A Carbamate Insecticide: A Case Study of Aldicarb

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Aldicarb, the active ingredient in the insecticide TEMIK, was introduced to the agricultural community over 25 years ago. It has been registered worldwide to control a wide variety of insect, mite, and nematode pests in agriculture. The toxicological research database supporting the registration and use of aldicarb was generated over more than 25 years and contains more than 280 animal studies on 12 species of animals, 2 clinical human trials, and over 20 human monitoring studies. This database, which includes biochemical aspects (metabolism and mode-of-action studies), acute toxicity and special short-term toxicity studies, long-term toxicity studies, and epidemiological observations in humans, serves as the starting point for the evaluation of the risks associated with the acceptance of levels of aldicarb residues in food and drinking water and for the more direct occupational exposure. This article highlights the available toxicological data and reviews worldwide regulation of aldicarb. Included in these discussions is a brief description of the toxicological end point upon which regulatory decisions have been based, namely acetylcholinesterase depression. Aldicarb, the N-methylcarbamic acid ester of 2-methyl-2-(methylthio) propionaldehyde oxime, was the first of a limited group of insecticidal oxime N-methylcarbamates that have properties distinct from N-methylcarbamates which have a phenolic constituent, instead of the oxime moiety. Aldicarb is highly water-soluble (approximately 6000 ppm), nonvolatile, relatively stable under acidic conditions, and is easily degraded under alkaline conditions. These properties are important determinants of its systemic action in plants and of its problematic environmental behavior. Possible environmental hazards involving the chemical include groundwater contamination and (more recently) excessive terminal residues in certain foods. — Environ Health Perspect 102(Suppl 11):23–27 (1994)

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Mammalian Toxicology

The toxicology database contains more than 280 animal studies on 12 species of animals, 2 clinical human trials and over 20 human monitoring studies (1,2). The signs and symptoms of acute aldicarb-poisoning are characteristic of that of other organophosphorus and carbamate insecticides. Poisoning results primarily from nicotinic and parasympathetic effects produced by inhibition of acetylcholinesterase in the peripheral somatic and autonomic nervous systems. The effects of acute overexposure to aldicarb and aldicarb metabolites are transient in nature, primarily because of rapid spontaneous recovery of the carbamoylated (inhibited) acetylcholinesterase and a swift rate of distribution and metabolism and excretion from the body. Complete recovery typically occurs within 3 to 6 hr of exposure. Aldicarb, like all cholinergic N,N-dimethyl, N-methylcarbamate, and organophosphate insecticides, exerts its neurotoxic effects through inhibit-

ing acetylcholinesterase in nerve synapses and myoneural junctions. Acetylcholinesterase inhibition by these insecticides involves the formation of an enzyme-inhibitor complex followed by the reaction of this inhibitor at the active site of the enzyme, which generates either a carbamoylated or phosphorylated enzyme. Phosphorylated acetylcholinesterase is relatively stable, so that inhibition is virtually irreversible after a phenomenon defined as aging has occurred. However, carbamoylated acetylcholinesterase can be readily, and spontaneously hydrolyzed to regenerate the original form of the active enzyme. Although the carbamoylated enzyme is sufficiently stable to disrupt cholinergic transmission, acetylcholinesterase activity is rapidly regenerated following subacute doses. Repeated subacute dosing with cholinergic N-methylcarbamate insecticides does not lead to cumulative intoxication, based on what is known about the insecticides' mode of action and the general physicochemical properties of the chemical class.

While not being readily defined in pharmacokinetic terms, the qualitative and quantitative metabolic pattern of degradation in plants and animals is well known. Aldicarb is quickly oxidized to aldicarb sulfoxide and more slowly to aldicarb sulfone, before undergoing hydrolytic breakdown to noncholinergic agents. Aldicarb sulfoxide is a more potent inhibitor of acetylcholinesterase than is aldicarb itself, but

aldicarb sulfone is less active than aldicarb, the original sulfide. These inhibitory relationships generally agree with the acute mammalian toxicity relationships observed with aldicarb and its metabolites.

Considerable evidence supports the view that the toxicological responses of humans to aldicarb and its metabolites are similar or identical to those of laboratory animals. Aldicarb has a high acute mammalian toxicity ($LD_{50} = 0.3–1.5$ mg/kg) following oral or parenteral administration to laboratory animals. Dermal toxicity is also high (rabbit dermal $LD_{50} \sim 5$ mg/kg), but is dependent on the administration vehicle used. The acute mammalian toxicity of aldicarb sulfoxide is similar to aldicarb; whereas that of aldicarb sulfone is lower ($LD_{50} \sim 20–25$ mg/kg). Acute studies show that aldicarb is not an eye or skin irritant and does not induce a dermal-contact sensitization response. In a significant array of in vivo and in vitro bioassays, aldicarb has been shown to be nonresponsive to all measured immunological parameters. Multigeneration animal reproduction studies show no adverse reproductive effects; no developmental effects were noted in teratology studies. Dominant lethal studies were also negative. Although the highest dose level tested (1 mg/kg) approximated the acute oral LD_{50} value, no significant effects were found by any of the measurements associated with fertility, gestation, viability, or lactation. There was no evidence of con-

genital malformation in any of the treated groups. There have been several reports of aldicarb causing a depression of fetal blood and brain acetylcholinesterase activity (*3–5*). This was shown in rats when aldicarb was administered on day 18 of gestation and fetal tissues monitored soon thereafter. Although statistical significance was reported with respect to the treated and control group comparisons, the levels of depression concomitant of 12 and 18% for fetal blood and brain, respectively, were not associated with toxic signs or resulting pathology. As multigeneration reproduction studies examining behavior in rodent pups derived from aldicarb- and aldicarb metabolite-exposed mothers have been consistently negative, it is difficult to imagine a long-term or residual effect following *in utero* exposure, irrespective of slight degree of acetylcholinesterase depression measured in fetal tissue.

Genetic toxicity studies (mutagenesis) in rats were negative, as demonstrated in an array of short-term bioassays. Aldicarb has been tested for carcinogenicity and shown to be negative in several *in vivo* model bioassay systems using a variety of administration routes, including oral and dermal. Other than intermittent inhibition of acetylcholinesterase (an acute effect), there has been no evidence that aldicarb or its metabolites display any adverse chronic effects when administered to rats or mice in lifetime studies.

In a preliminary 14-day range-finding study in dogs (NN Hamanda, unpublished data), acetylcholinesterase inhibition was noted at doses exceeding 0.1 mg/kg. A 1-year study in dogs (NN Hamada unpublished data) was designed to produce maximal acetylcholinesterase depression by limiting feeding time to 2 hr/day to mimic a bolus administration of aldicarb, and also by using rapid analyses (within 4 hr of feeding) of erythrocyte and plasma acetylcholinesterase levels under analytical conditions that minimize dissociation of the carbamate–acetylcholinesterase complex. Aldicarb exposure, at doses up to 0.235 mg/kg, resulted in no observable adverse effects other than transient inhibition of erythrocyte and plasma acetylcholinesterase activity. The no-effect level for acetylcholinesterase inhibition was 0.025 mg/kg.

Human Studies

The availability of direct observations on the toxicity of aldicarb (or for that matter any chemical) to human subjects reduces some of the uncertainty inherent in the extrapolation to humans of the results

observed with laboratory animals. A considerable database exists on the acute, subchronic, and chronic effects of aldicarb and its metabolites on several species of laboratory animals (rats, mice, guinea pigs, dogs, primates, and rabbits) as well as humans. These reports have served as the basis for several risk assessments by the U.S. Environmental Protection Agency (U.S. EPA) (*6*), the Safe Drinking Water Committee of the National Academy of Sciences' National Research Council (SDWC/NAS/NRC) (*7–10*), by Cornell University (CF Wilkinson, unpublished data), and by the Food and Agricultural Organization (FAO) and World Health Organization (WHO) Joint Meeting on Pesticide Residues (JMPR) (*11–13*).

Studies examining the acute effects of aldicarb administered orally to human volunteers show the same pattern of rapid acetylcholinesterase inhibition and rapid recovery seen in experimental animal models (NN Hamada, unpublished data). In human subjects following two preliminary analyses of blood acetylcholinesterase activity, groups consisting of four adult male volunteers each were given aqueous solutions of aldicarb at acute oral doses of 0.025, 0.05, or 0.1 mg/kg; in a similar trial, two subjects were given doses of 0.05 or 0.26 mg/kg (*1,2,13*). In both trials, individuals were monitored prior to aldicarb exposure and served as their own controls. Observation for signs of poisoning and measurements of whole-blood acetylcholinesterase activity was made for 6 hr following treatment. As this is one of the most meaningful studies in defining an acute human response to aldicarb exposure, the data from the larger trial are presented in Table 1.

Acute cholinergic signs and symptoms of overexposure were observed only in subjects exposed to a dose of 0.1 mg/kg or higher. Clinical signs of overexposure were not noted at doses of 0.05 mg/kg or lower. By 6 hr after administration, acetylcholinesterase activity had returned to normal, and clinical cholinergic signs and symptoms had disappeared with no medical treatment. A dose-related depression from pre-trial values of whole blood acetylcholinesterase was observed in all individuals, mainly 1 to 2 hr after exposure.

A second clinical trial was reported in 1992 by the manufacturer Rhône Poulenc Ag Company and reviewed by the JMPR (*2*). These unpublished data were generated by Inveresk Clinical Research, Edinburgh, Scotland, as ICR Project 003237, March 11, 1992.

There are several advantages to using these human exposure data for regulatory risk assessment. first, the study describes the time course of whole blood acetylcholinesterase depression and recovery, allowing the development of mathematical models to describe the degree and duration of acetylcholinesterase depression (whole blood acetylcholinesterase activity is to a great extent composed of red blood cell acetylcholinesterase activity). Second, since the data were obtained from humans, there is little need for an interspecies extrapolation factor, as is typical for risk assessments where animal data provide the sole basis for human risk assessment. Last, the conditions of exposure used probably represent a worst case situation, since the bioavailability of aldicarb is almost surely greatest from a single bolus ingestion of an aqueous solution. In 1986, the SDWC/NAS/NRC intensively examined the data from the human study using a statistical model to

Table 1. Symptomatology and effects on whole-blood acetylcholinesterase in human volunteers.

Subject number	Body weight, kg	Aldicarb ingested mg	Aldicarb ingested mg/kg	Predose, hr 18	Predose, hr 1	Postdose, hr 1	Postdose, hr 2	Postdose, hr 4	Postdose, hr 6	Symptoms
1	94.5	9.5	0.1	167	85	58	68	107	123	Yes[b]
2	86.5	8.7	0.1	149	112	69	45	83	119	Yes[b]
3	82.5	8.3	0.1	218	185	57	47	84	120	Yes[b]
4	65.0	6.6	0.1	176	175	55	35	120	149	Yes[b]
5	97.5	4.0	0.05	129	191	77	93	139	152	No
6	87.0	4.4	0.05	171	159	64	62	136	134	?-No[c]
7	77.5	3.0	0.05	168	155	50	97	142	152	No
8	71.5	3.6	0.05	210	171	100	81	156	172	No
9	92.5	2.3	0.025	194	225	122	131	168	205	No
10	82.5	2.1	0.025	163	191	82	85	140	146	No
11	79.5	2.0	0.025	—	147	74	100	154	135	No
12	89.5	2.2	0.025	—	143	94	100	132	140	No

[a] Observed hydrolysis rate of acetylcholine (μm/hr/ml). [b] Present in first 2 hr after ingestion; none visible after 4 hr. [c] Possible symptom in first hour; none thereafter.

Table 2. Maximum inhibition of cholinesterase as specified by SDWC/NAS/NRC.

Dose, mg/kg	Mean inhibition, %
0.100	73
0.50	64
0.025	47

Table 3. Projected cholinesterase depression at lower dose levels by SDWC/NAS/NRC.

Dose, mg/kg	Mean inhibition, %
0.01	30
0.005	20

project the acetylcholinesterase depression response to low exposure levels (10). To reflect maximal inhibition, calculations were based on each individual's highest pretrial values and maximum depression at either 1 or 2 hr after administration. Table 2 shows the mean maximum depression reported by the Committee.

Whole-blood acetylcholinesterase depression was on the order of > 60% without clinical signs of overexposure, as seen in the mid- and low-dose groups.

The Committee's model, which considered the most conservative control acetylcholinesterase activity values and the maximum acetylcholinesterase depression values, using probit and logit regression analyses of these data, projected the enzyme depression at lower doses (Table 3).

To explore the inherent safety to humans of an acceptable daily intake of aldicarb residues of 0.005 mg/kg, cynomolgus monkeys were fed bananas and watermelon containing actual terminal residues resulting from aldicarb treatment (JA Trutter, unpublished data). The assessment by the SDWC/NAS/NRC suggested that an intake of 0.005 mg/kg of aldicarb residues would produce no overt signs of toxicity, but would induce a short-term low-level depression of blood acetylcholinesterase activity. The aim of the primate study was to confirm the safety of ingesting residues this size.

Bananas and watermelons were treated with aldicarb at exaggerated schedules to assure adequate residues in the fruit. Following analytical determination of actual residues in the two commodities to be consumed, intake of the treated crop was adjusted with control fruit to provide a dose of exactly 0.005 mg/kg. The animals were offered the fruit as the first meal of the day, and they consumed it immediately. Individuals were monitored for clinical signs, and plasma and erythrocyte

acetylcholinesterase activities were measured periodically for 24 hr after feeding. With both commodities, fed individually in two independent trials, there was no sign of acute cholinergic distress or any signs of overexposure in any animal. Depression of plasma acetylcholinesterase activity was evident within 1 to 4 hr after ingestion and reached a maximum of 35%. Erythrocyte acetylcholinesterase activity was not depressed. As expected, rapid recovery of all enzyme activity was observed, agreeing with prior observations of aldicarb-induced acetylcholinesterase depression and recovery in human volunteer studies. Acetylcholinesterase depression in humans and nonhuman primates was similar with respect to onset, duration, magnitude, time of recovery, and absence of adverse signs of cholinergic distress. It was concluded that acute ingestion of residues by humans to an acceptable daily intake (ADI) value of 0.005 mg/kg would be toxicologically insignificant.

Regulatory Assessments

The no-observable-effect-level (NOEL) of a material is considered to be the daily dose that produces no sign of toxicity in a population of test animals (or humans) and is usually derived from the results of long-term toxicity studies. Although the NOEL does not refer specifically to a toxic effect, it obviously implies that the monitored effect is of an adverse nature and, without proof to the contrary, it is often assumed any biological effect resulting from exposure to a chemical is of real or potential toxicological meaning. In recent years, regulatory authorities have begun using the acronym NOAEL (no-observable-adverse-effect-level), but generally tend to use some of the same effects as end points for risk assessments. Usually, NOEL values are established from dose–response data gotten with any species of laboratory animals (rats, mice, dogs, etc.). When human data are available they usually take precedence over animal data, although human trials often involve few replicates and cover short experimental periods. Where human data are not available, human sensitivity is usually assumed to be that of the most sensitive animal species.

In defining safety to humans, an uncertainty factor is generally applied in the risk assessment. This takes into consideration the degree of uncertainty in extrapolation of animal data to the human experience and to reflect the variability within the human population itself. When one ascribes to the safety factor mechanism for

regulatory risk assessment, and good quality toxicological data are available with different animal species showing a fairly uniform species response, a relatively low safety margin can be applied. This is particularly true if appropriate human data are available and doubly so if the effect is readily reversible. The safety factor may need to be greater if the available data are questionable, where few species have been studied, and particularly, where no human data are available. In short, the magnitude of the safety factor employed is determined by the adequacy of the database; it is a reflection of the degree of uncertainty associated with the data.

Extrapolation of the maximum dietary level causing no adverse effects in experimental animals to the establishment of an average daily intake (ADI, also known as the reference dose [RfD] by the U.S.EPA) for humans typically involves the use of an arbitrary uncertainty or safety factor. A safety factor of 100 has been widely accepted historically, although this may be increased or decreased depending on the amount and types of toxicological data upon which the assessment is based. According to a 1977 SDWC/NAS/NRC report "Drinking Water and Health" (7) the following guidelines have been adopted and been reaffirmed several times: a) A safety factor of 10 may be applied when valid experimental data from studies on prolonged ingestion by man are available, and where there is no evidence of carcinogenicity. b) A safety factor of 100 may be applied in cases where data on prolonged human studies are not available or are scanty (e.g., only acute exposures), where valid results on long-term animal feeding studies are available with several species, and where there is no evidence of carcinogenicity. c) An uncertainty factor of 1000 should be applied where there are no long-term or acute human data, where animal data are scanty, and where there is no evidence of carcinogenicity.

These are also the general guidelines that have been followed by the FAO/WHO's JMPR in establishing acceptable daily intake values for residues of pesticides and their metabolites.

Regulatory History

A considerable database exists defining the acute, subchronic, and chronic effects of aldicarb and its metabolites on several species of laboratory animals (rats, mice, guinea pigs, dogs, primates, and rabbits) and on humans. These data have been used extensively to address regulatory require-

Table 4. Chronological regulatory history.

Year	Source	ADI, mg/kg bw
1969	FDA	0.001
1970s	U.S.EPA-OPP	0.003
1977, '80, '83	SDWC/NAS/NRC	0.001
1979	JMPR	0.001
1981	U.S.EPA-OPP	0.003
1982	JMPR	0.005
1983	Cornell University	0.003 – 0.01
1986	SDWC/NAS/NRC	0.001
1986	U.S.EPA-ODW/OPP	0.001
1990	U.S.EPA-ODW/OPP	0.0002
1992	JMPR	——

ments. A brief history of the resulting regulatory activities associated with aldicarb is presented in Table 4 using the health standard, the ADI (now U.S.EPA's RfD), as the basis for discussion.

The U.S. Food and Drug Administration (FDA) (preceding U.S.EPA's formation) first assessed safety of aldicarb and issued crop tolerances for aldicarb residues in 1969. Over the first decade of its registered life, a generally accepted NOEL of 0.125 mg/kg bw/day for aldicarb and its metabolites (primarily the sulfoxide) was based mainly on observed levels of acetylcholinesterase depression in rat studies. The first ADI was established at 0.001 mg/kg. During the 1970s, the ADI was increased to 0.003 mg/kg, based on data from newer studies with rats.

In 1977, the SDWC/NAS/NRC (7), while stating that "it is not likely that [aldicarb] will appear as a major contaminant in drinking water," defined a NOEL of 0.1 mg/kg from studies with rats and dogs. Using a safety factor of 100, the committee recommended an ADI of 0.001 mg/kg. In later evaluations (in 1980, 1983, 1986) this committee reaffirmed its initial recommendation despite using different criteria (11).

In 1979, the JMPR applying a safety factor of about 100 to a NOEL of 0.125 mg/kg recommended an ADI for humans of 0.001 mg/kg (12).

In 1981, the EPA reconfirmed its ADI of 0.003 mg/kg, using the NOEL of 0.125 mg/kg with a safety factor of about 40. The JMPR, in 1982, evaluated other toxicity data on aldicarb, primarily reviewing a dietary study of aldicarb administered in drinking water, and recommended an increased ADI of 0.005 mg/kg, maintaining their assessment of a NOEL but reducing the margin of uncertainly in their extrapolation of animal data to human risk (11). In 1983, using a Cornell University kinetic model, Wilkinson showed that a safe range for the upper ADI value for

aldicarb and aldicarb metabolites would be 0.003 to 0.01 mg/kg confirming the JMPR's assessment.

In 1986, with no new toxicological information but working within the framework provided by the SDWC, the U.S.EPA's ADI for aldicarb was reduced to 0.001 mg/kg, to conform to technical evaluations in various agency offices. In data from a recent dog study, aldicarb at dose levels to 0.235 mg/kg displayed no observable adverse effects other than inhibition of peripheral erythrocyte and plasma acetylcholinesterase activity. The no-effect level for acetylcholinesterase inhibition was 0.025 mg/kg. In 1990, the ADI was again reduced to 0.0002 mg/kg presumably as a result of the newest dog study and possibly as a result of the occurrence of terminal residues in certain food commodities, for some of which tolerances had never been established. In 1992 the JMPR, reviewing the results of a second human trial and considering the reported effects of food containing aldicarb residues, recommended an ADI of 0.003 mg/kg (13). The NOEL reported for this trial was 0.025 mg/kg.

Cholinesterase Depression as a Toxicological Basis for Risk Assessment

Both organophosphorus and carbamate insecticides are established inhibitors of acetylcholinesterase. Since this is the biochemical lesion from which toxicity ultimately results, the measurement of circulating acetylcholinesterase levels, especially in blood (plasma and red cell), has had widespread application as a measure of human exposure. No active biological function has ever been defined for any of the blood acetylcholinesterase isozymes. Their physiological function in the body is unknown, although they commonly act as indicators of exposure and, subsequently, as indicators of potential adverse effects. There are two major types of enzymes that hydrolyze acetylcholine. One of these is acetylcholinesterase ("true" acetylcholinesterase) associated with erythrocytes (red cells) and nervous tissue, and the other is a nonspecific, "pseudo" cholinesterase associated with blood plasma (or serum) and found in many other tissues. Acetylcholinesterase measurements using whole blood include both erythrocyte and plasma acetylcholinesterases activity with the major contribution to total activity coming from the erythrocyte fraction. These enzymes are generally separated by differential centrifugation before assay. Those measurements using

brain tissue also include true and pseudocholinesterase activity and are generally not differentiated with respect to true or pseudo- cholinesterase activity except by substrate specificity. This differentiation is rare.

Although acetylcholinesterase measurements are undoubtedly valuable in confirming human or animal exposure to carbamate or organophosphorus insecticides, Wilkinson (CF Wilkinson, unpublished data) suggested that using them as indicators of an "adverse toxic effect" raised some important questions *a*) What are the major problems inherent in measurements of acetylcholinesterase activity in individual animals or populations and what can be considered normal variation? *b*) What is the meaning of acetylcholinesterase depression in terms of toxicity and/or the development of toxic symptoms, and how does it relate to an impairment of normal physiologic function? *c*) Is it possible to establish a biological threshold of acetylcholinesterase inhibition that shows an adverse toxicological effect? *d*) Is it proper to use values of acetylcholinesterase depression in setting NOEL and ADI values or for other regulatory purposes?

Some of these questions have been addressed recently by the U.S.EPA's Science Advisory Panel and are undoubtedly going to be further considered in depth by an U.S.EPA Working Group on Cholinesterase, which recently examined some of these issues, initially addressing analytical methodology. The first of these questions has been discussed in detail by individuals who have reviewed both inter- and intraindividual variation in blood acetylcholinesterase levels (plasma and erythrocyte) and experimental error in the available method. It has been concluded that, based on observed intraindividual variations of about 10% (resulting from unknown physiological, nutritional, or other factors), a plasma or red cell acetylcholinesterase depression of 15 to 25% would be considered meaningful based on a known pre-exposure value. If acetylcholinesterase depression in an individual is compared with values measured in many unexposed individuals, the interindividual variation (15–25% for plasma and 10–15% for red cell activity) is such that depression values of at least 33 and 20%, respectively, would be needed to show meaningful decreases in plasma and red cell activities.

The toxicological importance of acetylcholinesterase inhibition and its relationship to the development of overt signs of cholinergic poisoning is a complex issue.

The results differ depending on the type and location of the acetylcholinesterase measured and the particular inhibitor in question. There appear to be few simple correlations between the inhibition of plasma, erythrocyte, or brain acetylcholinesterase levels by different compounds. Usually, exposure of animals to an organophosphorus or carbamate insecticide leads to a rapid decrease in either plasma or erythrocyte acetylcholinesterase (or both), but the extent of the inhibition will vary with the chemical.

There is also evidence suggesting that the clinical effects of exposure may be related to the rate of acetylcholinesterase inhibition, instead of the absolute level of inhibition. Humans have experienced no ill effects from repeated low-level occupational exposure, which gradually reduced their blood acetylcholinesterase to levels so low one would have expected severe illness if the rate of decline had been rapid, as happens after a single large bolus dose. Adaptation to decreased levels of acetylcholinesterase may be explained by a physiological adaptation to increased levels of acetylcholine or by enhanced synthesis of new enzyme. Industrial workers with 90% of their blood acetylcholinesterase inhibited have shown no signs or symptoms of overexposure, while others have been seen to be severely ill with a similar degree of acetylcholinesterase inhibition. Consequently, it is extremely difficult to establish any hard and fast rules on the amount of peripheral acetylcholinesterase inhibition that can be expected to lead to toxic manifestations. Generally, toxic effects are unlikely to be encountered if the red cell and plasma acetylcholinesterase activities stay above 50% of their normal values; a toxicological threshold of 50% depression might ultimately be an acceptable value.

In extrapolating from a safe dose level shown in animals, to an acceptable safe levels for human intake, it is assumed an additional safety factor should be incorporated to account for the possibly greater susceptibility of juveniles. Very few data are available to allow meaningful comparisons between adult and juvenile toxicities of organophosphorus or carbamate insecticides. One very early report in 1963 of studies with 15 organophosphorous and carbamate insecticides showed that weaning rats were more susceptible than adult animals to cholinergic agents, although the differences usually were quite small, 12 of the 16 chemicals tested showed less than a 2-fold increased toxicity to weanings than to adults, with one chemical actually show-

ing a lower toxicity to weanings than to adults. In a 1980 report with the carbamate insecticide carbofuran, no biologically meaningful differences between juvenile and adult rats were observed with respect to LD_{50} values, erythrocyte and brain acetylcholinesterase depression, or the rate of onset or recovery from toxic signs (*11*). Although the available data do not provide an adequate basis for any firm conclusions, they strongly suggest that juvenile animals may not differ from adults in their susceptibility to cholinergic agents.

Lastly while there is not a large difference in the general assessment of human safety (the 25-fold range of 0.2–5 µg/kg for the ADI), the differences in the impact of the regulatory assessment of the ADI have made an important difference in the commercial life and value of aldicarb. While we have seen small differences in the overall human health assessment, the continuing erosion of the ADI (RfD), the subsequent reduction of food residue tolerances and the reduced drinking water advisory levels has had, and will continue to have, a profound effect of shortening the very significant commercial agricultural life of aldicarb.

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