US EPA ARCHIVE DOCUMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Tolerance for Aldicarb (Temik) of 0.2 ppm on Bananas

DATE: September 8, 1976

FROM: Toxicology Branch

TO: Product Manager #12 (Sanders)
and Mr. Bruce Jaeger, RTF

Pesticide Petition No.: 6E1792

Union Carbide

Conclusion:

Other considerations permitting, the requested tolerance of 0.2 ppm aldicarb on Bananas can be toxicologically supported.

Conclusion for RTF only:

Aldicarb is listed in the Feb. 17, 1976 FR as having data gaps in ONC and RN, line 343, category II chemicals. The present submission satisfies the ONC data gap.

Prior studies on aldicarb were also reviewed and prior reviews on this chemical were evaluated. TB concludes that the prior studies are valid for the determination of hazards associated with the use of aldicarb.

Review:

Data submitted with this petition:

18-Months feeding study (CD-1 mouse)

This is the first mouse study submitted and is dated 10/4/72. 44 animals per sex per level were fed aldicarb in the diet at levels of 0.7; 0.4; 0.2; 0.1; and 0.0 mg/kg. The principal findings of this study were:

1. At the 0.7 mg/kg level there were some early deaths recorded (first 90 days). This situation was corrected by mixing the chemical with the diet with the aid of acetone solvent. After this change the deaths in all groups including controls were equal.

2. The weight changes were not different in treatment and control groups, with the exception that males in the 0.7 mg/kg group showed a faster increase in weight from day 420 on, but the differences, although significant, were minimal.

3. Pathology: The number of hepatomas was increased in male mice versus the control values, in animals examined at the termination of the experiment.

feeding levels:	0.7	0.4	0.2	0.1	0.0
hepatomas/no. animals	7/25	6/30	2/26	7/33	1/37

4. Furthermore, animals dying in the later part of the study, after 490 days showed an increase in lymphoid neoplasms. This was especially so in males at the highest dose level (7/8). But 3/5 females at the 0.1 mg/kg level and 3/10 female control animals showed the same condition.

The mouse feeding study was repeated.

Second 18-month mouse feeding study

This study is dated 11/12/74. 50 male mice per dose level were used. The mouse strain employed was the same as in the prior study. The exposure levels were 0.7; 0.3; 0.1 mg/kg; and three control groups. Two of the control groups were treated just as the experimental groups. The third control group was used as a cohort group for animals dying during the study; that is, animals from this group were sacrificed at random whenever a mouse from the treatment groups expired prematurely. The principal findings of this study were as follows:

1. No increased mortality was noted in the treatment groups.

2. Weight gains were similar in all groups.

3. The incidence of hepatomas at term was not different for treatment groups than for control groups

feeding level:	0.7	0.3	0.1	Contr A	B
hepatomas/animals	5/35	4/37	7/37	6/34	8/43

4. The animals dying during the study still showed a high incidence of lymphoid neoplasia,

mg/kg	Lymphoid Neoplasia		total No. of Mice	Incidence, %
	Present	Absent		
0.7	3	4	7	43
0.3	2	3	5	40
0.1	6	4	10	60
0-A	5	6	11	45
0-B	1	4	5	20
0-C	0	18	18	0

but the frequency was not different between the treatment groups and especially control group A. The fact that control group C did not show this condition appears to indicate that lymphoid neoplasia is one of the reasons of early death in this strain of mice (animals of group C were sacrificed as matched controls for the dying animals).

whose conclusion?

The petitioner analysed the two mouse feeding studies statistically. It is concluded that the incidence of hepatomas in animals at term was exceptionally low in the first control group (1/37). When sampling any population for the natural occurrence of an effect it is possible to obtain low, normal, and high values according to a normal random distribution. The two control groups of the second study showed a "normal" incidence of hepatomas. The apparent increase in hepatomas in the treatment groups of the first study is therefore explained by the variability of the control sampling per se.

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Essentially the same rationale applies to the frequency of lymphoid neoplasias observed in the animals dying before term. The overall incidence of this phenomenon is about 40% which has been observed in treatment groups and control groups of both studies. Again some groups show less lymphoid neoplasias but this too can be attributed to a random sampling of the total population; furthermore, the low values coincided mostly with those groups where few animals died and thus the effect of low numbers further invalidated the apparent significance of the findings.

Rat 3-generation reproduction study

Study dated October 28, 1974. Harlan-Wistar rats were exposed to 0.7; 0.3; and 0.2 mg/kg aldicarb; furthermore, two control groups were used. The study was started with 20 females and 10 males, the same number of animals at the following generations were preserved to continue the study. The only effect noted in this study was less weight gain in animals of the 0.7 mg/kg level, but the effect was minimal in nature. The indexes of fertility and gestations were all normal. Some animals of the F2a parent and the F3a pups generation were examined by gross- and histo-pathology, no adverse effects were noted. The observed NEL for reproductive performance is 0.7 mg/kg.

Dominant lethal mutagenicity study

F2 males of the reproduction study were used in the d.l. study. These males were mated for 10 weeks to new batches of virgin females, and the gestation of these females was studied. There were no increases in late or early resorption sites. The number of pregnant females, total implants, viable fetuses, and litters with all pups viable, as well were not affected by the chemical.

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90-day Dog feeding study

Dogs (4 per sex per level) were exposed to aldicarb at levels of 0.7; 0.3; 0.2; and 0.0 mg/kg. The parameters studied were body weights, diet consumption, cholinesterase, organ weights, hematology, blood biochemistry; urinalysis, and gross and microscopic pathology. The only effects were noted at the high dose and consisted of an increase of adrenal weights in males, and a decrease of testis to body weight ratios. These changes although significant were small: Average adrenal weights for controls were 9.3 g. The test group showed an average weight of 1.1 g; the testis/bw ratio was 0.20 for controls and 0.15 for the test group. Cholinesterase activity was normal at 33 and 84 days (the only sample points used).

A conservative observed NEL for this study is 0.3 mg/kg.

Cholinesterase inhibition of aldicarb metabolites in the rat

Aldicarb sulfoxide (ASO) and the sulfone (ASO_2) were tested in rats in a feeding study lasting 56 days. The ASO was given at levels of 1.0, and 0.3 mg/kg/day and the ASO_2 was given at levels of 16.2, and 2.4 mg/kg/day. The choline esterase inhibition was not consistent and fluctuated over the duration of the experiment. Plasma and brain ChE was depressed in males by ASO at the higher level at 14 days; plasma ChE was depressed for males at the lower levels at days 1 and 28. In females ASO depressed ChE in erythrocytes at the high level on days 7 and 28, and at the lower level on day 14. ASO_2 depressed ChE in males and females at the high level in plasma, erythrocytes and in the brain, depression was consistent and pronounced (70% depression) but no clinical cholinergic signs were noted. At the lower level ASO_2 showed some erratic ChE depression in males and females in the plasma.

Acute oral and dermal LD50 of several Temik formulations

The LD50 values were not determined exactly; the approximations are listed below for comparison.

Oral (rabbit):

Formulation	LD50 (in mg/kg)	
Temik 10 G	> 10	< 20
Temik 10 G	> 5	< 10
Temik 15 G	> 6.6	< 13.3
Temik 15 G	> 3.3	< 6.6

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Dermal Rat

Formulation		LD50 (in mg/kg)	
10 G	[redacted]		≈2.5 dry
			≈0.8 moist
10 G		>2.5	<5.0 dry
		>0.4	<0.8 moist
15 G			≈0.8 moist
			≈2.5 dry
15 G		>0.2	<0.4 moist

Inhalation exposure

Rats were exposed to all the above formulation in a static experiment for 8 hours. No animals died as a result of this exposure.

Prior Studies

These studies were reviewed for purposes of validation of data; in some instances the actual studies were reviewed but without going into all details; the review of prior reviewers were taken into consideration as well.

1. 2-year rat feeding study. Observed NEL 0.3 mg/kg (PP #3F1414)
2. Hen neurotoxicity study. 4.5 mg/kg - no delayed neurotoxicity, and demyelization. (PP #9F0798).
3. Teratogenicity, Rat. 1 mg/kg did not produce teratogenic effect. Aldicarb was fed from day 5-15, but also during the entire period of gestation. (PP #9F0798)
4. By reference only in review of Dr. G. Whitmore (April 16, 1969, PP #9F0798).
   (a) 2-year dog feeding study, NEL 3.3 ppm
   (b) 2-year rat feeding study, NEL 2 ppm
   (c) 3-generation rat reproduction study, NEL 2 ppm

Summary

For aldicarb there are at least two each (a) rat 2-year feeding studies, (b) rat reproduction studies, (c) mouse oncogenic studies. Furthermore, there are a dog 2-year study, teratogenic study, neurotoxicity study, dominant lethal study, 90-day dog feeding study available. All these studies are acceptable, although in some of the details they may not satisfy the present requirements, especially as number of animals are concerned, but in the overall intent these studies are scientifically sound. It can therefore be concluded that the long-term toxic effects and the carcinogenic potential of aldicarb has been studied sufficiently to allow a conclusion about the safety of temik (aldicarb).

acute?

INERT INGREDIENT INFORMATION IS NOT INCLUDED

The AOI for man has been calculated to be 0.18 mg/day, based on a 6 ppm NEL in long term feeding studies and a safety factor of 100*. Established tolerances would maximally expose man to 0.101 mg/day, the temporary tolerance on oranges would maximally add 0.02 mg/day, the presently requested tolerance on bananas would add maximally another 0.004 mg/day, bringing the grand total to 0.125 mg/day, which is still below the calculated AOI of 0.18 mg/day.

*Although aldicarb is a cholinesterase inhibitor we do not use the customary 10X safety factor, since the acute and long-term toxic effects are caused by nearly the same amount of chemical.

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RE for OEC 4/8/76