted in death in 1 hour. Neither the instillation of an excess of 1% solution in dimethylphthalate nor about 1 mg of powdered aldicarb produced corneal irritation.

Potentiation. When aldicarb was fed to rats jointly with each of 9 other cholinesterase-inhibiting pesticides listed below there was no greater than additive effect.

Diazinon®, Dipterex®, EPN, Guthion®, Malathion, Methyl Parathion, Parathion, SEVIN®, Trithion®.

Human Ingestion. A clinical peroral study complete with urine and blood analyses was conducted with 12 adult male volunteers who each ingested a single dose of aldicarb in aqueous solution. Dosage levels used were 0.025, 0.05 and 0.1 mg aldicarb/kg body weight. Mild signs such as excess saliva, sweating and weakness did develop at the high level (0.1 mg/kg) but not from the other dosages. Whole blood cholinesterase inhibition occurred rapidly at all doses, yet both returned to normal in 4 to 8 hours in all subjects. The percentage of dose excreted in the urine over the 8-hour period was equal regardless of dosage levels. About 2 ppm aldicarb carbamates in the urine within



the 8-hour period after exposure appeared to be the incipient level for symptoms. From this test it was concluded that man is no more sensitive to aldicarb toxicity than the rat.

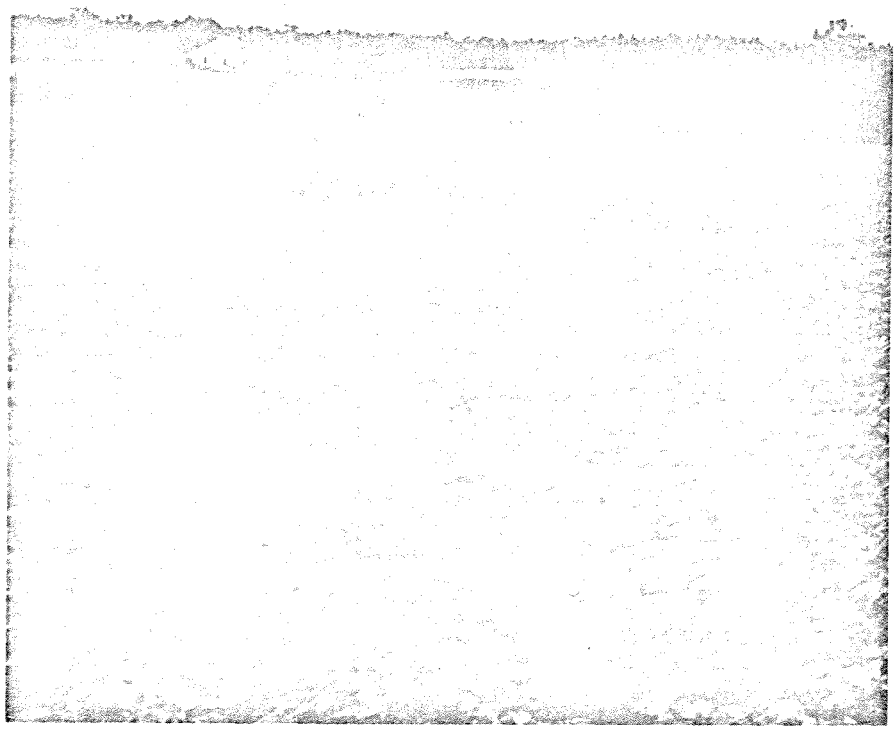
Subacute and Chronic Studies

Demyelination. No potential for demyelination was detected from 30 daily peroral doses to chickens as high as 4.5 mg/kg/day, (one-half the peroral LD_{50} dose per day), while a positive control group receiving 0.1 mg/kg/day of tri-ortho-cresyl phosphate showed typical symptoms.

Feeding Studies. Ninety-day studies in rats with aldicarb indicated the lifespan no-ill-effect level (NIEL) to be between 0.1 and 0.5 mg/kg/day. To determine the level, two separate 2-year feeding studies with rats were conducted. Aldicarb was originally fed at a high level of 0.1 mg/kg/day and did not produce any measurable ill effects. Subsequently, in the second 2-year feeding study, the maximum level of aldicarb fed, 0.3 mg/kg/day, resulted in the same findings. Thus, the NIEL in 2-year feeding studies was greater than 6 ppm in the daily rat diet.

A 2-year dog feeding study also produced no measured ill effects at 0.1 mg/kg/day or 3.3 ppm in the diet, the highest level fed. In another study, groups of 2 male and 2 female beagle dogs were fed diets including approximately 0.2, 0.3 and 0.7 mg of aldicarb/kg of body weight per day for 100 days. A control group, with no aldicarb in its diet, was concurrently observed. The highest dosage level produced no measured deleterious effects in regard to mortality, appetite, body weight change, cholinesterase inhibition and organ weights.

Based on previous experience with 7-day feeding studies with aldicarb, these data suggest that the no-ill-effect level in the dog diet is at least 0.3 mg/kg/day, or about 10 ppm in the daily diet.



In a 3-generation reproduction study with rats, the highest dosage fed, 0.1 mg/kg/day, was without measured effect on any quantitative criteria concerning reproduction. There were no lesions detected histopathologically nor were any congenital malformations noted among the newborn. Preliminary data from another 3-generation reproduction study in progress indicate no detectable adverse effects from 0.7 mg/kg/day.

In a controlled mating study with rats, there was no observed teratogenic effect and no disturbance of the reproductive process. Feeding the compound from days 1 to 7 of pregnancy, days 5 to 15, or throughout pregnancy, all resulted in no differences from the non-treated controls. The highest dosage fed, 1 mg/kg/day, is equivalent to 1 peroral LD_{50} each day of gestation.

Observations and measurements made during the many toxicological tests clearly demonstrate lack of accumulative toxicity with aldicarb.

Pharmacodynamics

In the anesthetized dog, 50 mg/kg of aldicarb administered intravenously caused a 50% increase in the depressor response to 0.5 mg/kg injected acetylcholine. This is strong evidence of potent *in vivo* anticholinesterase action. Subsequent dosing with aldicarb and treatment with atropine sulfate identified the latter as a most reliable antidote.

Pretreatment with atropine sulfate at 1 mg/kg intraperitoneally 30 minutes prior to intraperitoneal injection of 0.4 mg/kg aldicarb protected 4 of 5 mice. A dosage of 6 mg/kg of Banthine® given subcutaneously 45 minutes prior to an LD_{50} dose protected rats, as did 4 mg/kg of atropine sulfate. Mice in unprotected groups died.

Atropine sulfate given intravenously at 10 mg/kg protected rats dosed with twice the peroral LD_{50} of aldicarb. Experimental combinations of antidotes have protected test animals up to 6 times the acute oral LD_{50}. Injections with 2-PAM (pyridine-2-aldoxime methiodide) failed to provide antidotal action. Barbiturates such as morphine and phenobarbital are contraindicated.

On the basis of animal studies, mouth-to-mouth resuscitation if breathing ceases, followed by sterile solutions of dextrose or physiological saline injected intravenously are suggested supportive treatments for humans until atropine sulfate becomes available.

Symptoms of Poisoning

Aldicarb is an inhibitor of cholinesterase, and symptoms of overdosage in man may be expected to include headache, giddiness, nervousness, blurred vision, weakness, nausea, cramps and discomfort in the chest. Signs of overdosage include sweating, myosis, tears, salivation, excessive respiratory secretions, vomiting, impaired breathing, muscle twitching, convulsions and coma.

The syndrome produced by severe cholinesterase depression, as it occurs in animals, is characterized by muscarinic effects, followed by nicotinic symptoms occurring at myoneural junctions resulting in muscular fasciculation and sometimes ataxia. The muscarine signs are listed more or less in

Table 23. Dermal toxicity of TEMIK 10G and 15G on dry and wet skin.

Animal	Approximate LD_{50} (mg/kg)			
	TEMIK 10G		TEMIK 15G	
	dry	wet*	dry	wet*
Rabbit	>4800	>4800	>4800	>4800
Rat, male	2100	566	3150	566
female	3970	673	3970	1010

*Wetted with 0.85% saline solution to simulate heavy sweating.

their order of occurrence: salivation, lacrimation, bronchial constrictions, loss of control of urinary and anal sphincters, bloody tears, vomiting, loss of balance and collapse. Nicotinic effects may be evident as tremors and/or muscular fasciculations. Progressive bradycardia, anoxia, clonic convulsions and coma are followed by death.

Toxicology of TEMIK Granules

Toxicological studies with the aldicarb granular products, now being marketed, show that the formulation has minimized the obvious problem of handling risks of a highly toxic active ingredient.

A bonding agent on the large granules (10/40 mesh) helps prevent dustiness in shipment and reduces handling hazards. Respirable dust is largely removed in manufacture to reduce inhalation exposure. Since the granules are not palatable oral exposure is not likely.

Since its commercialization, millions of hectares have been treated with TEMIK formulations by thousands of farmers, and the number of reported exposures have been less than 12 per year. No fatalities have been reported.

Acute Toxicity

Acute peroral tests with TEMIK 10G were difficult to perform since granules were poorly accepted by rats. Two methods were used: (1) The toxicant was extracted and administered by stomach intubation. (2) The granules were manually placed into the esophageal tract. Under these conditions the acute LD_{50} values were 6.2 mg/kg and 7.1 mg/kg, similar to those for aldicarb when considered on an active ingredient basis. When the granules were enclosed in a gelatin capsule and inserted into the stomach of rabbits, the LD_{50} value was 17.8 mg/kg for TEMIK 10G and 10.6 mg/kg for TEMIK 15G.

Dermal toxicity of TEMIK 10G and 15G was evaluated with rats and rabbits. Results of several 4-hour, covered-skin-penetration tests are in Table 23.

The single skin application of dry TEMIK 10G or 15G to male rabbits and male or female rats resulted in little or no mortality. When the granules were moistened with saline solution toxicity was somewhat increased indicating a greater hazard of exposure to wet than dry skin.

Subsequent skin penetration tests were conducted with several formulated products including TEMIK 10G and TEMIK 15G with 4-hour contact under impervious covering of the clipped skin of the belly area of rats. Results are compiled in Table 24.

Table 24. Approximate dermal toxicities (LD_{50}) of several formulated pesticides in 4-hour covered-skin-penetration tests with rats.*

Product Name	Common Name	Formulation	LD_{50}
Dasanit®	Fensulfothion	10G	>12.8 g/kg
Diazinon®	Diazinon	14G	>12.8 g/kg
Di-Syston®	Disulfoton	10G, 15G	>12.8 g/kg
Furadan®	Carbofuran	10G	>12.8 g/kg
Galecron®	Chlordimeform	95 SP	>12.8 g/kg
Mocap®	Prophos	10G	>12.8 g/kg
TEMIK®	Aldicarb	15G	6.3 g/kg
TEMIK®	Aldicarb	10G	4.5 g/kg
Vapam®	Metham-sodium	32% EC	2.9 ml/kg
Tox-DDT	"4-2"	40% tox + 20% DDT	2.8 ml/kg
Thimet®	Phorate	10G	1.8 g/kg
Meta-Systox R®	Oxydemetonmethyl	25% EC	1.5 ml/kg
Dowfume W-85®	DD	83% EC	1.0 ml/kg
Methyl Parathion	Methyl parathion	46% EC	0.9 ml/kg
Guthion®	Azinphosmethyl	50 WP	0.7 g/kg
Azodrin®	Monocrotophos	56% EC	0.7 ml/kg
Parathion	Parathion	80% Flow	0.3 ml/kg
Systox®	Demeton	26% EC	0.3 ml/kg
Di-Syston®	Disulfoton	66% EC	0.2 ml/kg
Phosdrin®	Mevinphos	47% EC	<0.05 ml/kg

*These data were derived under similar conditions.

Subacute Toxicity

When TEMIK 10G was applied to wetted, abraded skin of male rabbits in a 15-day, 6-hour/day study, some depression of weight gain occurred at 100 mg/kg. However, using 200 mg/kg of formulation on dry skin produced no adverse effects. The no-ill-effect level in a subsequent 14-day, 6-hour/day trial using male albino rabbits on wetted, abraded skin was 50 mg/kg, consistent with the acute dermal toxicity of aldicarb.

To estimate potential hazard to barefoot humans or to farm animals exposed to treated soil, rats with bellies shaved 3 times per week were confined for 28 days on soil thoroughly mixed with TEMIK 10G at 560 kg/ha. The results of the test show no difference between rats in the group exposed to TEMIK and in the non-treated control.

There was no measurable effect from inhalation of air circulated over warm, moist soil freshly treated with TEMIK 10G at 110 kg/ha. Under these simulated greenhouse conditions, rats were exposed for 5 days, 8 hours/day, with no significant differences in body weight gain or depression of whole blood cholinesterase over non-treated controls.

Odors emanating from TEMIK granules are due to traces of low-toxicity impurities. Although the aroma is objectionable to some, it does serve as a means for detection.