Aldicarb

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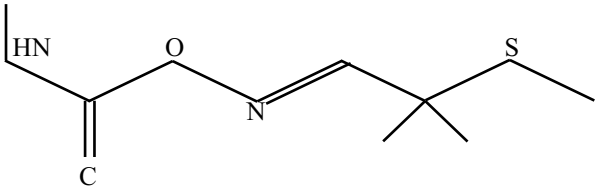
I. IDENTIFICATION

Chemical Name: 2-Methyl-2-(methylthio) propionaldehyde o-(methylcarbamoyl)-oxime
Synonyms: Aldicarbe; 2-Methyl-2-(methylthio) propanal O-[(methylamino) carbonyl] oxime; Carbamic acid, methyl-, O- ((2-methyl-2-(methylthio) propylidene)amino); ENT 27093; OMS 771;
Union Carbide 21149; UC-21149
CAS Number: 116-06-3
Chemical Family: Oxime carbamate
Molecular Formula: $C_7H_{14}O_2N_2S$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1–11]

Physical State and Appearance: White to colorless crystalline solid
Odor Description: Odorless or slight sulfurous smell
Molecular Weight: 190.23
Conversion Factors: 1 mg/m^3 = 0.13 ppm
1 ppm = 7.8 mg/m^3
Melting Point: 98°C–10l°C (208°F–214°F)
Boiling Point: Decomposes before boiling, above 100°C
Vapor Pressure: 0.0001 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 0.13 ppm at 25°C (77°F)
Flash Point (open-cup): 170°C (338°F)
Autoignition Temperature: 360°C (680°F)
Specific Gravity: 1.195 at 25°C (77°F)
Other Solubility: 350 g/L in acetone and chloroform; 250 g/L in ethanol; 200 g/L in isopropane and ethyl ether; 150 g/L in chlorobenzene; 100 g/L in toluene, DMSO, and ethanol; 50 g/L in xylene
Solubility in Water: 4.93–6 g/L at 25°C (77°F)
Stability: Stable under ambient conditions
Reactivity and Incompatibilities: Unstable in strong alkali solutions; reacts with strong oxidizing agents. When heated, aldicarb emits oxides of nitrogen and sulfur. Combustion products are expected to be moderately to highly toxic.
Octanol-water partition coefficient (log P_{ow}) = 0.7–1.36

III. USES

Aldicarb (marketed as a diluted solid formulation under the trade name Temik®) is a systemic pesticide used to control mice, aphids, and nematodes. It is applied below the soil surface for absorption by the plant root systems, or alongside plants once they have emerged.[1,5,11–13]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Oral Toxicity

Mouse	LD_{50}: 0.3–1.6 mg/kg[14–18]
Rat:	LD_{50}: 0.5–1.19 mg/kg[7,14–16,19,20]
Rabbit	LD_{50}: 1.3 mg/kg[14]

2. Eye Toxicity and Irritation

Aldicarb produced signs of acetylcholinesterase (AChE) inhibition and death within 15 minutes when 0.1 mL of a 25% suspension in propylene glycol was instilled into rabbit eyes. Instillation of 0.5 mL of a 15% suspension in propylene glycol caused death within 30 minutes, and of 0.5 mL of a 5% suspension in propylene glycol within 48 hours (1 of 2 animals). As a 25% solution in dimethyl phthalate, 0.05 mL aldicarb caused death within one hour. A 1% solution in dimethyl phthalate was not lethal (additional details unavailable). Instillation of 10 mg of aldicarb wettable

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powder caused anticholinesterase symptoms after 8 minutes, and death after 30 minutes. Neither aldicarb technical-grade nor aldicarb wettable powder produced any evidence of corneal irritation. However, eyes were pale and had pinpoint pupils after instillation.[15]

In a separate study, instillation of 25 mg aldicarb into the eyes of rabbits caused conjunctival irritation in all test animals, which lasted for 24 hours.[10] A solution of Temik® 5G [0.5% w/w (5 g/kg) aldicarb] caused transient conjunctival irritation, but was not otherwise irritating to the rabbit eye.[14]

It was reported that aldicarb is not irritating to the eye.[18] However, a manufacturer states that undiluted aldicarb is a lachrymator.[7]

3. Dermal Toxicity

Rat: LD_{50}: >10 mg/kg; 4-hr exposure in corn oil[14]

Rabbit: LD_{50}: >20 mg/kg; 24-hr application in water[14]

LD_{50}: 5.0 mg/kg; 24-hr application as a 5% solution in propylene glycol[15]

LD_{50}: 283 mg/kg; as a 15% dry powder[21]

Aldicarb is absorbed rapidly through the skin when administered in oil or other organic solvents. Its skin toxicity is roughly 1000 times that of other carbamate pesticides.[22] However, dermal toxicity is highly variable, depending on the vehicle used.[18]

4. Dermal Irritation

Aldicarb is not irritating to rabbit skin, even at lethal doses.[14,15]

5. Dermal Sensitization

Intradermal injection of 0.7 mg/kg aldicarb in saline, and of a solution containing 75% Aldicarb wettable powder (modified Lansteiner test], did not cause any sensitization reactions in guinea pigs.[10,14] Additionally, Temik® 150G [15% w/w (150 g/kg) aldicarb] is reported by the manufacturer to be non-sensitizing.[21]

6. Inhalation Toxicity

Rat: LC_{50} (4-hr): 3.9 mg/m^3 as a solution in dichloromethane

All deaths occurred within 24 hours of dosing. Clinical signs of toxicity included ataxia, tremors, hypoactivity, increased respiratory rate, lacrimation, exophthalmos, and red periocular encrustration. Other signs seen at lower concentrations or post-exposure were perioral/periocular/perinasal wetness, discolored and unkempt fur, hypoactivity, slow mid-air righting reflex, abdominal breathing, and decreased respiratory rate. All signs were reversible. Principal findings upon necropsy were discolored lungs, periocular encrustration and staining, and lenticular and corneal opacity.[23]

Aldicarb wettable powder administered at a concentration of 6.7 mg/m^3 active (13.3 mg/m^3 of the formulation) caused death in 5 of 6 female rats following a 30-minute exposure, but was not lethal after a 15-minute exposure. Four of the 5 deaths after the 30-minute exposure occurred during the exposure period. Necropsy of animals that died on study revealed petechial hemorrhage of the lungs and traces of blood in the intestines. Anticholinesterase symptoms were observed after 30 minutes of exposure, but not after 15 minutes.[15]

"Substantially saturated vapors" of aldicarb wettable powder, evolved under static conditions at room temperature, were not lethal to female rats after 8 hours of exposure.[15]

B. Subacute Toxicity

No effects were observed in a range-finding study in which aldicarb (0.5% in acetone) was topically applied to the hair-free backs of 5 C3H/HeJ mice, 5 times a week for 2 weeks.[24]

C. Subchronic Toxicity

Groups of young adult Wistar rats (10/group/sex) were exposed to 0, 0.075, 0.3, 1, 2, 4.8, and 19.2 ppm aldicarb in drinking water for 29 days. Animals were tested at weekly intervals for changes in body weight/food consumption, and plasma and erythrocyte AChE activity was measured on Days 8, 15, and 29; brain AChE levels were measured at study termination. Body weight gain and water consumption were reduced at 19.2 ppm, at all time points. Food consumption was decreased in high-dose males at all time points, but only on Day 7 in females. Plasma and erythrocyte AChE activity was also reduced at all time points at 19.2 ppm. A No Observed Effect Level (NOEL) was not identified in this study.[25]

Groups of ten CFE rats/sex were administered aldicarb in the diet at dose levels of 0, 0.02, 0.1, or 0.5 mg/kg/day, for a maximum of 93 days.

Mortality was increased at the top dose. Also, a decrease (not statistically significant) in plasma cholinesterase was noted in high-dose females only; these animals also exhibited a decrease in food consumption. There were no histopathological changes or other toxicologically relevant findings at any dose. A No-Observed-Adverse-Effect Level (NOAEL) of 0.1 mg/kg/day was identified in this study.[26]

Groups of four Beagle dogs/sex received 0, 0.2, 0.3, or 0.7 mg/kg/day aldicarb for 99 or 100 days. Animals were evaluated for changes in body weight, organ weight, serum chemistry including erythrocyte, plasma and brain cholinesterase, hematology, urinalysis, and gross histopathology. There were no deaths observed. In male animals, there was a slight increase in absolute adrenal and relative testicular weights, without histopathological correlates. No other effects of toxicological concern were seen at any dose tested, and there were no statistically significant differences in mean brain AChE levels across the treatment groups. A NOAEL of 0.3 mg/kg/day was identified in this study.[27]

A 6-hr application of a moistened Temik® formulation to the abraded skin of male rabbits at doses of 5, 10, and 20 mg/kg/day for 15 days caused plasma AChE inhibition at the two highest doses as well as decreased body weight gain at all doses. However, dry applications of 20 mg/kg to intact skin, using the same dosing regimen, caused no treatment-related effects.[14]

D. Chronic Toxicity/Carcinogenicity

CD-1 mice (44/sex/group) were exposed in the diet to 0, 0.1, 0.2. 0.4, or 0.7 mg/kg/day aldicarb for 18 months. During the first three months of the study, mortality was increased in females at ≥ 0.2 mg/kg/day and in all animals at ≥ 0.4 mg/kg/day. As a result, the compound was subsequently dissolved in acetone (to increase dispersion) prior to mixing it with feed, after which survival rates were unaffected by treatment. A statistically significant increase in hepatomas compared with controls was seen in males at 0.1 and 0.7 mg/kg/day, but not at 0.2 or 0.4 mg/kg/day. There was also an increase in lymphoid neoplasias in males, at 0.7 mg/kg/day.[28] To better understand these findings, a follow-up 18-month study was conducted using 50 male mice/group, at dose levels of 0, 0.1, 0.3, and 0.7 mg/kg/day aldicarb dissolved in acetone. In this study, there was no increase in mortality and no increase in liver or lymphoid neoplasms was observed at any dose level (NOAEL = 0.7 mg/kg/day). The authors attributed the findings seen in the initial study to uneven test compound concentrations in the dry dietary admixture used for the first 3 months.[29]

Rats (20/sex/dose) were administered aldicarb in the diet at levels corresponding to 0, 0.005, 0.025, 0.05, or 0.1 mg/kg/day for 2 years. There were no toxicologically significant clinical or histopathological findings at any dose, and no treatment-related increases in neoplasms were seen; a NOAEL of ≥ 0.1 mg/kg/day was identified.[30]

F344 rats and B6C3F1 mice (50/group/sex) were administered aldicarb in the feed at levels of 2 to 6 ppm (equivalent to 0.1 to 0.3 mg/kg/day for rats, or 0.3 to 0.9 mg/kg/day for mice) for at least 103 weeks. No toxicological effects were observed in the treated animals compared with controls. In this assay, aldicarb exhibited no evidence of carcinogenicity to rats and mice.[14, 31]

Beagle dogs (5/sex/group) were administered concentrations of 1, 2, 5, or 10 ppm aldicarb in the diet, for one year. These concentrations correspond to dose levels of approximately 0, 0.03, 0.05, 0.13, or 0.24 mg/kg/day. Although decreased plasma cholinesterase was measured at all doses, no clinical signs were observed that could be definitely linked to treatment. A NOEL was not identified for this study.[32]

A 2-year study was conducted using Beagle dogs (3/sex/dose) at dietary levels corresponding to 0, 0.025, 0.05, or 0.1 mg/kg/day aldicarb. There were no toxicologically significant clinical or histopathological findings at any dose, and no treatment-related increases in neoplasms were seen; a NOAEL of 0.1 mg/kg/day was identified.[33]

Aldicarb (0.25% in acetone) was topically applied to the hair-free backs of 40 C3H/HeJ mice, three times a week for the first half-month and twice a week thereafter for the lifetime of the animals. Due to excessive mortality, the concentration was reduced to 0.125% after the first 2 months. No increased incidence of tumors was observed.[25]

A transplacental host-mediated hamster cell culture assay was conducted in which cultured fetal cells (5 or 6 passages) obtained from pregnant hamsters receiving single intraperitoneal injections of 0.01 or 0.05 mg/kg aldicarb on Gestation Day 10 were injected subcutaneously into young adult nude mice. No evidence of cell transformation in culture or of tumor induction in mice was observed.[34]

The International Agency for Research on Cancer (IARC) classified aldicarb as a Group 3 agent (not classifiable as to its carcinogenicity in humans),

based on inadequate data in animals and a lack of human data.[35]

E. Reproductive/Developmental Toxicity

Aldicarb was administered to pregnant female Dutch Belted rabbits (16/group) at 0, 0.1, 0.25, or 0.5 mg/kg/day via gavage on Gestation Days 7–27. Does at the two highest doses exhibited decreased body weights, pale kidneys and hydroceles on the oviducts. Although all treatment groups showed a statistically significant reduction in number of implantations and in fetal viability, values were within the range of historical controls. No fetal malformations were observed in this study. NOELs of 0.5 mg/kg for both fetal effects and maternal toxicity, and a NOEL of 0.25 mg/kg/day for "overall developmental toxicity," were identified in this study.[32]

Aldicarb was administered to CD rats at 0, 0.125, 0.25, or 0.5 mg/kg/day via gavage on Gestation Days 7–15. Decreased body weights and food consumption were observed in the dams at the two highest doses; at 0.5 mg/kg/day, mortalities were seen. At the top dose, there was a significant decrease in fetal body weight, along with an increased incidence of dilated lateral ventricles in the brain and poor ossification of the sixth sternal vertebrae. At ≥ 0.25 mg/kg/day, ecchymoses (small hemorrhages) of the trunk were seen. NOAELs of 0.125 mg/kg/day were identified for both maternal and fetal toxicity.[32]

The effect on reproductive performance was evaluated in rats exposed over three generations. Treatment was initiated 84 days prior to mating of the first generation. Aldicarb was administered in the diet at a dose of 0.05 or 0.1 mg/kg/day to all three generations. Following exposure for three generations, aldicarb treatment caused no significant difference from control animals to indices of reproduction or histopathological changes. A NOAEL of 0.1 mg/kg/day was identified in this study.[10]

Groups of rats (26/sex/dose) were administered aldicarb in diet at 0, 0.2, 0.3, and 0.7 mg/kg/day for 90–100 days, then mated to produce the respective F_1, F_2, and F_3 generations. With the exception of decreased body weight of F_2 pups at the highest dose, no adverse reproductive effects were seen. A NOAEL of 0.3 mg/kg/day was identified for developmental toxicity.[32]

Groups of rats were administered aldicarb in diet at 0, 0.1, 0.4, 0.7–0.9, and 1.4–1.7 mg/kg/day for 70 days, then mated twice to obtain F_{1A} and F_{1B} litters. No effects on reproductive parameters were observed. Decreased pup weights and viability were seen at the highest dose at Lactation Day 4. Decreased body weights, red blood cell counts, and plasma cholinesterase levels were seen in F0 animals at 0.7/0.9 mg/kg/day. NOAELs of 0.4 and 0.7–0.9 mg/kg/day were identified for parental systemic and developmental toxicity, respectively.[32]

When given orally to pregnant rats, evidence of AChE inhibition in fetal tissues was observed at doses that did not produce this effect in the dams. This finding suggests that sequestration occurs in fetal tissues, possibly because of the inability of the fetus to catabolize certain chemicals.[36] Other data obtained from rats and humans have demonstrated that young mammals treated with aldicarb exhibit a neurological and biochemical pattern of toxicity that differs from that seen in adults.[37–39]

F. Genotoxicity/Mutagenicity

No evidence of a mutagenic response, with or without S9 metabolic activation, was observed in two Ames bacterial mutagenicity assays with aldicarb.[40,41] An assay for mitotic recombination using *Saccharomyces cerevisiae* also showed no evidence of genotoxicity.[40]

Aldicarb technical grade was reported to cause DNA damage in *S. typhimurium* strain TA1538 (DNA repair-deficient) bacteria. However, no effects were seen in strain TA1978 (DNA repair-proficient) bacteria or in two strains of *E. coli*.[42]

When tested in L5178Y mouse lymphoma cells, aldicarb produced a borderline mutagenic response, but only in the presence of S9 activation (concentration not specified).[15] Inconclusive results (positive with S9 only) were obtained in a second study, while a third study found positive results with or without S9.[43] The overall weight of evidence suggests that aldicarb was mutagenic in this assay.

No evidence of mutagenicity was seen when aldicarb was tested in CHO/HGPRT cells, with or without S9. In addition, an Unscheduled DNA Synthesis study was also negative.[10]

Aldicarb did not cause single-strand DNA breaks in cultured human skin fibroblasts at a concentration of 10^{-5} M.[45] However, it induced sister-chromatid exchanges (SCEs) in cultured human lymphocytes, with or without S9 activation, at concentrations ≥ 40 µg/mL. The incidence of SCEs was slightly greater in the presence of S9; in addition, the highest concentration tested, 250 µg/mL, inhibited mitosis in the presence of S9. These results were attributed to metabolic transformation of aldicarb to a genotoxic N-nitroso derivative.[46] In a second study, an increase in SCEs was

seen in cultured human lymphocytes treated with 5 μmol/L aldicarb, but only in the absence of S9.[47] Additionally, in a similar study, aldicarb produced an increased incidence of chromosomal aberrations as well as chromatid/chromosome gaps in human lymphocytes at 350 μg/mL, with or without S9, and the response was greater in the presence of S9.[48]

An increased incidence of chromosomal aberrations, both structural and numerical, was seen in bone marrow of rats injected intraperitoneally with 1.2, 6.7, or 12.1 μg/kg aldicarb, either as a single dose or repeated daily for five days. The numerical aberrations were primarily in the form of endomitosis, suggesting that this compound exerted a direct effect on the mitotic spindle.[49] By contrast, in a similar study, aldicarb did not induce chromosomal aberrations in mouse bone marrow cells.[50]

A dominant lethal assay was performed in which male Harlan-Wistar rats (F_2 progeny from a multigeneration study in which animals received aldicarb in the diet, at doses of 0, 0.2, 0.3, and 0.7 mg/kg/day, or its metabolite, aldicarb sulfone, at dosages of 0, 0.6, 2.4, and 9.6 mg/kg/day) were mated with virgin females. No evidence of mutagenicity was observed in these studies.[10]

Structural and chromosomal abnormalities were seen in mice receiving single or 5 consecutive daily intraperitoneal injections of aldicarb (in a 1:1 water/acetone vehicle).[8]

A more recent study of the genotoxic effects of aldicarb found an increased incidence of micronuclei in cultured Chinese hamster ovary cells beginning after 24 hours at a concentration of 16 μg/mL, and after 48 hours at 8 μg/mL. In addition, peripheral blood from Balb/c mice treated orally or intraperitoneally with 0.025, 0.125, or 0.25 aldicarb had an increased incidence of micronucleated reticulocytes 24–72 hours following a single dose by both routes, as well as 24 and 48 hours after 3 consecutive daily intraperitoneal (but not oral) treatments. A decrease in circulating reticulocytes was also observed after three intraperitoneal doses of 0.125 and 0.25 mg/kg.[51] By contrast, no increase in micronucleated polychromatic erythrocytes was seen in NMRI mice orally administered aldicarb, even at toxic/lethal concentrations.[47]

Overall, data on the genotoxic potential of aldicarb are considered weak/equivocal.

G. Immunotoxicity

In two studies where female Swiss-Webster and B6C3F1 mice were administered aldicarb in drinking water for 34 days, at concentrations of 0.1–1,000 ppb (estimated intake 0.04–364 μg/kg/day), there were no observed effects on splenic antibody-forming cells, circulating antibodies, or T- and B-lymphocyte function.[52,53] However, when mice were treated with aldicarb administered in drinking water at concentrations ranging from 1–1000 ppb, for a period of 14–34 days, a significant reduction in the splenic plaque-forming response to sheep red blood cells was seen; this effect was greater at 1 ppb than at 1,000 ppb, suggesting an inverse dose-response relationship.[54] When a similar study was conducted at doses ranging from 0.01–1000 ppb, with duration of treatment 30, 60, 90, or 180 days, an immunosuppressive response was seen at all doses and dosing intervals investigated. The data were adjusted to account for non-uniformity and variability of the responses, and an inverse though polyphasic dose-response relationship for dose was found.[55]

Whole spleen cells were isolated from C3H mice pretreated with a single intraperitoneal injection of aldicarb, at a concentration of 0, 0.00005, 0.0005, 0.005, 0.05, or 0.5 μg/kg. When these cells were subsequently exposed to a mitogenic agent, concanavalin A (ConA), or to a monoclonal anti-CD3 antibody, a decrease in splenic T-cell responsiveness was observed in cells from animals that received ≥ 0.005 μg/kg/day. However, the response of purified T lymphocytes from animals treated with 0, 0.05, 0.5, and 5 μg/kg was not affected by treatment. To further characterize these findings, T cells from controls and animals treated with 0.5 μg/kg aldicarb were mixed with splenic macrophages from normal syngeneic C3H mice exposed to either 0 or 0.5 μg/kg aldicarb, with subsequent ConA challenge. Although a decrease in responsiveness was seen in both normal and treated T cells mixed with aldicarb-exposed macrophages, both normal and treated T cells responded normally when mixed with untreated macrophages. On the basis of these results, the authors concluded that aldicarb treatment did not directly interfere with T lymphocyte function, but instead it affected macrophage accessory cell functions necessary for T lymphocyte activation. Additional experiments confirmed that treatment with aldicarb led to decreased IL-1 production by macrophages.[56,57]

Groups of C57BL/6 mice were exposed to aldicarb in drinking water, at concentrations of 0, 0.1, 1, and 10 ppb, daily for 28 or 90 days. In animals exposed for 28 days, there was a shift in the percentages of activated splenic T-lymphocyte subsets in the 1- and 10-ppm groups, but not at any dose in the 90-day groups. Also observed after

28 days, but not 90 days, was an increase in mitogen-stimulated lymphocytes. No changes in antigen-specific T-cell responsiveness or in macrophage phagocytosis of fluorescent microspheres were seen with treatment. The study authors concluded that the immunomodulatory effects of aldicarb were indirect, and suggested that the bone marrow or lymphocyte subpopulation network might be the ultimate target for aldicarb-induced toxicity. An apparent reversibility of effects (based on a lack of findings in animals treated for 90 days) was also noted.[58] This is consistent with a previous study which observed that aldicarb selectively modulated macrophage-mediated cyototoxicity against tumor target cells, without exerting any effect on cytotoxicity mediated by natural killer cells.[59]

A series of experiments were performed in which 10 groups of 6 male mice/group (white outbred Swiss-Webster strain ND4 or wild Wisconsin deer mice) were administered drinking water containing 0 or 10 ppb aldicarb, alone or in combination with nitrate and/or andrazine, and repeated at various seasons of the year. The duration of dosing ranged from 22 to 103 days. During one Spring experiment only, which lasted 103 days, animals receiving aldicarb alone exhibited a decrease in spleen weight and free thyroxine index (an indicator of thyroid function), and there was a decrease in splenic plaque-forming cells in groups exposed to aldicarb in combination with another pesticide. In other experiments, behavioral changes were also observed. However, with the exception of seasonal variability, with mice being more sensitive to the effects of these chemicals in Winter and least sensitive in Fall, there were no consistent trends in parameters studied across most or all 8 experiments that were performed.[60]

Overall, the results of these studies suggest a potential indirect immunotoxic effect associated with exposure to aldicarb.

H. Other Studies

In vitro studies with cultured human breast and endometrial carcinoma cells found that carbamate pesticides, including aldicarb, slightly inhibited estrogen and progestin binding in these cells, suggesting a potential for these compounds to act as endocrine disruptors.[61] Weak evidence of a decrease in somatotropin levels was seen at Week 7, but not at Weeks 13 or 16, in male Sprague-Dawley rats treated daily with 1 ppb aldicarb in drinking water; a slight but not statistically significant decrease was also seen at Week 7, at 10 ppb.[62]

I. Metabolism/Pharmacokinetics

Aldicarb is readily and almost completely absorbed from the gastrointestinal tract with signs of systemic toxicity occurring approximately 5 min following oral administration to rats. It is also readily absorbed through the gum and skin. Aldicarb and its metabolites are widely distributed throughout the mammalian body with no indication of bioaccumulation or sequestration into tissues or bodily fluids.[6,14,36]

The basic metabolic pathway of aldicarb appears to be the same in all species studied, including plants, vertebrates, and invertebrates. It is extensively hydrolyzed and oxidized to sulfoxide and sulfone derivatives, with the major metabolite in rats being aldicarb sulfoxide. Aldicarb sulfoxide is also pharmacologically active, with AChE-inhibitory potency equal to or greater than that of unchanged aldicarb. Aldicarb sulfone (also known as aldoxycarb) is also active, but is much less potent (about 4%) than its parent. Other minor metabolites possess low orders of toxicity.[6,14,20,22,36,63,64]

Aldicarb sulfoxide and aldicarb sulfone are in turn rapidly converted to the corresponding oximes and nitriles, which are slowly degraded to inactive molecules. Extensive enterohepatic recirculation of parent compound and metabolites has been demonstrated.[6] Most of the excretion (80%–90%) takes place via the urine within the first 24 hours post-exposure, and elimination is complete in about 5 days; approximately 40% of an absorbed dose is eliminated as aldicarb sulfoxide, with an additional 30% as sulfoxide oxime.[13,14,20,36]

In contrast with the data reported above, a recent analysis of plasma aldicarb levels in a case of accidental and nonfatal poisoning found that AChE levels were decreased through 30 hours-post dosing, then rapidly returned to normal within 60 hours. The elimination kinetics was biphasic, with a terminal elimination half life of about 20 hours.[65]

Aldicarb can also undergo N-nitrosation in the gastric environment (i.e., mild acidity and temperature of 37°C), and in the presence of nitrites or nitrogen oxides. The degree of conversion to the N-nitroso intermediate is unknown.[66,67]

An important mechanism in the detoxification of aldicarb involves binding to non-selective esterase enzymes, such as carboxylesterase (CarbE). Aldicarb has a higher binding affinity for CarbE than for AChE, and single intraperitoneal injections of 0.1 mg/kg to rats (strain not specified) caused inhibition of both CarbE and AChE. It has

been postulated that CarbE's act as "false targets" for the pesticide, reducing the amount of free compound that may cause AChE inhibition. This hypothesis is supported by the finding that the most pronounced CarbE inhibition was observed in liver and plasma, and that the degree of CarbE inhibition was greater than AChE inhibition in brain and muscle. Additionally, pretreatment of animals with tetraisopropylpyrophosphoramide, an OP that inhibits CarbE, significantly increased the toxicity of aldicarb.[68]

V. HUMAN USE AND EXPERIENCE

A. Workplace Exposure

Occupational exposure to high levels of aldicarb is due to product handling, and most cases of poisoning occur during loading and application operations.[11]

An investigation of occupational exposures to aldicarb in California during the period between 1974 and 1976 found 38 cases of illness (31 of which were systemic) that were directly related to workplace exposures. There were four cases of contact dermatitis, and one case of chemical conjunctivitis in which dust from aldicarb granules was blown directly into the eye. At least 6 cases of systemic toxicity caused by dermal contact, in particular when exposure occurred under wet conditions, were reported.[69]

There was one case report of a farm worker who was run over by a tractor shortly after loading an undetermined number of Temik® 15G [15% w/w (15 g/kg) aldicarb] bags into a hopper without wearing proper protective equipment. Autopsy results showed an estimated body burden of 0.275 mg/kg. The highest concentrations of aldicarb metabolites were detected in plasma and skin (including dermis and subcutaneous fat from both hands). The highest total aldicarb concentration was detected in the kidney, suggesting that excretion was already taking place at the time of death.[70]

There was also one report of a foreman performing a mechanical aldicarb bagging operation, who developed symptoms that were consistent with AChE inhibition which persisted for longer than 6 hours. Quantitative data on his exposure were not provided. The individual returned to work the following day.[10]

Another case was identified of a certified applicator exposed to aldicarb while operating a ground rig applicator, without proper protective equipment. He was hospitalized exhibiting nausea, dizziness, and confusion. Laboratory analysis revealed a significant depression of AChE (values not reported).[71]

In a five-year prospective cohort study of respiratory outcomes in pesticide applicators and their spouses from Iowa and North Carolina (the Agricultural Health Study), there was no increased risk of wheezing among farmers who applied aldicarb to their crops.[72] However, a positive association with farmer's lung (the most common form of hypersensitivity pneumonitis) and aldicarb was identified for farmers, but not for spouses, in this study (data were adjusted for age, state of residence, and smoking status, including number of cigarettes smoked per day). No association between other hay and grain exposures and farmer's lung.([63,74] In addition, further study of participants in Iowa showed a slightly increased risk of colorectal and colon cancers (odds ratio = 1.6 and 2.1, respectively), but not of rectal cancer, among farmers and commercial pesticide applicators; family history of colorectal cancer among first-degree relatives, use of aspirin, alcohol intake, and dietary factors (e.g., fruit, vegetable, or meat consumption) were ruled out as potential confounders.[75]

In a ten-year retrospective study, an association between aldicarb use and an increased incidence of breast cancers was seen in rural areas, but not urban ones, of Leicestershire County, UK. However, given that no corresponding association was seen in a neighboring county, and that there was no consistent correlation between spatial application of the pesticide and breast cancers, the results are difficult to interpret.[76]

A small study of 41 workers in Ecuador who had been occupationally exposed to pesticides, including aldicarb, showed an increased incidence of various numerical and structural chromosomal aberrations. Owing to the small size of the sample population, and to the fact that details of exposure were not reported, the results of this study are difficult to interpret.[77]

B. Other Exposure Data

The primary route of human (non-occupational) exposure is through consumption of contaminated food and of water from contaminated wells. In the mid-1980s, there were highly publicized incidents in which misapplication of aldicarb-contaminated cucumbers and watermelons led to adverse effects in people. In 1990, the manufacturer of Temik® announced a voluntary halt on its sale for use on potatoes, because of concerns about groundwater contamination.[11]

Like other carbamates, aldicarb has a mechanism of action similar to that of organophosphate pesticides, but its effects are more readily reversible. Symptoms of aldicarb overexposure in humans are consistent with AChE inhibition, and have included dizziness, skeletal muscle weakness, epigastric cramping and pain, diarrhea, excessive sweating, pupils that are contracted and unreactive to light, blurred vision, breathing difficulty, and muscle twitching or convulsions. Bradycardia and heart conduction abnormalities have also been reported. Effects have a rapid onset (15 minutes to 3 hours) and disappear in 4 to 12 hours. Very high doses can result in death due to paralysis of the respiratory system.[11,78,79]

A number of individuals who ingested watermelons contaminated with aldicarb exhibited rapid-onset symptoms, including nausea, vomiting, diarrhea, profuse sweating, excessive tearing, muscle fasciculations, and bradycardia. In one report, the concentration of aldicarb sulfoxide detected in contaminated melons was about 2.7 ppm.[80] The lowest estimated toxic dose to affected individuals was 0.0011 mg/kg. Likewise, the lowest estimated toxic dose to humans across several outbreaks of aldicarb poisonings from contaminated cucumbers was 0.0011 mg/kg (upper end of the range 0.06 mg/kg); signs including nausea/vomiting, dizziness, loss of balance, disorientation, and fatigue were also observed in these instances. Laboratory analysis of the contaminated produce detected the presence of aldicarb sulfoxide residue, and occasionally aldicarb sulfone, but no unchanged aldicarb was measured.[64, 81]

Similar symptoms of poisoning were seen in all 20 individuals at a company picnic who ingested cabbage salad contaminated with 272.6 ppm aldicarb. The onset of symptoms was about 45 minutes, and resolved in about 4 hours. The CDC estimated that, if all individuals attending the picnic had consumed equal amounts of the salad, they would have been exposed to the pesticide at a dose of 0.2 mg/kg.[81]

Symptoms of mild to moderate aldicarb intoxication (malaise, dizziness, diaphoresis, sialorrhea, nausea and vomiting, muscle tremor, and abdominal cramps) occurred within 30 minutes in one man and two women belonging to the same family, who ingested contaminated collard greens. The man reported having used about 80 g aldicarb on each collard head for the previous 20 days. Symptoms resolved rapidly in the two women, while the man required atropine treatment and recovered more gradually. The amount ingested by each individual was not estimated.[82] Several outbreaks of violent illness in Nebraska 1977–78 were linked to aldicarb intoxication resulting from the ingestion of contaminated cucumbers.[83]

Aldicarb was detected in approximately 75% of private wells in a 100-square-mile farming area of Suffolk County, NY. The average concentration in these wells was 6.2 ppb, though in rare cases it ranged as high as 515 ppb. There were no hospital reports of any illnesses consistent with carbamate poisoning in this region.[84]

In a small study in Wisconsin, 23 women were exposed to aldicarb from contaminated wells (average concentration 16.1 ppb and ranging as high as 61 ppb). Although there were no reported clinical signs, these women were found to have slight alterations in immune function (increased T8 cell numbers and a decreased T4:T8 ratio) when compared with a cohort of 27 women who consumed water from a source with no detectable aldicarb levels.[85]

An experimental study which aldicarb was administered orally as a single dose at 0.025, 0.05, or 0.1 mg/kg was conducted with 12 human subjects (4 males/group). Although AChE inhibition was measured at all doses, only subjects receiving 0.1 mg/kg exhibited any overt symptoms (including malaise, weakness in the arms and legs, pupils that were contracted and nonreactive to light, epigastric cramping and pain, sweating of hands and forehead, air hunger , frequent yawning, salivation, slurred speech, nausea, and vomiting). The range of AChE inhibition at this dose was between 30% and 57%. The depression of AChE activity was greatest 1–2 hrs post-exposure, and was rapidly reversible; symptoms were absent and subjects reported feeling normal by 6 hrs. No symptoms were reported in subjects who received 0.025 or 0.05 mg/kg.[32]

A double-blind, placebo-controlled study was conducted in which 38 men and 9 women consumed a light breakfast which included an orange juice drink containing 0, 0.01, 0.025, 0.05, 0.06, or 0.075 mg/kg aldicarb. None of the women developed any clinical symptoms consistent with AChE inhibition. However, there was a statistically significant inhibition of plasma and blood AChE at all doses, with peak effects occurring one hour post-dose. In addition, men receiving 0.025 and 0.05 mg/kg exhibited localized and mild sweating, with profound diffuse sweating observed at higher doses. Based on these results, a NOAEL of 0.01 mg/kg was identified in this study.[32,86]

Following an analysis of available data, the U.S. Environmental Protection Agency estimated that

manifestation of the clinical signs of aldicarb poisoning generally occurs at doses between 0.002 and 0.1 mg/kg.[86]

In a 2005 survey of 2500 potable wells across the U.S., only 63 wells were found to have aldicarb residue levels in excess of 0.007 mg/L (7 µg/L), which is the current "safe level" established in the U.S.[87]

VI. RATIONALE

Aldicarb is a short-acting inhibitor of AChE which has a high order of acute toxicity in mammals. It may be absorbed through skin and across mucous membranes, and appears to possess irritant properties. Clinical signs of toxicity (including dizziness, weakness, tremor, gastric pain, and nausea/vomiting) occur within one hour of exposure and persist for at least several hours; medical intervention may be required. The primary target organs of toxicity are the central nervous and gastrointestinal systems, though recent evidence also suggests a potential to cause alterations in immune function (and/or endocrine disruption). Apart from minor effects on the immune system, whose duration and clinical relevance are unknown, a review of nonclinical and clinical data do not indicate any potential to cause significant long-term toxicity, including reproductive/developmental toxicity and carcinogenicity. Manifestation of the clinical signs of illness generally occurs at doses ranging from 0.002 to 0.1 mg/kg. Extrapolating from the low end of this dose range, an OEL of 10 µg/m^3 (0.001 ppm) is judged to provide sufficient protection from adverse health effects. A "Skin" notation is recommended because of the potential to cause significant systemic toxicity following direct contact.

VII. RECOMMENDED OEL

8-Hour Time-Weighted Average (TWA): 10 µg/m^3 (0.001 ppm), Skin.

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