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

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Caswell #11AA

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Jay Ellenberger, PM #12
Insecticide-Rodenticide Branch
Registration Division (TS-769)

THRU: William L. Burnam, Chief
Toxicology Branch/HED (TS-769)

11.18.83

SUBJECT: Aldicarb Registration Standard

Submission of the Toxicology Branch evaluation of Aldicarb toxicity data consists of:

1. Review of toxicity data for aldicarb, aldicarb sulfoxide and aldicarb sulfone.

2. "One-Liners" for the data base.

3. Data Summary Table A, a biblography indicating the toxicological data gaps and measures taken to fill them.

4. Policy discussion, compatability with Codex, tolerance assessment and ADI re-evaluation.

R. Bruce Jaeger 11/16/83
R. Bruce Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

11
17 Lbs

ALDICARB

Aldicarb, (2-methyl-2 [methylthio] propionaldehyde O-[methyl-carbamoyl]oxime), is the active ingredient of TEMIK® products. It is rapidly absorbed and metabolized in mammals to aldicarb sulfoxide, a major metabolite, which is subsequently and more slowly degraded to aldicarb sulfone. All three moities are inhibitors of cholinesterase enzymes, with aldicarb sulfoxide the more potent acetylcholinesterase inhibitor of the three. The rapid conversion in animals to aldicarb sulfoxide is probably responsible for the acute toxic reaction associated with aldicarb. All of the metabolites of aldicarb, both oxidative and hydrolytic, are rapidly and completely eliminated from the body, with 80-90% excreted within 24 hours, leaving no detectable residues by the fifth day. Data demonstrate that it is not stored in body tissues.

ACUTE TOXICITY

The acute toxicity of aldicarb, aldicarb metabolites and of TEMIK® formulations to several animal species is summarized in Table 1.

Aldicarb is very highly toxic to mammals by oral exposure. In all species tested, the acute oral toxicities of aldicarb and its formulations are similar. The oral toxicity of the formulations is basically that associated with ingestion of the active toxicant; the lower acute oral toxicity of the formulations reflects the reduced concentration of aldicarb as formulated on the granular material. The toxicity of aldicarb when injected intraperitoneally or intravenously is almost the same as when it is given orally, suggesting rapid absorption into the body.

Aldicarb is also highly toxic by dermal exposure; it readily penetrates the skin, especially when the skin is moist. In contrast, the dermal toxicity of TEMIK® formulations is extremely low, reflecting the greatly reduced availability of aldicarb from the formulations. Moistening granular TEMIK® formulations on the skin during dermal exposure slightly enhances penetration of aldicarb, which is demonstrated via increased toxicity.

The oral toxicities of aldicarb and its prinicipal metabolite, aldicarb sulfoxide, are similar, while the oral toxicity of aldicarb sulfone is approximately one twenty-fifth that of aldicarb. The other aldicarb metabolites are considerably less toxic than these.

When rats, mice, and guinea pigs were exposed to aldicarb, finely ground, mixed with talc, and dispersed in the air at a concentration of 200 mg/m^3 for five minutes, all animals died (63). At a lower concentration (6.7 mg/m^3), 15 minutes exposure was not lethal, but five of six animals died during a 30-minute exposure (64). Although aldicarb is extremely toxic when inhaled, it does not vaporize at ambient temperatures and thus does not produce toxic vapors. Exposure of rats for eight hours to air that had passed over technical aldicarb or granular TEMIK® formulations caused no mortality (56).

TABLE 1

ACUTE TOXICITY

Chemical	Species	Sex	Route	Vehicle	LD50 (mg/kg b.w.)	Reference
Aldicarb	Rat	Male	Oral	corn oil	0.88 - 0.93	63,50,86
		Female	Oral	glycerol formal and ethanol (9:1)	1.0	WHO 1966.
	Mouse	Male	Oral	corn oil	0.38-0.50	93,94
		Female	Oral	cottonseed oil	1.5	23
	G.P.		Oral	corn oil	1.0	50
	Rabbit		Oral	propylene glycol	1.3	50
	Rat	Female	Dermal	dimethyl phthalate	3.2-7.0	WHO, 1966.
		Male	Dermal	corn oil	>10	28
	Rabbit	Male	Dermal	propylene glycol	5.0	64
			Dermal	water	20	105
		Male	Dermal	corn oil	>10	27
	Rat	Male	i.p.	ethanol	0.57	35
		Male	i.v.	water	0.47	86
	Mouse	Female	i.p.	cotton-seed oil	0.3	23

TABLE 1 (Continued)

ACUTE TOXICITY

Chemical	Species	Sex	Route	Vehicle	LD50 (mg/kg b.w.)	Reference
Aldicarb sulfoxide	Rat	Male	Oral	corn oil	0.49-1.13	50,86,105
	Mouse	Male	Oral	corn oil	0.8-1.6	50
	G.P.	-	Oral	corn oil	0.8-1.8	50
	Rabbit	-	Oral	corn oil	0.4-1.8	50
	Rabbit		Dermal	water	>20	107
	Rat	Male	i.p.	water	0.47	105
	Rat	Male	i.p.	corn oil	0.71	35
Aldicarb sulfone	Rat	Male	Oral	corn oil	20-25	50,99,105
	Mouse	Male	Oral	corn oil	25	50
	G.P.	-	Oral	corn oil	>50	50
	Rabbit	-	Oral	corn oil	75	50
	Rabbit		Dermal	water	>20	107
	Rat	Male	i.p.	PEG 400	21.2	105
	Rat	Male	i.v.	PEG 400	14.9	105
Adicarb sulfoxide oxime	Rat	Male	Oral	water	8,060	51
Aldicarb sulfone oxime	Rat	Male	Oral	corn oil	1,590	51
Aldicarb sulfone nitrile	Rat	Male	Oral	undiluted	4,000	51
Aldicarb sulfone nitrile	Rat	Male	Oral	PEG 400	350	51

TABLE 1 (Continued)
ACUTE TOXICITY

Chemical	Species	Sex	Route	Vehicle	LD50 (mg/kg o.w.)	Reference
Aldicarb nitrile	Rat	Male	Oral	water	570	105
Hydroxymethyl aldicarb	Rat	Male	oral	water	42.9	13
2-Methyl-2-(methyl sulfinyl) propanol-1	Rat	Male	oral	undiluted	11,300	81
Aldicarb Formulations						
10G [redacted]	Rat	Male	oral	none	7.07	94
TSX (a)	Rat	Male	oral	corn oil	7.9	111
	Rat	Female	oral	corn oil	6.7	111
10G [redacted]	Rabbit	Female	oral	none	7.9-17.8	47,100
15G [redacted]	Rabbit	Female	oral	none	5.29-10.6	47,100
15G [redacted]	Rabbit	Female	oral	none	8.4	47
10G [redacted]	Rat	M & F	dermal	dry	2100->5000	47,83,91,94,100
10G [redacted]	Rat	M & F	dermal	water	283-673	46,47,77,80,100
15G [redacted]	Rat	M & F	dermal	dry	1980-6320	47,91,94,100
	Rat	M & F	dermal	water	283-1010	47,100
10G [redacted]	Rabbit	Male	dermal	dry	>4800	100
15G [redacted]	Rabbit	Male	dermal	dry	>4800	100
TSX (a)	Rabbit	Both	dermal	none	>2000	112

(a) TSX is a mixture of TEMIK (5.5%), Terrachlor fungicide (9.5%), and Terrazole fungicide (2.3%).

INERT INGREDIENT INFORMATION IS NOT INCLUDED

TERATOLOGY AND REPRODUCTION

Aldicarb:

Teratogenicity of aldicarb was investigated as part of a reproduction study (74) wherein aldicarb was given to groups ranging in size from five to twelve female rats throughout the gestation period, for the first seven days only, from day 5 through day 15 of gestation, or from the start of pregnancy through weaning of the pups. Females were sacrificed between days 19 to 21 or allowed to bear their young through weaning. No anomalies were seen in any offspring of any treated mothers at the maximum dose of 1 mg/kg. The treated groups did not differ from controls in standard parameters of reproduction (quantitative measures of fertility, gestation, viability, and lactation) or in standard parameters measured in teratology studies.

Two three-generation, one litter per generation, reproduction studies were performed (72,96). Rats were fed aldicarb for 90 or 100 days at doses of up to 0.7 mg/kg and mated to produce the respective F_1, F_2 and F_3 generations. All animals were maintained continuously on diets containing aldicarb. The F_3 animals were histologically examined either at weaning or at 90 days of age. No differences were found between treated and control groups in fertility, gestation, viability, or lactation. There was no mortality attributable to aldicarb, nor did gross or microscopic examination reveal any effects of the treatment.

Cambon et. al. (12) have evaluated the ability of aldicarb to cause a depression of blood, brain and liver cholinesterase in dams and fetuses. Aldicarb was administered to pregnant rats via gastric intubation in a single dose on day 18 of gestation. Dosage levels administered included 0.001, 0.01, and 0.1 mg/kg body weight. Acetylcholinesterase activity in the fetus was significantly lower at all dosages of aldicarb. In a number of instances the inhibition of acetylcholinesterase was greater in fetal than maternal tissue suggesting rapid placental transfer. The Cambon et. al. studies (1979,1980) measured only ChE inhibition without regard to fetal development or reproduction parameters. The authors concluded that the sensitivity difference observed in maternal and fetal AChE to insecticides is in the specific affinities of carbamate derivatives, such as aldicarb, for each fetal and maternal isoenzyme.

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Aldicarb sulfone:

An aldicarb sulfone reproduction study was modified to include a teratology bioassay with animals treated (1) from day 0 to day 20, (2) from day 6 to day 15 and (3) from day 7 to day 9 of gestation (114). All animals were sacrificed before parturition (day 20) and fetuses examined for skeletal and somatic (tissue) changes. Maternal toxicity was observed at the high dose (9.6 mg/kg). There were no teratologic changes noted in this study.

In a study similar to the aldicarb three generation study, aldicarb sulfone was administered in the diet to rats (10 male and 20 female/group) at dosage levels of 0, 0.6, 2.4 and 9.6 mg/kg to initiate a three generation, one litter per generation, reproduction study (114). There were marginal effects on the lactation index at 9.6 mg/kg. Aldicarb sulfone, at levels up to and including 9.6 mg/kg, had no adverse effect on reproduction under the conditions of this study.

NEUROTOXICITY

Aldicarb:

White Leghorn hens, aged 10 months to 2 years, were administered technical grade aldicarb orally either as a single dose of 4.5 mg/kg b. wt. or as daily doses for 30 days of 2.25, 4.5, or 9.0 mg/kg body weight. At the conclusion of dosing animals were observed for an additional 30 days for signs of ataxia or hind limb paralysis. Representative tissues from the brain, spinal cord and sciatic nerve were taken for histopathological examination (histopath was not presented, however). It was concluded that aldicarb is not neurotoxic at the doses administered based on observed symptomatology (36).

Aldicarb sulfone:

Adult white leghorns hens (40 each) were intubated to receive 250 mg/kg b. wt. suspended in corn oil. Two other groups, each with 10 hens, received either TOCP (500 mg/kg) or corn oil alone, and served as positive and negative control groups, respectively. The birds received single oral doses, 21 days apart, in a typical acute delayed neurotoxicity evaluation. The hens were observed every third day for 42 days. There were no neurological effects other than acute cholinergic signs of poisoning in the TOCP dosed group. There was no histological examination performed owing to the lack of demonstrated neurotoxic signs. Aldicarb sulfone did not cause delayed neurotoxic reactions under the conditions of the study (8).

SHORT-TERM STUDIES

Aldicarb. Among young rats fed aldicarb for seven days, mortality was observed at a dose of 16.0 and 8.0 mg/kg; at 4.0 mg/kg, no rats died although body weight decrease was evident and kidney and liver weight decreases occurred at all levels in females (4, 8, and 16 mg/kg) (88). Growth of young rats of both sexes was depressed at doses of aldicarb as low as 1.6 mg/kg (Weil and Carpenter, 1969c), but not affected by doses of 0.8 mg/kg or less in this and another study (50). There was also no mortality observed at the high dose of 3.2 mg/kg in either study. In another study (89) growth over seven days was depressed by a dose of 0.3 mg/kg of aldicarb in females, but not in males. The only organ weight change in this study was decreased liver weight in female rats, with no such effect in males. When rats (10 males and 10 females/group) were fed aldicarb at dosage levels of 0, 0.02, 0.1, and 0.5 mg/kg b.w. for 93 days, mortality was increased at the highest levels. Growth was retarded as was food consumption at the highest dose. The mortality resulted from a non-uniform dispersion of aldicarb in the diets (71).

When mice were fed aldicarb for seven days, mortality occurred at 1.2 mg/kg (the highest dose), but not at 0.6 mg/kg. There were no effects on growth or organ weights at any dose level (87). In mice (B6C3F1 strain), aldicarb in the diet at doses of up to 40 ppm (about 6.0 mg/kg) for 13 weeks caused no significant somatic effects or mortality (48).

Dogs (two of each sex), fed aldicarb for seven days, exhibited no growth depression or organ weight changes at doses up to 0.7 mg/kg (the highest in this study) (95). In a 100-day feeding study, the only effects on dogs were slightly decreased weight of the testes and slightly increased weight of the adrenal glands in males at 0.7 mg/kg (the highest dose); microscopic examination revealed no changes in these tissues (97). A dose of 0.3 mg/kg of aldicarb had no effect on organ weights.

Aldicarb was tested on rabbits and rats for subchronic dermal toxicity. Moist dressings containing aldicarb at doses of 5, 10, and 20 mg/kg body weight/day were applied to the abraded skin of male rabbits for six hours/day for 15 days (14). All three doses depressed growth, and the two highest doses inhibited plasma acetylcholinesterase activity. No effects were observed on kidney or liver weight or in hematological or histological examination. Rabbits with intact skin receiving dry applications of 20 mg/kg of aldicarb under the same regime showed no effects of the treatment. A similar study with rats (77) gave the same results with respect to depression of growth; other variables were not investigated.

The toxicity of aldicarb to chickens was examined by Schlinke (59) wherein groups of White Leghorn chickens (5/group), 6-7 weeks old, were orally dosed with 1.0, 2.5 or 5 mg aldicarb/ kg b. wt./day for 10 days. Administration was via gelatin capsule or oral drench. Birds were observed for body weight gain and mortality. There were no ill effects among chickens in the 1.0 mg/kg group, however, at the two higher doses birds exhibited decreased body weight gains and mortality (2/5 at 2.5 and 5/5 at 5 mg/kg).

Aldicarb sulfoxide:

Aldicarb sulfoxide in the diet at doses of up to 1.0 mg/kg for periods of time up to six months caused no mortality in rats (78,103). In two seven-day studies (50,89), aldicarb sulfoxide depressed growth in rats of both sexes at a dose of 0.8 mg/kg of aldicarb sulfoxide. In a six month study growth was depressed in males at 0.25 mg/kg. The lowest dose of aldicarb sulfoxide that reduced kidney or liver weights in either seven-day or six-month studies was 1.6 mg/kg (50,78,89); no effects on organ weights were seen at 1.3 mg/kg (78).

Aldicarb sulfoxide did not reduce brain acetylcholinesterase activity in rats during either seven-day or six-month studies at doses of up to 1.0 mg/kg (50,78). When rats were fed aldicarb sulfoxide for seven days, erythrocyte acetylcholinesterase activity was depressed at a dose of 0.8 mg/kg, but not at 4.0 mg/kg (50). In a more comprehensive study over a 56 day interval cholinesterase depression (plasma and RBC) was observed at 1.0 mg/kg with no effects being noted at 0.3 mg/kg b.w. (103). Over this period, depression of cholinesterase was not progressive at the highest dose level. In studies in rats lasting three and six months (78), plasma and erythrocyte acetylcholinesterase activity was very slightly (marginally) depressed at doses of 0.25 mg/kg in male rats and 0.5 mg/kg in female rats; while 0.125 mg/kg of aldicarb sulfoxide did not affect acetylcholinesterase activity.

Dogs fed aldicarb sulfoxide for three months demonstrated no depression of growth except during the first week of treatment at 0.5 mg/kg (the highest dose) (78). Body weights was not affected at doses of 0.25 mg/kg or less. The treatment had no effect on acetylcholinesterase activity. (However, in this study with dogs, a recovery period of 24 hours was allowed before acetylcholinesterase was assayed.) Aldicarb sulfoxide was without effect at any dose up to and including 0.5 mg/kg on blood chemistry, hematology or gross/micro histological examinations.

Aldicarb sulfone:

Aldicarb sulfone in the diet at doses of up to 20.0 mg/kg for seven days caused no mortaltiy in rats (50,89,90) nor in rats fed up to 16.2 mg/kg of aldicarb sulfone for periods of up to six months (79,103). In the six-month study, the highest dose of aldicarb sulfone (16.2 mg/kg) caused a transient but significant depression of growth, while doses of 5.4 mg/kg or less were without effect. In the seven-day studies, growth was significantly depressed at a dose of 5.0 mg/kg in males and 0.6 mg/kg for females. Liver and kidney weights of rats were reduced only at a dose of 20.0 mg/kg of aldicarb sulfone; these organs were unaffected at 5.0 mg/kg in seven-day studies (89) and at 16.2 mg/kg in a six-month study (79). In a seven-day dietary study with mice, reduction in body weight was noted at the highest dosage level, 38.4 mg/kg (101). No significant effects were noted at 9.6 mg/kg on growth, or tissue and organ weights.

In a seven-day study, erythrocyte and plasma cholinesterase depression were seen in rats of both sexes at a dose of 5.0 mg/kg of aldicarb sulfone, with no effect at 2.5 mg/kg (50). In a 56 day study plasma and rbc cholinesterase were depressed at 16.2 mg/kg but unaffected at 2.4 mg/kg (103). In a six-month study, erythrocyte acetylcholinesterase activity was reduced at a dose of 1.8 mg/kg, with no effect at 0.6 mg/kg; while plasma cholinesterase activity was depressed with no effect at 1.8 mg/kg (79). However, a similar three-month study showed plasma cholinesterase depression in both sexes at a dose of 1.8 mg/kg, with no effect at 1.2 mg/kg (79).

At relatively high doses, aldicarb sulfone also reduced brain acetylcholinesterase activity. This was observed in rats of both sexes fed aldicarb sulfone at 16.2 mg/kg for three months and at 5.4 mg/kg for six months (79), while brain acetylcholinesterase was unaffected by a dose of 1.8 mg/kg in the six month study. Rats fed aldicarb sulfone for seven days showed brain acetyl-cholinesterase depression at a dose of 20.0 mg/kg (50).

In dogs fed aldicarb sulfone for three months, growth was depressed although not statistically at doses of up to 5.4 mg/kg (the highest dose used) (79). There was no mortality nor were there any observed effects on tissues or organs. Acetylcholinesterase depression was not detected; a recovery period of 24 hours was allowed before the assay.

Mixture of aldicarb or aldicarb sulfoxide with aldicarb sulfone:

In rats, 1.2 mg/kg of a 1:1 mixture of aldicarb sulfoxide and sulfone in the diet for seven days reduced growth only in the females, and this effect was observed only at the first of three weighings (89). The treatment had no observed effect on the liver or kidney. Acetylcholinesterase measurements from this study were not appropriate for assessing enzyme depression.

In a seven-day study with mice, a 1:1 mixture of aldicarb and aldicarb sulfone caused no mortality at doses of up to 36 mg/kg (the highest used), but at 18 mg/kg, growth was depressed, and males showed severe cholinergic signs of poisoning (90). Although these effects were not seen at a dose of 6 mg/kg of the mixture, liver weight was reduced in both sexes. Kidney weight was affected only at 36 mg/kg. A level of 2 mg/kg in the diet was without adverse effects.

Groups of rats (10 male and 10 female rats/group) were administered aldicarb sulfoxide/sulfone in the drinking water, ad libitum, for 29 days (43). The aldicarb metabolites were present in a 1:1 ratio at dosage levels corresponding to 0, 75, 300, 1,200, 4,800 and 19,200 ppb. Growth, food and water consumption, clinical hematology and clinical biochemistry parameters were evaluated on a weekly basis. Blood cholinesterase analyses were performed on days 8, 15, and 29, while brain cholinesterase was examined on day 29. Animals were continuously exposed until blood samples were drawn or sacrifice was made. There was no mortality over the course of the study. Growth and food consumption were depressed at the highest dose level (equivalent to a daily intake of 1.44 mg/kg). Red blood cell and plasma cholinesterase in both males and females was depressed only at the highest dosage level, 19,200 ppb. There were no differences in the inhibition pattern with either sex. No effects were noted on growth or any clinical parameter at 4800 ppb (equivalent to a daily intake of approximately 0.40 mg/kg).

LONG-TERM STUDIES:

In studies lasting two years, rats were examined for potential neoplastic changes, as well as for the same effects as in the short-term toxicity studies summarized above. The highest doses of aldicarb and its metabolites used were in some cases slightly lower than those producing effects in the short-term studies. Because acetylcholinesterase activity was measured 24 hours after cessation of diety exposure, these measurments could not be used to evaluate enzyme depression.

Aldicarb:

Rats (20 of each sex per treatment) were fed aldicarb for two years in two separate studies using a maximum dose of 0.1 mg/kg (73) and 0.3 mg/kg (92), respectively. There were no differences from controls in mortality, growth, hematologic characteristics, or occurrence of of tumors or other histological abnormalities (73,92). At a dose of 0.3 mg/kg, plasma acetylcholinesterase activity in males was slightly depressed (92). No effect was seen on females at 0.3 mg/kg (92) or on either sex at 0.1 mg/kg (73).

In dogs (three per sex per dose), aldicarb in the diet at up to 0.1 mg/kg for two years produced no significant differences from controls in mortality, growth, acetylcholinesterase activity, hemotological values, or condition of organs and tissues (76).

Aldicarb metabolites:

In rats fed aldicarb sulfoxide (at doses of up to 0.6 mg/kg), aldicarb sulfone (at doses of up to 2.4 mg/kg), or a 1:1 mixture of these chemicals (at doses of up to 1.2 mg/kg), slight increases in mortality were experienced at the nighest dose levels (92). Growth was unaffected by aldicarb sulfoxide or aldicarb sulfone administered separately, but was slightly depressed by the 1:1 mixture at a dose of 1.2 mg/kg, primarily in males (0.6 mg/kg of the mixture did not affect growth). Hematocrit values were comparable in treated and control groups. All three of these treatments caused slight depression of plasma acetylcholinesterase activity in males at their highest doses. No differences between treated and control groups were found in gross or microscopic examination of organs and tissues or in tumor occurrence. NOELs determined were 0.3 mg/kg, 2.4 mg/kg, and 0.6 mg/kg, respectively.

CARCINOGENICITY

Oral Exposure

In long-term studies with rats and mice, dietary exposure to aldicarb did not increase the incidence of tumors. In the rat study doses of up to 6 ppm of aldicarb (about 0.3 mg/kg) for 103 weeks produced no increase of benign or malignant tumors compared with controls. Mice (B6C3F1) receiving aldicarb at 6 ppm (about 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 (48).

In a separate study with CD-1 mice (44 of each sex per treatment) (93), aldicarb at 0.7 mg/kg for 18 months resulted in a significantly higher incidence of hepatomas in surviving treated males than among surviving controls or mice that had died. At the same dose, lymphoid neoplasias were significantly more frequent among dead treated males than among dead controls (no surviving male mice had lymphoid neoplasia). During the first 2.5 months of this study, doses of 0.2 mg/kg or more in females and 0.4 mg/kg or more in males had acutely toxic effects, resulting in some mortality. This appeared to be due to inadequate dispersion of aldicarb crystals in the food: mice eating concentrations of these crystals could have received an excessive dose. For the rest of the study, aldicarb was dissolved in acetone before being mixed into the food; this appeared to eliminate the acute toxicity. These results occurred in the 1972 study only. A follow-up study using the same strain of mouse (50 of each sex per treatment) and the same highest dose (0.7 mg/kg) failed to detect any carcinogenic response (98). Further analysis showed that in the first study, the incidences of hepatomas and lymphoid neoplasias in the control groups were exceptionally low, apparently a chance occurrence; this caused the incidences in treated groups to appear significantly higher than controls. The incidences of these tumors in treated groups were comparable to their incidences in both control and treated groups in other studies (98).

In another study with CD-1 mice (50 of each sex per treatment) (114), aldicarb sulfone at 9.6 mg/kg/day for 18 months (79 weeks) did not produce any deleterious effects when included in the diet. The criteria of effects that were evaluated included: mortality, growth and food consumption, life span, and gross and microscopic examination of tissues and organs for histologic changes. Based on these criteria, aldicarb sulfone did not affect tumor incidence or produce any pathologic alteration in the CD-1 mice.

In a separate 2-year feeding study using rats (92), aldicarb sulfone when ingested at dietary levels up to and including 2.4 mg/kg b. wt. per day was not oncogenic in rats according to the conditions of the test.

Dermal Exposure

Aldicarb in acetone solution applied to the shaved backs of male mice (C3H/HeJ strain) for 28 months did not increase the incidence of tumors over that in the controls (75). The dose of aldicarb was initially a 0.25% solution applied three times a week; after two weeks, application was reduced to twice weekly, and after two months, the concentration of aldicarb was reduced to 0.125% because mortality was comparatively high during the first 2 months. Mortality over the 28-month study did not differ significantly between treated and control mice.

MUTAGENICITY

Aldicarb, aldicarb sulfoxide and aldicarb sulfone have been tested for mutagenic potential in the Ames Salmonella/Microsome Plate Assay, using five histidine-requiring strains of Salmonella typhimurium (TA-98, TA-100, TA-1535, TA-1537 and TA-1538), both with and without metabolic activation (31). Aldicarb and aldicarb sulfone were also evaluated for dominant lethal effects in rats (96,115). Although results from all of these studies were negative, substantial questions have been raised by Toxicology Branch concerning the laboratory procedures utilized. Additional information has been requested and until received these studies are considered "unacceptable".

N-nitroso aldicarb

The N-nitrosamide derivative of aldicarb (formed in a laboratory reaction of aldicarb with sodium nitrite at low pH) has been shown to be carcinogenic in vitro in mammalian cell culture test systems (57) and in vivo in rats (40).

The muagenicity of N-nitrosamide derivative of aldicarb has been demonstrated in human cell cultures (9) and in a Salmonella assay (60). The N-nitrosamide derivative is extremely unstable in the environment. Despite exhaustive studies to detect this chemical, there is no evidence at present that an N-nitrosamide derivative of aldicarb is a naturally occurring product resulting from the use of aldicarb.

STUDIES ON BEHAVIOR

The effect of acute administration of aldicarb on avoidance behavior in rats was investigated and compared with the effects of other carbamate esters (35). Rats trained to avoid electrical shock were injected intraperitoneally with aldicarb, and their ability to avoid shock was tested over the six hours immediately after treatment. The lowest dose to interfere with avoidance behavior was 0.266 mg/kg. The ratio of the behaviorally effective dose to the acute i.p. LD_{50} was smaller for aldicarb than for the other carbamates tested. Because the behaviorally effective dose is closer to a lethal dose with aldicarb than with other carbamate, products containing aldicarb would be less likely than other carbamate products to affect behavior since the exposure levels (i.e., TMRC) are several orders of magnitude less than the effect level.

OBSERVATIONS IN HUMANS

Studies examining the acute effects of aldicarb administered orally to human volunteers revealed the same pattern of rapid acetylcholinesterase depression and rapid recovery seen in experimental animals. Adult male volunteers (four per treatment) were given aldicarb orally in aqueous solution at doses of 0.025, 0.05, or 0.1 mg/kg (32); in a similar study, two subjects were given doses of 0.05 or 0.26 mg/kg (Cope and Romine, 1973). All subjects showed a slight degree of whole-blood acetylcholinesterase depression within one or two hours of treatment, although the maximum depression noted at 0.025 mg/kg and 0.05 mg/kg was within the normal range of variation seen in the control population. Only doses of 0.1 and 0.26 mg/kg produced clinical signs and symptoms typical of a cholinergic response from anticholinesterase poisoning, seen within an hour of aldicarb administration. The symptoms were mild at 0.1 mg/kg, but at 0.26 mg/kg, poisoning was acute, and atropine was administered. In the first study (32), where signs and symptoms of poisoning were observed at 0.1 mg/kg, acetylcholinesterase activity returned to normal and poisoning symptoms disappeared spontaneously within five to eight hours of treatment (without administration of antidote).

Human exposure to aldicarb was assessed under a variety of actual working conditions (field and greenhouse) in which TEMIK® pesticides were handled. Exposure, as determined by detection of blood acetylcholinesterase inhibition, with or without clinical signs or symptoms, depended primarily on the means by which the formulated product was applied. When exposed workers were removed from the exposure situation, depressed acetylcholinesterase levels returned rapidly to normal and symptoms, if any, subsided; no lasting effects on the health of workers were noted (11,52,61,70, 109,7).

Two separate incidences of suspected carbamate poisoning in Nebraska were reported in the Morbidity and Mortality Weekly Report, March 30, 1979). The incidences occurred in 1977 and 1978 and involved a total of 14 persons (6 men, 8 females) who became ill after ingestion of locally grown hydroponic cucumbers. The signs and symptoms of the illness were typical of cholinesterase inhibition (e.g., diarrhea, abdominal pain, blurred vision, nausea, vomiting). None of the patients received specific medical treatment and recovered quickly and completely. Analysis of the cucumbers and the hydroponic mixture in the second incident detected 6.6-10.7 ppm aldicarb residues in the cucumbers, with 1.8 ppm in the water-nutrient solution. If aldicarb residues were present in these cucumbers as a result of applying it to the

water-nutrient solution then it is clearly a misuse of Temik formulations in that: (1) there is no registered use for aldicarb on cucumbers, (2) there are also no registered hydroponic uses for aldicarb, and (3) residue levels in the contaminated cucumbers were several orders of magnitude greater than any federally established tolerance (limits determined to constitute safe levels in specific racs).

A review of the labels for Temik 10G and 15G demonstrate that the Agency has taken great care (i.e., Restricted Use) to develop use directions and label warnings which, if followed, will adequately protect the authorized applicators. A review of Agency files did not reveal any deaths which could be attributed to the proper use of aldicarb.

Furthermore, the Agency carried out on epidemiological study in Suffolk County in late 1979 and reported no evidence of ususual symptomology that could be associated with aldicarb residues in drinking water or food commodities. An epidemiology study titled "Agricultural Pesticides: Results of a Preliminary Study" by Drs. Varma, Zaki and Sternman does not support the suggestion of spontaneous abortions in the human population on Long Island being associated with exposure to aldicarb contaminated drinking water. There were specific problems identified by the Agency concerning the design and manner in which this study was conducted and therefore, no valid conclusions could be made.

METABOLISM (Including Absorption, Distribution and Excretion):

When aldicarb is given orally to mammals, it is absorbed readily, distributed widely in the body, and excreted rapidly. The presence of aldicarb metabolites in tissues, urine, and feces has been examined in several mammalian species following administration of radiolabelled aldicarb under a variety of treatment regimes. Similar results have been found in all species tested (for both sexes) and under all treatment regimes.

When male rats were administered single oral doses of radiolabelled aldicarb, most of the aldicarb metabolites were excreted within 24 hours; after four days, more than 95% of the administered dose had been excreted, and no residues were detected in body tissues (39). Within the first 24 hours of another study, 80% of the administered dose of aldicarb was eliminated in the urine and 5% in the feces. Although radioactive metabolites were found at low levels in a variety of tissues during the first days affter treatment, there was no indication that residues accumulated in the body; by the fifth day, residues were no longer detected (6).

To measure the excretion of subacutely administered aldicarb, dogs were maintained on diets containing aldicarb both before and after being given a single ^{14}C-labelled dose of aldicarb (66). Each dog received 0.75 mg/day of aldicarb in the diet for 20 days, a single radiolabelled dose on the 21st day, and unlabelled aldicarb for 10 more days. Of the radioactivity recovered in the urine, 90% was found within 24 hours of administration of the radiolabelled aldicarb. Thus, the pattern of excretion of aldicarb in the urine by dogs following subacute dosing was similar to that found for rats after acute dosing.

When lactating dairy cows received a single dose of aldicarb, approximately 83% of the dose appeared in the urine within 24 hours, with traces of residues noted in the feces and milk (25,58). Subchronic dosing of cows with aldicarb gave very similar patterns of excretion; trace levels of residues were found in body tissues following continuous treatment (24).

A single oral dose of aldicarb to laying hens was rapidly excreted in the feces. Traces of residues were noted in the tissues within 6 hours of treatment and in the eggs within 24 hours. Residues in both tissues and eggs declined rapidly. The results were the same following administration of aldicarb for 21 days (33). Thus, hens showed patterns of rapid distribution in body tissues and rapid excretion of aldicarb very similar to those of the mammals tested.

The patterns of distribution and excretion of orally administered aldicarb metabolites are the same as for aldicarb. This has been demonstrated for aldicarb sulfone and aldicarb nitrile in dogs and rats (4,65,67,68); for aldicarb sulfone in hens (33) and for a aldicarb sulfoxide and aldicarb sulfone in dairy cows (58). In addition, water-soluble aldicarb residues from bean plants were found to be readily absorbed from the gastrointestinal tract of rats and rapidly excreted in the urine (41).

In summary, aldicarb ingested by animals is rapidly absorbed and metabolized and is not stored in body tissues. Its metabolites were mostly excreted in the urine within 24 hours, and elimination is complete in about five days.

The basic metabolic pathway for aldicarb appears to be the same in all species studies (including plants and a variety of vertebrates and invertebrates). This pathway is shown in Figures 1 and 2. Aldicarb is rapidly oxidized to aldicarb sulfoxide; then, more slowly, aldicarb sulfoxide is partially oxidized to aldicarb sulfone. Aldicarb and both carbamate metabolites, the

sulfoxide and sulfone analogs, are converted to the corresponding oximes, which are, in turn, slowly degraded to the corresponding nitriles, aldehydes, acids, and alcohols.

Aldicarb given orally to rats as a single acute dose was excreted primarily as aldicarb sulfoxide (40%), and the sulfoxide oxime (30%); only trace amounts of aldicarb were found in the urine (6,39). The major urinary metabolites in dogs and in dairy cows were the same as in rats (25,66), and the pattern of aldicarb metabolism was found to be similar in hens (33), insects (10,42), and plants (42,5).

The principal metabolites found in milk following acute administration of aldicarb to cows were aldicarb sulfoxide and sulfoxide oxime and nitrile (25). When dairy cows were given aldicarb for 14 days, however, the major metabolite in the milk was aldicarb sulfone and its nitrile derivative, with little aldicarb sulfoxide and relatively large amounts of the sulfoxide oxime present. This suggests that more complete metabolism occurs with continuous dietary exposure to aldicarb (24).

The fates of acutely administered aldicarb metabolites have been studied in rats, confirming the pattern shown in Figures 1 and 2. When rats were given aldicarb sulfoxide, about half of the dose was rapidly degraded and eliminated as hydrolytic products in the urine; very small amounts of aldicarb sulfone were found. When rats were given aldicarb sulfone, the unchanged aldicarb sulfone comprised about 80% of the urinary metabolites (4,6).

EFFECTS OF ALDICARB ON ENZYMES AND OTHER BIOCHEMICAL PARAMETERS:

The most important biochemical effect of aldicarb and its methyl-carbamate ester metabolites (as with the class of methyl-carbamates in general) is their ability to inhibit acetylcholinesterase in a rapidly reversible reaction (15). (Note: the normal function of the enzyme acetylcholinesterase is to degrade the neurotransmitter acetylcholine. Failure to degrade acetylcholine at the appropriate time results in neurological disruption that is evident in various signs and symptoms of poisoning.) When aldicarb comes in contact with acetylcholinesterase, it forms a reversible complex, competing with acetylcholine for the active site of the enzyme. The aldicarb-acetylcholinesterase complex dissociates rapidly, and the acetylcholinesterase is released unaltered (hence the description of the enzyme inhibition as "reversible".) Following a single dose of aldicarb, formation of the enzyme-inhibitor complex is rapid, with recovery of the enzyme beginning within a few minutes. Complete recovery occurs rapidly, within hours.

A major difference in the toxicology between organophosphate and carbamate insecticides is that the former almost irreversibly phosphorylate the acetylcholinesterase of tissues, whereas the carbamates cause reversible carbamylation of the enzyme. The reversibility of reactions of certain organophosphates and acetylcholinesterase resulting in a phosphorylated or "aged" (an irreversibly-inhibited) enzyme depends primarily on synthesis of new enzyme. In humans, exposure to organophosphates can cause depression of plasma cholinesterase to persist for 1 to 3 weeks; red blood cell depression can last up to 12 weeks. In cases of carbamate poisoning, plasma and red blood cell cholinesterase may be depressed, but they commonly revert to normal within a few hours after exposure (45).

In vivo studies show aldicarb sulfoxide to be 23 times as effective an acetylcholinesterase inhibitor as aldicarb and 60 times as effective as aldicarb sulfone. As aldicarb in the body is metabolized to aldicarb sulfoxide, this metabolite is most likely responsible for the cholinergic effects noted with aldicarb (10).

The transience of acetylcholinesterae inhibition by aldicarb (and methyl-carbamate esters in general) makes it difficult to assay accurately. In routine toxicological studies, animals often are placed on a control diet 24 hours before terminal sacrifice, when an assay for several clinical chemistry parameters are to be made. By this procedure, acetylcholinesterase inhibition by carbamates cannot be detected, because enzyme activity completely recovers within a few hours after treatment is stopped. This was demonstrated in experiments with rats fed aldicarb sulfoxide or aldicarb sulfone for one week and then assayed for acetylcholinesterase activity either immediately or after 24 hours (78,79). In both cases, the immediate assay revealed acetylcholinesterase depression, and the delayed assay did not. Similar experiments in which rats received aldicarb sulfone for three months or aldicarb sulfoxide for six months gave the same results (78,79). In the later case, acetylcholinesterase depression was as high as 89%, yet recovery was complete in 24 hours.

Even with no delay between cessation of aldicarb treatment and the assay, reversible acetylcholinesterase depression is difficult to detect using routine procedures. Spontaneous reversal of inhibition is rapid, and inhibition is reversed by simple dilution. Furthermore, because acetylcholine and aldicarb compete for the enzyme's active site, acetylcholinesterase inhibition is reduced by adding substrate (acetylcholine) to measure the reaction. (It should be noted that this effect also occurs

naturally in the body, and probably results in the spontaneous rapid recovery from cholinergic signs of poisoning following acetylcholinesterase inhibition.) Thus, the assay for acetylcholinesterase inhibition must be very rapid (taking less than five minutes) and must employ minimal dilutions and minimal amounts of substrate.

SIGNS OF POISONING AND ANTIDOTAL STUDIES

Aldicarb is extremely poisonous, a toxic dose rapidly producing severe cholinergic signs of poisoning. These parasympathomimetic responses included salivation, lacrimation, nausea and vomiting, evacuation of bowel and bladder, constriction of the pupils, piloerection, ataxia, muscle spasms and general muscular weakness, labored respiration, convulsions, and death. The immediate cause of death is usually respiratory failure. The speed of onset of these symptoms and their severity depend on the dose and route of exposure. In all cases, atropine sulfate is an effective antidote.

Atropine has been shown to limit the muscarinic effects of aldicarb and its metabolites (38,84). The nicotinic effect of aldicarb at myoneural junctions has proven more difficult to control. Decamethonium, a skeletal-muscle relaxant, is not very effective with aldicarb, nor is tubocurare, although a combination of decamethonium and atropine is effective (37). Oximes, widely used in treatment of organophosphate poisoning, are frequently effective against carbamate poisoning as well. The oximes 2-PAM, P2S, and obidoxime act as antidotes to aldicarb, both alone and with atropine (35,49). In mice, the oxime toxogonin, doubles the LD_{50} of subsequently-administered aldicarb (62). In vitro acetylcholinesterase inhibition is not affected by P2S or obidoxime (49); the mode of action of oximes against acetylcholinesterase inhibition appears to be different for carbamates than for organophosphates. Although atropine is a more effectiev antidote than the oximes tested, certain oximes appear to be valuable in treatment of aldicarb poisoning.

ACCEPTABLE DAILY INTAKE (ADI)

The toxicological data considered in support of tolerances for aldicarb (and its ChE inhibiting metabolites) include a 2-year rat feeding/oncogenicity study with a no observed effect level (NOEL) (other than ChE inhibition) of 0.3 milligrams (mg)/kilogram (kg) of body weight (bw) per day; a rat oncogenicity study which was negative for oncogenic effects at 0.3 mg/kg (highst level tested, HLT); a 100 day dog feeding study and a 2-year dog feeding study with NOELs (other than ChE inhibition) of 0.7 (HLT) and 0.1 mg/kg bw/day (HLT), respectively; an 18-month mouse feeding/ oncogenicity study with a NOEL of 0.7 mg/kg bw/day (HLT); a 2-year mouse oncogenicity study with a NOEL of 0.9 mg/kg bw/day (HLT);

a 6-month rat feeding study using aldicarb sulfoxide (considered the more potent cholinesterase inhibitor) with a cholinesterase inhibition NOEL of 0.125 mg/kg bw/day; a 3-generation reproduction study in rats with a 0.7 mg/kg bw/day NOEL (HLT); a rat teratology study which was negative at 1.0 mg/kg bw/day (HLT); and a hen neurotoxicity study which was negative at up to 4.5 mg/kg bw/day.

The most suitable study for defining the amount of aldicarb and/or aldicarb sulfoxide which appears to be without appreciable risk as it appears in the diet (mg/kg bw/day) is the 6-month rat feeding study using aldicarb sulfoxide (Weil and Carpenter, 1968). This study demonstrated a NOEL of 0.125 mg/kg bw/day for cholinesterase inhibition, and is considered appropriate as a basis for the ADI for both aldicarb and aldicarb sulfoxide because the latter compound (a metabolite) is an equally potent, if not more so, cholinesterase inhibitor as aldicarb.

The determination and/or calculation of an Acceptable Daily Intake (ADI), in one form or another (i.e., Temporary, Provisional, etc.), for pesticide residues in foods (racs - raw agricultural commodities) is a single unique practice commonly employed by several regulatory and advisory authorities whose primary objective and responsibility is directed toward the safe use of pesticides. A review of the history for aldicarb will reveal that both regulatory and advisory opinions have differed. Since its use was introduced, based on the evaluation of the "available data" at the time each opinion was expressed. As additional data and information have been generated and evaluated the concerns and understanding of aldicarb's toxicity to mammals, including man, have been advanced and refined. The toxicity data for aldicarb reviewed in the late 60's to early 70 s painted a picture of extreme concern for its lethal effects. This was based on the low acute oral LD_{50}, the steep dosage-mortality curve (from acute testing) and the lethality in a subchronic feeding study which demonstrated an extremely narrow margin between no efect and death (e.g., 0.1 vs. 0.5 mg/kg). A 100-fold margin of safety was recommended because aldicarb was believed equally toxic (i.e., the same on a mg/kg basis) following either acute oral or dietary exposures. It is now known this effect has not been borne out in any further studies with aldicarb or its ChE inhibiting metabolites. A review of all available toxicity data, involving repeat dietary exposure, clearly demonstrate that even at the highest level tested (HLT), ranging from 0.3 to 4.0 mg/kg bw/day, mortality was rarely, if ever, evidenced at dietary doses equal to or greater than the acute oral LD_{50} for the respective species. It is unusual for an animal to tolerate more than the equivalent of an LD_{50} dose, daily. Aldicarb, aldicarb sulfoxide and aldicarb sulfone are "unusual" then in this respect, which apparently reflects reduced bioavailability as residues in the diet and the rapid reversibility of anticholinesterase effects in vivo. The

conclusion reached by all of the regulatory and/or advisory authorities is that all of the available toxicity data, including human studies, have provided no indication that aldicarb or its ChE inhibiting metabolites have any untoward toxicity other than that associated with anticholinesterase activity.

The ADI for aldicarb and its ChE inhibiting metabolites, and data base in support thereof, have undergone extensive critical review within the last year. The 1982 Joint Meeting on Pesticide Residues (JMPR) (29) re-evaluated the data in support of the ADI in light of additional data received on aldicarb and its ChE inhibiting metabolites. They determined that the new evidence supported earlier feeding studies which showed that feeding of aldicarb at relatively high doses (i.e. relative to LD50) does not produce toxic effects expected from the LD50. In the light of the toxicological data on aldicarb, the reduced bioavailability when administered in the diet, and the rapid spontaneous recovery of the carbamylated cholinesterase, the meeting revised the ADI and recommended 0.005 mg/kg body weight.

A committee, chaired by Dr. C. Wilkinson, from the Institute for Comparative and Environmental Toxicology at Cornell University completed their evaluation in 1982 and subsequently a report was issued in January 1983, entitled: "A Toxicological Evaluation of Aldicarb and its Metabolites in Relation to the Potential Human Health Impact of Aldicarb Residues in Long Island Groundwater" (108). The Cornell document represents the most comprehensive and accurate discussion of the toxicology of aldicarb, and presents a novel "kinetic" approach for calculating on ADI. They applied this model directly to the available human data and concluded that "a reasonable range for the ADI of aldicarb/aldicarb metabolites would be 0.003 to 0.01 mg/kg, the currently accepted value of 0.003 mg/kg being the most conservative and upper value (0.01 mg/kg) being a dose that causes a depression of whole blood cholinesterase approximating the range of normal intra-individual variation".

Subsequently, in 1983 the Assistant Administrator for EPA formed an Aldicarb Review Committee whose membership was a cross-section of several offices within EPA, and chaired by Dr. J. Stara (Director, OHEA, Cincinnati). Discussions and evaluations of pertinent data and relevant scientific reviews (i.e. JMPR, Cornell University, NAS) were conducted. Although a formal report is, at this time, not yet available, the recommendation of the Committee was for an ADI for aldicarb and its sulfoxide metabolite of 0.0038 mg/kg/day. This ADI results from dividing the subchronic rat NOEL of 0.125 mg/kg/day

(Weil and Carpenter, 1968) by a 33-fold "uncertainty" factor. The 33-fold uncertainty factor represents an "intermediate" uncertainty factor between 10 and 100, and is consistent with previously established EPA guidelines in supporting intermediate uncertainty factors (U.S. EPA 1980, FR 45 No. 231, November 28, 1980, 79347).

EXPRESSION OF THE TOLERANCE/COMPATABILITY WITH CODEX

The expression of U.S. EPA tolerances for aldicarb is compatable with expression of Codex MRLs. That is, the limits are for the sum of aldicarb, its sulfoxide and its sulfone, determined as aldicarb sulfone and expressed as aldicarb.

U.S. TOLERANCES

Tolerances for aldicarb are established at 40 CFR 180.269 and include several commodities (RACs). See the computer printout which is appended.

004022

File last updated 11/1/82

ADI change not recorded per

ACCEPTABLE DAILY INTAKE DATA

RAT,Older NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
0.125	2.50	33	0.0038	0.2273

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Potatoes(127)	1.000	5.43	0.08140
Cottonseed (oil)(41)	0.100	0.15	0.00022
Peanuts(115)	0.050	0.36	0.00027
Sugar,cane&beet(154)	0.050	3.64	0.00273
Sweet Potatoes(157)	0.100	0.40	0.00060
Meat, red(90)	0.010	10.81	0.00162
Milk&Dairy Products(93)	0.002	28.62	0.00086
Oranges(108)	0.300	2.17	0.00975
Bananas(7)	0.300	1.42	0.00639
Beans,dry edible(10)	0.100	0.31	0.00047
Soybeans (oil)(148)	0.020	0.92	0.00028
Coffee(36)	0.100	0.75	0.00112
Pecans(118)	0.500	0.03	0.00023
Grapefruit(65)	0.300	0.99	0.00446
Lemons(82)	0.300	0.17	0.00078
Limes(85)	0.300	0.17	0.00078
Sorghum(147)	0.200	0.03	0.00009

MPI	TMRC	% ADI
0.2273 mg/day(60kg)	0.1120 mg/day(1.5kg)	49.30

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Unpublished,Tox Approved 7G1955,8H5193,8F2096

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Hops(73)	50.000	0.03	0.02250
Feed -- -(214)	1.000	0.03	0.00045
Tomatoes(163)	0.100	2.87	0.00431

MPI	TMRC	% ADI
0.2273 mg/day(60kg)	0.1393 mg/day(1.5kg)	61.29

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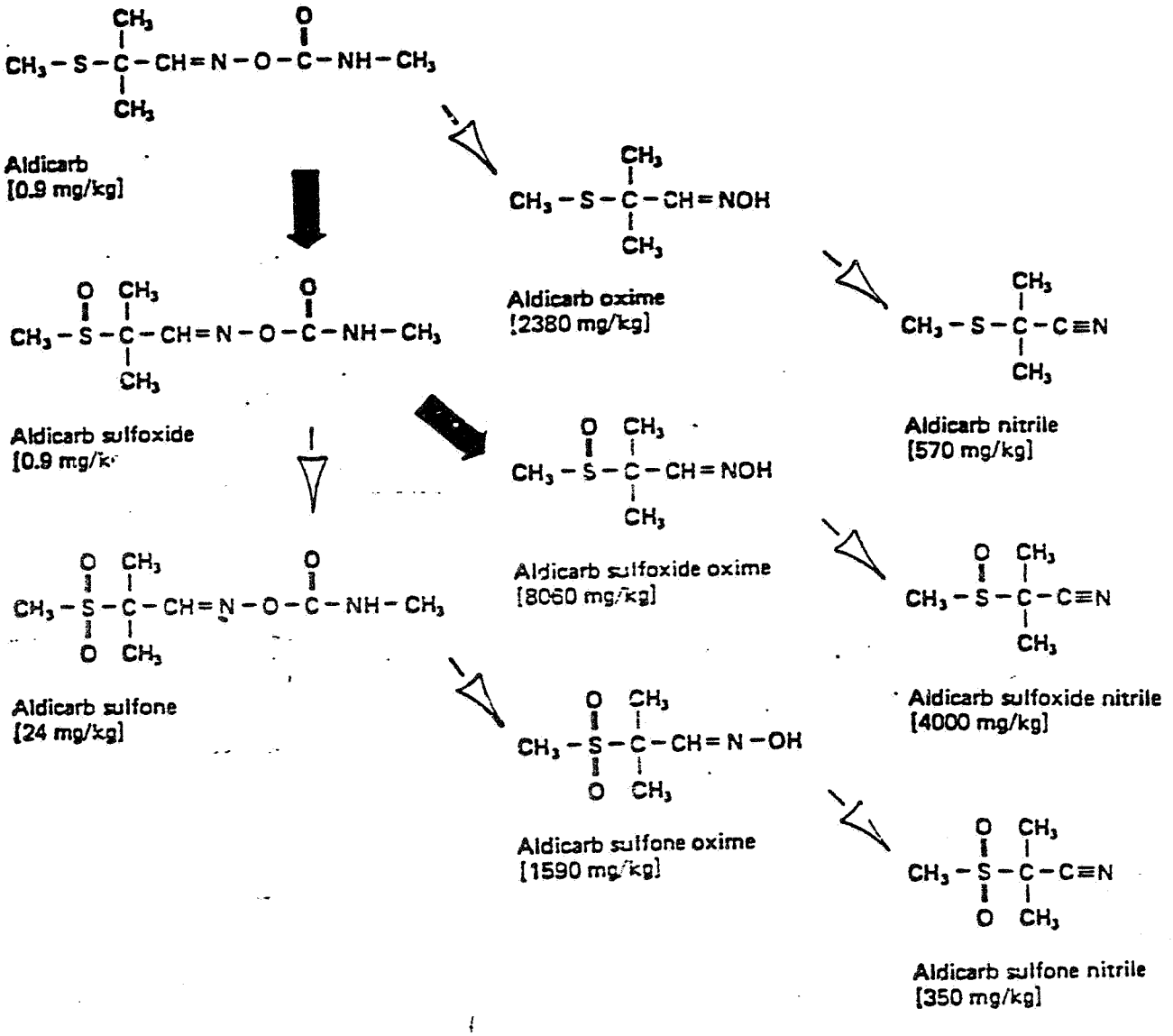
Current Action 2F2679

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Corn,all types(38)	0.050	2.51	0.00188
Poultry(128)	0.040	2.94	0.00177
Eggs(54)	0.020	2.77	0.00083

MPI	TMRC	% ADI
0.2273 mg/day(60kg)	0.1438 mg/day(1.5kg)	63.26

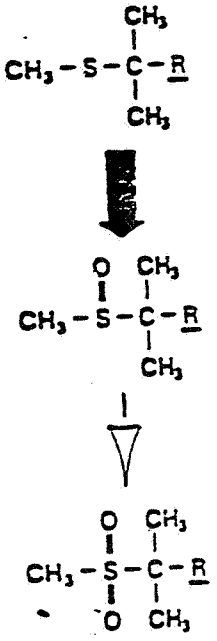
****

Figure 1. Metabolism of aldicarb. (Value in brackets is acute oral LD_{50} for rats.)



Footnote: Heavy dark arrow denotes major pharmacokinetic pathway.

Figure 2. Miscellaneous metabolites of aldicarb. (Value in brackets is acute oral LD_{50} for rats.)



R may be:

$-CH_2-OH$

alcohol-derivative
[> 11,000 mg/kg]

$-C(=O)-NH_2$

Amide derivative
[> 15,000 mg/kg]

$-CHO$

Aldehyde derivative

$-C(=O)-OH$

Acid derivative
[5700-7500 mg/kg]

Footnote: Heavy dark arrow denotes major pharmacokinetic pathway.

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c. Pesticide Petition #6G0473, G. E. Whitmore, Pesticide Review Branch, Div. of Toxicology. Memorandum 9/8/67.

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e. Memorandum of conference between EPA and Union Carbide dated 6/29/71 (Conference held 6/2/71).

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j. Memorandum: "Aldicarb in sugar beets," G. E. Whitmore, Div. of Regulation and Pesticide Control, Pesticide Petition #OF1008. 4/6/71.

	Design	
7-Day (Mouse) Weil, Woodside, Bernard 1974	Diet - 0, 0.15, 0.6, 2.4, 9.6, 38.4 mg/kg	Yes 00057339
	Results	
	Body wt. depressed at 38.4 Organ wt. - normal ChE not determined	
Long-term Studies		
	Design	
18-Month Onco. (Mouse) Woodside, et. al. 1977b	Diet - 0, 0.15, 0.6, 2.4, 9.6 mg/kg b. wt.	Yes 00100388 minimum
	Results	
	Body wt. - sporadic Gross/Micro - normal Not oncogenic NOEL = 9.6	
	Design	
2-Year Feeding (Rat) Weil, Woodside, Bernard, et. al. 1972	Diet - 0, 0.6, 2.4 mg/kg b. wt. ChE > 24 hrs.	Yes 00029943 minimum
	Results	
	Not oncogenic at 2.4	

Acute Oral LD_{50} (Rat) 21.4 mg/kg (M)

Aldicarb Sulfoxide: Aldicarb Sulfone (1:1)

Study/Author/Date	Brief Description	Copy of Report Available
	Design	
7-Day (Rat) Weil & Carpenter 1970d	Diet - 0, 1.2 mg/kg 7 week old rats	Yes 00053348
	Results	
	Growth depressed in females Liver/kidney - normal	
	Design	
29-Day Water Inclusion (Rat) Mirro, et. al. 1982	In drinking water - 0, 1.2, 4.8, 19.2 ppm ChE < 24 hrs.	Yes
	Results	
	No mortality Food/water consumption depressed at 19.2 (M/F) Body wt. depressed at 19.2 (M/F) Brain/RBC/Plasma ChE depressed at 19.2 NOEL = 4.8	
	Design	
2-Year Feeding (Rat) Weil, Woodside, Bernard, et. al. 1972	Diet - 0, 0.6, 1.2 mg/kg b. wt. ChE > 24 hrs.	Yes 00029943
	Results	
	Mortality, initially at 1.2 Growth depressed at 1.2 Hematocrit - normal Plasma ChE slight depression at 1.2 (M) Gross/Micro - normal Tumor incidence - no effect NOEL = 0.6	

Aldicarb: Aldicarb Sulfone (1:1)

Study/Author/Date	Brief Description	Copy of Report Available
	Design	
7-Day (Mouse) Weil & Carpenter 1970	Diet - 0, 2, 6, 18, 36 mg/kg	Yes 00053348
	Results	
	No mortality ChE severely depressed at 36 Growth depressed at 18 (Reduced b. wts. at all levels) Kidney wt. depressed at 36 Liver wt. depressed at 6 NOEL = 2	

Tox Chem No. 11A - Aldicarb | MRID # | File Last Updated 8/17/82 | Current Date

Study/Lab/Study #/Date	Material	~~EPA Accession No.~~	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grad Doc. No.
Mutagenic - Ames PH-301-OC-004-80 25 Day Inhalation - Dog Hazleton Lab. Project No. 400-636 4/9/82	Aldicarb Analytical Standard Treated field grown tobacco	00042482	50, 166, 500, 1666, 5000 ug/plate (+) metabolic activation Negative Tested at levels of 1x and 2x the label directions, which are equal to 3 or 6 lbs. active ingredient per acre No treatment related effects were reported		UNAcceptabl ~~001767~~ Supplemer tary 002165

11AA - Aldicarb Sulfone | MRID# | PI Date Updated 6/7/82 | Current Date

Study/Lab/Study #/Date	Material	~~EPA~~ Accession ~~No.~~	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic - Ames, Pharmakon, Lab, #PH 301-UC-004-80 6/20/80	Analytical Standard	(Acc # 243142) 00042482	Negative in stains TA1535, TA1537, TA1538, TA98 and TA100.		~~Guideline~~ Unacceptable
Mutagenicity - Ames PH 301-UC-003-80	Aldicarb Sulfone analytical standard	00042482	50, 166, 500, 1666, 5000 ug/plate (-) metabolic activation Negative		Unacceptable ~~001768~~

094022

Tox Chem No. 111A Aldoxycarb (Aldicarb Sulfone) EPA (MRID#)

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Oral LD_{50} - Rat Mellon Inst. #37-10 3/29/74	Technical Sample # 36-366	096728	LD_{50} 21.4 (14.5-31.7) mg/kg male rat in corn oil	I	Minimum 001375
Acute Dermal LD_{50} - Rat Mellon Inst. #37-49 3/28/74	Sulfone Technical 1-FSM-91	096728	LD_{50} 1000 (478-2090) mg/kg male rat in corn oil	II	Minimum 001375
Acute Dermal LD_{50} - Rabbit Mellon Inst. #37-49 5/28/74	Technical 1-FSM-91	096728	LD_{50} 193.9 (100-275-8) mg/kg (recalculated) male rabbit	I	Minimum 001375
Acute Inhalation LC_{50} - Rat Mellon Inst. #37-49 5/28/74	Technical 1-FSM-91	096728	LC_{50} > 0.13 mg/L/4 hr. (0.5% aerosol in H_2O) single dosage.	I	Supple-mentary 001375
Acute Oral LD_{50} - Rat Mellon Inst. #37-49 5/28/74	UC21865-75% WP 24-RZB-41	096729	LD_{50} = 23.8 (13.4-42.2) mg/kg. in H_2O males only (24 hr)	I	Minimum 001375
Acute Dermal LD_{50} - Rat Mellon Inst. #37-49 5/28/74	UC21865-75% WP 24-RZB-41	096728	LD_{50} = 1410 (354-5650) mg/kg in H_2O Male	II	Minimum
Acute Oral LD_{50} - Rat Mellon Inst. #37-49 5/28/74	UC21865-75% WP 24-RZB-41	096728	LD_{50} = 23.3 (15.8-34.5) mg/kg rat males in corn oil	I	Minimum 001375
Acute Oral LD_{50} - Rat Mellon Inst. #42-64 6/25/79	24-RZB-41 75WP	Microfisch	LD_{50} 37.5 (25.8-54) mg/kg female rat in H_2O	I	Minimum 001375
Acute Dermal LD_{50} Rat Mellon Inst. #37-49 5/28/74	24-RZB-41 75% WP	096729	LD_{50} 707 (763-1081) mg/kg male rat (4 hr)	II	Minimum 001375

4C1

Tox Chem No. 11A Aldicarb

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute Dermal LD_{50} - Rabbit Mellon Inst. #37-49 5/28/74	24-RZB-41 75% WP	096728	LD_{50} 1414 (648-3084) mg/kg Male rabbit 24 hr. in H_2O	II	Minimum 001375
Acute Inhalation LC_{50} - Rat Mellon Inst. #37-49 5/28/74	24-RZB-41 75% WP	096728	LC_{50} > 0.17 mg/L 4 hr. male rat LC_{50} > 0.17 mg/L 8 hr. aerosol 0.5% in H_2O	I	Supple- mentary 001375
Acute Inhalation LC_{50} - Rat Mellon Inst. #37-49 5/28/74	24-RZB-41 75% WP	096728	LC_{50} approx. 0.8 mg/L 1 hr. male rat dust LC_{50} < 0.15 mg/L 4 hr. male rat dust	II	Minimum 001375
Acute Inhalation LC_{50} - Rat Mellon Inst. #42-64 6/25/78	24-RZB-41 75 WP	Microfisch	LC_{50} 0.209 (.150-.291) mg/L 4 hr. male rat dust LC_{50} 0.271 (.196-374) mg/L 4 hr. female rat dust	II	Minimum 001375
9 Day Inhalation - Rat Mellon Inst. #40-29 3/16/77	UC21865-75WP 30-RZB-1	096728	ChE NOEL = < .0014 mg/L/6 hr./day/ 9 days (plasma inhibition) RBC NOEL = 0.006 mg/L/6 hr./day/ 9 days RBC LEL = 0.018 mg/L/6hr/day/ 9 days		Minimum 001375
26 Day Dermal - Rabbit Mellon Inst. #40-13 2/4/77	UC21865 99.75% Technical 28-RZB-40	096729	Systemic NOEL = 0.35% (7 mg/kg/day) (male) Systemic LEL = 0.7% (14 mg/kg/day) (reduction in body wt.) (male)		Minimum 001375
Delayed Neurotoxicity FDRL #5233 1/26/77	UC21865 Technical Sulfone CHP-37-524	096728	Negative for Delayed neurotoxicity after 2 LD_{50} doses. hen, chickens 2x 250 mg/kg 41 days (Single oral dose 21 days apart; ChE depressed; no histopath. exam.)		Minimum 001375

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
56 Day Feeding - Rat Mellon Inst. #38-115 9/18/75	UC21865 Technical 99.76%	096728	LEL = 16.2 mg/kg ChEI RCB & plasma, from both sexes rat. 19 hr. off test material NOEL = 2.4 mg/kg both sexes		Minimum 001375
3-6 Month Feeding - Rat Mellon Inst. #31-143 11/27/67	UC21865 22-WJB-77B	096728	3 Month systemic NOEL = 16.2 mg/kg ChEI LEL = 1.8 mg/kg plasma NOEL = 0.6 mg/kg ChEI RBC LEL = 1.8 mg/kg male NOEL = 0.6 mg/kg ChEI Brain LEL = 5.4 mg/kg male NOEL = 1.8 mg		Minimum 001375
			6 Month Reduced body wts. Systemic LEL = 16.2 mg/kg males ChEI LEL = 1.2 mg/kg females Plasma NOEL - 0.6 mg/kg RBC LEL = 1.8 mg/kg males & females NOEL - 0.6 mg/kg Brain LEL = 1.8 mg/kg males & females NOEL = 0.6 mg/kg		Minimum 001375
3 Month Feeding - Dog Mellon Inst. #31-142 11/1/68	Temik Sulfone 99.9% pure Sulfoxide free	096728	Systemic LEL = 5.4 mg/kg (wt loss) Systemic NOEL = 1.9 mg/kg See Report for ChE determinations		Minimum (Supp for ChE effects) 001375
18 Month Oncogenic - Mouse Mellon Inst. #40-38 3/25/77	Aldicarb Sulfone Technical 99.76% pure 0.24% Sulfoxide	096728	Negative for oncogenic effects at 9.6 mg/kg/day (HDT)		Minimum 001375

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism - Rat Mellon Inst. #31-130 10/15/68	S-methy ^{14}C Temik Sulfone 25-ORD-25	096728	No carcass C^{14} residue after 7 days 0.6% excreted as $^{14}CO_2$ 74.2% excreted in urine 1.8% excreted in feces metabolites not determined		Minimum 001375
Antidote - Rat Mellon Inst. #31-139 10/28/68	Temik Sulfone UC21865 30-LKP-176	096728	10 mg/kg iv atropine sulfate protected against 50 mg/kg (2 oral LD_{50}s)		Minimum 001375
Additive Toxicity Study Mellon Inst. #33-7 1/20/70	Temik Sulfone 99.9% free of sulfoxide	096728	Less than additive LD_{50} with parathion		001375
3-Generation Reproduction - Rat Mellon Inst. #40-1 1/11/77	Aldoxycarb 99.76% + 0.24% sulfoxide	096728	LEL = 9.6 mg/kg Lactation wt. loss males NOEL = 2.4 mg/kg NOEL = 9.6 mg/kg for reproductive effects (HDT)		Minimum ~~Supple-~~ ~~mentary~~ ~~001375~~
Teratology - Rat Mellon Inst. #40-1 1/11/77	Aldoxycarb Technical	096728	Teratogenic NOEL = 9.6 mg/kg (HDT) Maternal toxic NOEL = 2.4 mg/kg Maternal toxic LEL = 9.6 mg/kg		Minimum 001375
Dominant Lethal - Rat Mellon Inst. #40-1 1/11/77	Aldoxycarb Technical	096728	Invalid due to double male breeding of females		Invalid 001375
Primary Eye Irritation - Rabbit Mellon Inst. #38-87 7/21/75	Aldoxycarb WP 75	Microfisch	PIS = 0	IV	Minimum 001375
Sensitization - Guinea Pig Mellon Inst. #40-12 2/22/77	UC21865 Technical 78-JAD-43 UC21865 75WP 28-RZB-40	096729	Technical - negative PS =0 75WP - slight positive 24 hr. PS = 11.2 48 hr. PS = 4.8		Minimum 001375

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolites	Sulfocarb nitride Sulfone oxime Methane Sulfonic acid	096728	(Approx) LD_{50} = 0.35 mg/kg LD_{50} = 1.59 (0.97-2.59) g/kg LD_{50} = 0.28 (0.146-0.54) ml/kg 1:4 LD_{50} = 6.17 (4.57-8.33) g/kg		Supplementary 001375
Mutagenicity Pharmakon Lab. Scranton, PA 6/20/80	Aldicarb Sulfone Analytical Std.	243142	Ames tests with and without activation - negative		Unacceptable 001375
2 Year Feeding/ Oncogenic - Rat Mellon Inst. #35-82			Negative for oncogenicity at 2.4 mg/kg (HDT) NOEL = 2.4 HDT for system effects other than cholinesterase inhibition LEL = ? NOEL = ? for cholinesterase inhibition		Minimum 001375 Minimum 001375 Invalid 001375

11AA Aldicarb Sulfoxide

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Mutagenic - Ames PH 301-00-002-80	Aldicarb Sulfoxide analytical standard	00[illegible]/2481	50, 166, 500, 1666, 5000 ug/plate (+) metabolic activation Negative		UN Acceptable ~~001769~~

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k. Pesticide Petition #6E1792, R. Engler TB/RD, memorandum 9/8/76.

l. Pesticide Petition #8H5183, H. W. Spencer, TB/RD, memorandum 9/29/78.

m. Pesticide Petition #8F2096, H. W. Spencer, TB/RD, memorandum 1/29/79.

n. Pesticide Petition #9G2147, R. A. Gessert, TB/RD, memorandum 4/26/79.

o. Memorandum from DAA (E. Johnson, EPA) to Union Carbide (R. Back), 3/20/80.

p. Pesticide Petition #9F0798, G. E. Whitmore, Pesticide Review Branch, Div. of Toxicology. Memorandum 4/16/79.

q. Memorandum from DAA (E. Johnson, EPA) to Union Carbide (R. Oldford), 4/3/81.

r. Memorandum from AA (J.A. Todhunter, EPA) to Inspector General (Mr. M. Novick), 12/8/81.

s. Transcripts of the Proceedings of the Scientific Advisory Panel Hearings on Aldicarb, 2/1/80.

DCR-26434:TOX-35:Bruce/SharonLittle:9/2/83:CM#2-Rm816:557-3715

TABLE A

GENERIC DATA REQUIREMENTS FOR ALDICARB, A. SULFOXIDE, A. SULFONE

Data Requirement	Composition[1]	Use Patterns[2]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3]
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Oral LD_{50} - Rat	TGAI	A,B,E,F	Yes	See a. below	No
81-2 - Dermal LD_{50}	TGAI	A,B,E,F	Yes	See b. below	No
81-3 - Inhalation LC_{50} - Rat	TGAI	A,B,E,F	Yes	00073345, 00101943	No
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	A,B,E,F	Yes	00080699, 00100387	No
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding-Rodent, Non-rodent	TGAI	A,B,E	Yes	See c. below	No
82-2 - 21-Day Dermal	TGAI	A,B,E,F	Yes	See d. below	No
82-3 - 90-Day Dermal	TGAI	A,B,E,F	No		No
82-4 - 90-Day Inhalation - Rat	TGAI	A,B,E,F	No		No
82-5 - 90-Day Neurotoxicity - Hen/Mammal	TGAI	A,B,E,F	No		No

1/ Composition: TGAI = Technical grade of the active ingredient.

2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.

3/ Data must be submitted no later than _____.

a. 00060194, 00069745, 00100382, 00069922, 00053342, 00057333, 00030423, 00035372, 00049330, 00100386, 0010389, 00054410, 00035376, 00100390, 00053343, 00035375, 00100391, 00101917, 00079566, 00053341, 00080698, 00061087, 00054442, 00100392, 00102070, 00044739, 00055536, 00029295, 00100393, 00080710, 00028645, 00028646, 00028647, 00100384, 00057332, 00091241, 00080708,

b. 00030424, 00030425, 00055535, 00060195, 00102143, 00069919, 00080811, 00101914, 00035378, 00055537, 00035370, 00035371, 0510121.

c. 00057337, 00100381, 00069917, 00044737.

d. 0510121, 00058632, 00080701, 00080825.

TABLE A

GENERIC DATA REQUIREMENTS FOR ALDICARB, A. SULFOXIDE, A. SULFONE

Data Requirement	Composition[1/]	Use Patterns[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§158.135 Toxicology (continued)					
CHRONIC TESTING:					
83-1 - Chronic Toxicity - 2 species: Rodent	TGAI	A,B,E	Yes	See a. below	No
and Non-rodent	TGAI	A,B,E	Yes	Weil, 1966	No
83-2 - Oncogenicity Study - 2 species: Rat and	TGAI	A,B,E	Yes	NIH, 00029943	No
Mouse preferred	TGAI	A,B,E	Yes	See b. below	No
83-3 - Teratogenicity - 2 species	TGAI	A,B,E,F	Partially	Woodside 1977, 00058631	Yes (Rabbit)[c]
83-4 - Reproduction, 2-generation	TGAI	A,B,E	Yes	Woodside 1977, 00069918, 00044736	No
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A,B,E	Yes	00042482, 00079923, 00073207	No
84-2 - Chromosomal Aberration	TGAI	A,B,E	No		Yes[d]
84-2 - Other Mechanisms of Mutagenicity	TGAI	A,B,E	Partially	00044736	Yes[d]

1/ Composition: TGAI = Technical grade of the active ingredient.

2/ The use patterns are coded as follows: A= Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aquatic, Food Crop; D=Aquatic, Non-Food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=domestic Outdoor; I=Indoor.

3/ Data must be submitted no later than _____.

a. 00057340, 00053350, 00029943, 00060196, Weil 1965.

b. NIH, 00081413, 00044732, 00044733, 00044734, 00100388.

c. Received by TB but not yet reviewed.

d. See 40 CFR§§158.105 and 158.135 (FR 47 No. 227, 11/24/82 and FR 48 No. 12, 1/18/83) for additional Mutagenicity data required.

TABLE A
GENERIC DATA REQUIREMENTS FOR ALDICARB, A. SULFOXIDE, A. SULFONE

Data Requirement	Composition[1/]	Use Patterns[2/]	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?[3/]
§158.135 Toxicology (continued)					
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	A,B,E,F	Yes	See a. below	No
85-2 - Domestic Animal Safety	Choice	A,B	Yes	00035380, 00075794, 00080812, 00060554, 00101921, 00035377	No

1/ Compostion: PAI = Pure active ingredient; PAIRA = Pure active ingredient, radiolabelled; Choice = Choice of several test substance determined on a case-by-case basis.
2/ The use patterns are coded as follows: A=Terrestrial, Food Crop; B=Terrestrial, Non-Food; C=Aqautic, Food Crop; D=Aquatic, Non-food; E=Greenhouse, Food Crop; F=Greenhouse, Non-Food; G=Forestry; H=Domestic Outdoor; I=Indoor.
3/ Data must be submitted no later than _____.

a. 00102023, 00080709, 0035372, 00081414, 00080813, 05008717, 00028644

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Aldicarb:

Study/Author/Date	Brief Description	Copy of Report Available
3-Gen. Reproduction (Rat) Weil & Carpenter 1964	Design 0, 0.05, 0.1 mg/kg b.w. in the diet for 90 days, then mated; 3-Gen./1 litter per gen. Results Micro - normal (only the lesions found were reported). No pup anomalies or abnormalities. NOEL = 0.1 mg/kg	Yes 00069918 minimum
3-Gen. Reproduction (Rat) Weil & Carpenter 1974a	Design 0, 0.2, 0.3, 0.7 mg/kg b.w. in diet. 3-Gen./1 litter per gen. Results Decreased b. wt. of F_2 pups (M/F) at 0.7 No other effects. NOEL = 0.7 mg/kg	Yes 00044736 minimum
Teratology (Rat) Weil & Carpenter 1966a	Design 0, 0.04, 0.2, 1.0 mg/kg b. wt. in the diet. (a) day 0 "to" wean (b) day 0 "to" day 7 (c) day 5 "to" day 15 Results Body weight normal. NOEL = 1.0 mg/kg	Yes 00058631 minimum

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Neurotoxocity (Hen)
Johnson & Carpenter
1966a

Design

(a) Single oral 4.5 mg/kg b. wt. Yes
(b) Daily oral 0, 2.25, 4.5, 9 00080699
mg/kg b. wt. (for 30 days). Minimum
(c) LD_{50} = 9 mg/kg

Results

9 mg/kg - death 4/6; no ataxia
some weight loss;
acute signs of
poisoning.
Not neurotoxic at 4.5 mg/kg
based on "observed symptomatology".

Short-term Studies:

Design

7-Day (Rat)
Weil & Carpenter
1970d

Diet - 0, 4, 8, 16 mg/kg b. wt. Yes
6 week old rats.

Results

Mortality at 8 & 16
B. wt. decrease at all levels.
Males - kidney wt. decrease at 8
liver wt. decrease at 4,
and 8.
Females - kidney/liver wt. decrease
at all levels.

Design

7-Day (Rat)
Weil & Carpenter
1969b

Diet - 0, 0.8, 1.6, 3.2 mg/kg (Possibly
b. wt. in PM
7 week old rats. files)

Results 00035379

No mortality.
B. wt. decrease at 1.6.
Males - kidney wt. decrease at
all levels.
- liver: body wt. decrease
at all levels.
Females - liver: body wt. decrease
at 1.6.
kidney wt. decrease at
3.2.
ChE > 24 hr. (However, plasma
decrease at 3.2).

7-Day (Rat) Nycum & Carpenter 1968	Design Diet - 0, 0.4, 0.8, 1.6, 3.2 mg/kg b. wt. Results Body wt. decrease at 3.2 No effect on liver or kidney. RBC ChE decreased at 3.2. ChE < 24 hr. NOEL = 0.8 (ChE)	(Possibly in PM file) 00100384
7-Day (Rat) Weil, Carpenter, Woodside, Bernard, et. al. 1970	Design Diet - 0.3 mg/kg b.wt. Results No effect on growth in males. Female body wt. decreased. Male - no effect on liver/kidney. Female - liver wt. decrease. ChE > 24 hrs.	Yes
7-Day (Mouse) Weil & Carpenter 1970c	Design Diet - 0, 0.1, 0.3, 0.6, 1.2 mg/kg b. wt. Results Mortality at 1.2 Growth - no change Liver/kidney wt. - no change ChE not determined	Yes
7-Day (Dog) Weil & Carpenter 1973	Design Diet - 0, 0.2, 0.3, 0.7 mg/kg b. wt. Results No mortality Gross liver/kidney wts. - no effect ChE > 24 hours - Normal NOEL = 0.7	Yes 00060197

0040

99-100 Day (Dog) Weil & Carpenter 1974b	Design Diet - 0, 0.2, 0.3, 0.7 mg/kg b. wt. Results No mortality Growth - no effect No effect on females Males - testes wt. decrease, adrenal wt. increased at 0.7 No microscopic changes ChE > 24 hrs (normal) NOEL = 0.3	Yes 00044737 minimum
93-Day (Rat) Weil, Woodside, Bernard, et.al. 1963	Design Diet - 0, 0.02, 0.1, 0.5 mg/kg b. wt. (non-uniform dispersion of aldicarb in the diet) Results Mortality increased at 0.5 Body wt./Food Consump. decrease at 0.5 Rel. Liver/kidney wts. - normal Histopath. - normal Plasma ChE decrease at 0.5 ChE > 24 or < 24 hrs ? (unknown) NOEL = 0.1	Yes 00069917 minimum
Long-term Studies		
2-Year Feeding (Rat) Weil & Carpenter 1965	Design Diet - 0, 0.005, 0.025, 0.05, 0.1 mg/kg b. wt. Results No mortality Growth - no effect Liver/kidney wts. - normal Hematology - normal Histopath. - normal ChE > 24 hrs. NOEL = 0.1 mg/kg b. wt. (HDT too low - another test run)	(Possibly in PM files) Supplementary

004022

	Design	
2-Year Feeding (Rat) Weil & Carpenter 1972a	Diet - 0, 0.3 mg/kg b. w.t. Results No mortality Growth - normal Hematology - normal ChE > 24 hrs (male, plasma decreased) Not oncogenic NOEL = 0.3	Yes 00029943 Minimum
	Design	
2-Year Onco. (Rat) NIH, 1979	Diet - 0, 2, 6 ppm [Also: 13 wks 0, 5, 10, 20, 40, 80, 160, 320 ppm - micro exam. of 0 and 80 - no differences] Results No mortality Not carcinogenic in F344 rat at 6 ppm (0.3 mg/kg)	Yes Minimum
	Design	
2-Year Feeding (Dog) Weil & Carpenter 1966c	Diet - 0, 0.025, 0.05, 0.1 mg/kg, day; Dogs 8-20 months old Results No mortality Growth - normal Hematology - normal ChE - normal (ChE > 24 or < 24 hr ? unknown) Gross, micro - normal NOEL = 0.1	Possibly in PM files Minimum

	Design	
2-Year Onco. (Mouse) NIH, 1979	Diet - 0, 2, 6 ppm [Also: 13 wks 0, 0.5, 1.0, 2.5, 5, 10, 20, 40 ppm - micro of 0, 20, 40 ppm - normal]	Yes minimum
	Results	
	No mortality Not carcinogenic in B6C3F1 mouse at 6 ppm (0.9 mg/kg)	
	Design	
18-Month Feeding (Mouse) Weil & Carpenter 1972c	Diet - 0, 0.1, 0.2, 0.4, 0.7 mg/kg b. wt. CD-1 mice	Yes 00044732 minimum
	Results	
	Mortality at 0.4 and 0.7 in females because of improper mix of aldicarb in the diet resulted in consumption of small crystalline particles of aldicarb. Hepatomas increased in male survivors at 0.7. Lymphoid neoplasia in males which died at 0.7. NOEL = 0.4	
	Design	
18-Month (Mouse) "Confirmatory Test" Weil & Carpenter 1974d	Diet 0, 0.1, 0.3, 0.7 mg/kg b. wt. CD-1 mouse	Yes 00044733 minimum
	Results	
	No mortality Growth - normal Tumor incidence - no effect (particularly hepatomas, lung adenomas, lympnoid neoplasias) Not oncogenic NOEL = 0.7	

Humans:

	Design	
Single Oral Haines 1971	Single oral aqueous solutions of 0.025, 0.05, 0.1 mg/kg b. wt.; Adult males (4/dose level); ChE measured up to 6 hrs post treatment	Yes 0010911
	Results	
	Acute signs of ChE depression at 0.1 within 1 hr. No signs at 0.05 ChE decreased in all volunteers within 1-2 hrs. Complete reversal within 6 hrs.	
	Design	
Single Oral Cope/Romine 1973	Single oral aqueous solutoins of 0.05, 0.26 mg/kg b. wt. Adult males (2)	(Possibly in PM files)
	Results	
	Acute signs of ChE depression at 0.26 No signs of ChE depression at 0.05	

Acute Oral LD_{50}	(Rat)	0.6	1.2 mg/kg	(0.84) M/F
	(Mouse)	0.38	1.5 mg/kg	M/F

Aldicarb Sulfoxide

Study/Author/Date	Brief Description	Copy of Report Available
Short-term Studies		
7-Day (Rat) Nycum & Carpenter 1968b	**Design** Diet - 0, 0.4, 0.8 mg/kg b. wt. **Results** Body wt. decrease at 0.8 Liver/kidney wt. - no effect RBC ChE decrease at 0.8 NOEL = 0.4	(Possibly in PM files) 00100384
7-Day (Rat) Weil & Carpenter 1970d	**Design** 7 week old rats (2 different strains - (a) and (b) Diet - 0.4, 0.8, 1.6 mg/kg b. wt. Che > 24 hr. **Results:** Strain (a) ChE - normal Growth decreased at 0.8 (Males/Females) Liver/kidney wts decreased at 1.6 Strain (b) Growth decreased at 0.8 Liver/kidney wt. - normal RBC ChE - normal	Yes 00053348

Acute Oral LD_{50} (Rat) 0.49 1.13 mg/kg (M/F)1

	Design	
*6-Month Feeding (Rat) Weil & Carpenter 1968b	Diet - 0, 0.125, 0.25, 0.5, 1.0 mg/kg b. wt. ChE determined < 24 hrs. and > 24 hrs. 15M/15F per group	Yes 00100331 Minimum
	Results	
	No mortality Growth depressed at 0.25 (males) Growth depressed at 1.0 (females) ChE depressed (plasma, RBC) at 0.25 (males) ChE depressed (plasma, RBC) at 0.5 (females) Liver/kidney - normal NOEL = 0.125	
	Design	
56-Day Feeding (Rat) Weil, Woodside, Peterson, et.al. 1975	Diet - 0.3, 1.0 mg/kg b. wt. ChE > 24 or < 24 hrs. ? (unknown)	Yes 00057341 Minimum
	Results	
	2/30 deaths at 1.0 (only 2/360 died throughout the study) Body wt. depressed at 1.0 1st week ChE depressed at 1.0 (plasma/RBC - marginal) NOEL = 0.3 "to" 1.0 (very sporadic results)	

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* Used as basis for the ADI

	Design	
3-6 Month Feeding (Rat) Weil & Carpenter 1968b	Diet - 0, 0.0625, 0.125, 0.25, 0.5, 1.0 mg/kg b. wt. ChE determined < 24 hrs. 5M/5F per group	Yes 00100381 minimum
	Results	
	Brain ChE - no effect Plasma/RBC ChE depressed at 0.25 (male) Plasma/RBC ChE depressed at 0.5 (female) (89% ChE depression completely reversed in 24 hrs.) NOEL = 0.125	
	Design	
90-Day Feeding (Dog) Weil & Carpenter 1968b	Diet - 0, 0.0625, 0.125, 0.25, 0.5 mg/kg b. wt. ChE > 24 hrs. 3M/3F per group	Yes 00100381 minimum
	Results	
	No mortality Body wt. slight depression at 0.5 Hematology/Blood Chem. - normal ChE - normal Gross/Micro - normal NOEL = 0.25	
Long-term Studies		
	Design	
2-Year Feeding (Rat) Weil & Carpenter 1972a	Diet 0, 0.3, 0.6 mg/kg b. wt. ChE > 24 hrs.	Yes 00029943 minimum
	Results	
	Slight increase in mortality at 0.6 Growth - normal Plasma ChE depressed in males at 0.6 Gross/Micro - normal Tumor incidence - no difference NOEL = 0.3	

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Aldicarb Sulfone

Study/Author/Date	Brief Description	Copy of Report Available
	Design	
3-Gen. Reproduction (Rat) Woodside et. al. 1977a	Diet - 0, 0.6, 2.4 and 9.6 mg/kg b. wt. for 100 days, then mated 3-Gen./1 litter per gen.	Yes minimum
	Results	
	Body wt. decrease in males at 9.6 ChE depressed at 9.6 No effects on reproduction up to and including 9.6 (marginal effects on lactation - pup survival decreased at 9.6) NOEL = 2.4	
	Design	
Teratology (Rat) Woodside et. al. 1977a	Oral - 0, 0.6, 2.4, 9.6 mg/kg at one of the following intervals: (a) day 0 "to" day 20 (b) day 6 "to" day 15 (c) day 7 "to" day 9	Yes minimum
	Results	
	Maternal tox. at 9.6 - diarrhea, ChE depression Not teratogenic at 9.6	
Short-term Studies		
	Design	
7-Day (Rat) Nycum & Carpenter 1968b	Diet - 0, 0.4, 1.0, 2.5, 5, 20 mg/kg b. wt. ChE > 24 hrs ? (unknown)	(Possibly in PM files) 00100334

004022

	Results Growth depressed at 20 Gross liver/kidney - no effect Plasma/RBC ChE depressed at 5 Brain ChE depressed at 20 (M/F) NOEL = 2.5	
	Design	
7-Day (Rat) Weil & Carpenter 1970d	Diet - 0, 0.6, 5, 20 mg/kg b. wt. Two strains of 7 week old rats ChE > 24 hrs.	Yes 00053348
	Results Strain (a) and (b): (a) Growth depressed at 5 for males Growth depressed at 0.6 for females Liver/kidney wt. depressed at 20 ChE - normal (RBC) (b) Growth depressed at 5 Liver/kidney wt. depressed at 20 ChE - normal (RBC)	
	Design	
56-Day Feeding (Rat) Weil, Woodside, Peterson, et. al. 1975	Diet - 0, 2.4, 16.2 mg/kg b. wt. ChE > 24 or < 24 hrs. ? (unknown)	Yes 00057341 minimum
	Results No mortality Body wt. depresed at 16.2 ChE depressed at 16.2 (plasma/RBC) NOEL = 2.4	
	Design	
6-Month Feeding (Rat) Weil & Carpenter 1968c	Diet - 0, 0.2, 0.6, 1.8, 5.4, 16.2 mg/kg b. wt. ChE < 24 and > 24 hrs. 15M/15F per group	Yes 00057337 minimum

	Results No mortality Growth depressed at 16.2 Liver/kidney micro - normal RBC/Plasma ChE depressed at 1.8 Brain ChE depressed at 5.4 No ChE depression at 0.6 (at 5.4 all ChE depression returned to normal in 24 hrs.) NOEL = 0.6	
	Design	
3-Month Feeding (Rat) Weil & Carpenter 1968c	Diet - 0, 0.2, 0.6, 1.2, 1.8, 5.4, 16.2 mg/kg b. wt. ChE < 24 and > 24 hrs. 5M/5F per group	Yes 00057337 minimum
	Results Plasma ChE depressed at 1.8 RBC ChE depressed at 5.4 Brain ChE depressed at 16.2 NOEL = 1.2	
	Design	
90-Day Feeding (Dog) Weil & Carpenter 1968c	Diet - 0, 0.2, 0.6, 1.8, 5.4 mg/kg b. wt. ChE > 24 hrs.	Yes 00057337 minimum
	Results No mortality Body wt. depressed at 5.4 (not statistical) Hematol./Blood Chem - normal Gross/Micro - normal NOEL = 1.8	
	Design	
Neurotoxicity (Hen) Babish & Salerno 1977	40 hens intubated with 250 mg/kg b. wt. Single oral doses 21 days apart	Yes 00100387 minimum
	Results Che depressed Not neurotoxic (no histopath. exam.)	