

US EPA ARCHIVE DOCUMENT

Dr. Schmidt

007611

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

Date: December 7, 1973
Reply to:
Attn of:
Subject: Aldicarb - Answer to CB's questions deferred to
TB in the memo by Dr. M. J. Nelson - 12/2/73
To: Mr. Lee TerBush, Acting Chief
Coordination Branch
Registration Division

Pesticide Petition No. 3F1414

Union Carbide Corp.
1730 Penn. Ave., N.W.
Wash., D. C. 20006

1. Dr. Nelson stated that a slight over-usage of the maximum application rate (1.7x) may result in a 3 - 4 fold increase in the carbamate residues on potatoes. According to a 2-year rat study - reported in my memo of 9/25/73 - the metabolites, aldicarb sulfoxide and aldicarb sulfone, are approximately 3 times less toxic than the parent compound. Therefore, if a slight over-usage was made the amount of toxic substances would only be equal to the parent compound. In addition to this there would not be any economical advantage of over-use. The cost per acre at the proposed use is approximately \$30. Increasing this cost with no increase in insecticide protection would prove to be an economic loss.
2. In regards to the "Hogging Down" of peanuts this practice is not done anymore due to the more efficient harvesting processes. If hogs are to obtain peanuts to produce specialty meats, they are fed prescribed amounts to obtain the desired effects. Not allowed to roam a field to get what they can.
3. Dr. Nelson states that the metabolite residues sulfoxide/sulfone will have an average ratio of 3.6/1 in tubers. According to Dr. Back and data in the petition the combined toxicity of these two compounds will be approximately 3-fold less than the parent compound. However, when taken separately the sulfoxide metabolite has approximately the same toxicity as the parent compound while the sulfone has only 1/10 the toxicity of the parent compound. In projecting these residue amounts to actual residues one could easily approach the 1 ppm level of just the sulfoxide metabolite.

1/53

In a memorandum of conference 6/29/71 Dr. G. E. Whitmore stated that "enough raw potatoes are consumed that the question of the safety of 0.5 ppm of aldicarb on this commodity would be most important and that we would have to be assured that consumption of the 0.5 ppm on new potatoes would not be an acute hazard." The toxicity of the sulfoxide metabolite is approximately the same as aldicarb. Since with a slight increase in application the levels of this single metabolite can approach 0.9 ppm on potatoes, it is the opinion of TB that this level would present a toxicity hazard for the consumer. Although we do not establish residue tolerances on the basis of misuse of a pesticide, it is apparent from the submitted data that residues of the metabolites can vary between a 1.1 - 8.7/1 ratio with proposed application rates.

Recommendations

TB finds that the proposed tolerance of 1 ppm of aldicarb and its sulfoxide and sulfone metabolites on potatoes cannot be supported by the toxicity data and therefore must recommend against the establishment of such a tolerance. However, residues of 0.5 ppm in peanut hulls and 0.1 ppm in peanuts will not present a hazard and therefore recommends these tolerances be established.

Robert P. Schmidt 12/10/73

Robert P. Schmidt, D.V.M.
Toxicology Branch
Registration Division

cc:
CB
EEB
Div. File
Br. File
PP No. 3F1414

RPSchmidt/ccw 12/7/73
R/D Init: CHWilliams 12/7/73
Init: CHWilliams

*CHW
12/10/73*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Dr. Schmidt

007611

SUBJECT: Temik - Request for the establishment of tolerances for combined residues of the insecticide and nematocide Aldicarb (2-methyl-2-(methylthio)propionaldehyde O-(methylcarbamoyl)oxime) and its cholinesterase inhibiting metabolites aldicarb sulfoxide and aldicarb sulfone in or on the RAC potatoes at 1 ppm, peanut hulls at 0.5 ppm and peanuts at 0.1 ppm. DATE: September 25, 1973

FROM:

TO: Mr. Lee TerBush
Acting Chief
Coordination Branch

Pesticide Petition No.: 3F1414 - Union Carbide Corporation
1730 Pennsylvania Ave., N.W.
Washington, D.C. 20006

Related Petitions: 6G0473, 7F0573, 8F0637, 9F0798, 0F1008, 2F1188.

Toxicity Studies:

In his review of PP# 6G0473 (3/18/66) Dr. G. E. Whitmore reported the following data:

Acute Studies:

Rat oral 1% Temik in corn oil LD₅₀ - 0.95 mg/kg
Rabbit dermal 5% Temik in propylene glycol LD₅₀ - 5 mg/kg
Inhalation LD₁₀₀ 200 mg/M³ - 5 minutes 6 rats, 6 mice and 3 guinea pigs

Subacute Study:

Rat oral 93-day NEL 0.1 mg/kg/day

Chronic Study:

Rat oral 2-year NEL 2 ppm
Dog oral 2-year NEL 3.3 ppm

3-Generation Rat Reproduction Study NEL 2 ppm

Dr. Whitmore concluded that these data were sufficient to allow a temporary tolerance of 0.2 ppm in or on cottonseed and potato tubers.

In his review of 3/28/67, PP# 7F0573, Dr. Whitmore stated "The largest amount of Temik that can be considered safe in the whole human diet would be 1/100 of the demonstrated no-effect level of 2 ppm or 0.02 ppm. Based on a 1500 gm intake, not more than 0.03 mg daily intake could be allowed. The requested 0.5 ppm in or on potatoes would result in a possible intake of 0.0525 mg. He concluded that the above data would not support the proposed tolerance of 0.5 ppm in or on potatoes."

In the review of 9/8/67, Dr. Whitmore states that "More recently data obtained via PHS have indicated this material is extremely toxic to humans. This "human exposure" material was not available to us at the time of our original evaluation." He concluded that a tolerance of 0.5 ppm on potatoes would not be considered safe.

In petition 9F0798 review 4/16/69, Dr. Whitmore states that 2.25 mg/kg body weight did not produce any signs of demyelination in mature white leghorn hens. A teratogenic study in rats was submitted and results show that levels of 0.06, 0.3 and 2.0 ppm produced no abnormalities or anomalies.

Subacute studies of the sulfoxide and sulfone metabolites. The no-effect ChE diet levels were found to be:

Temik Sulfoxide (ASO)

Rats	0.125 mg/kg (1.5 ppm)
Dogs	0.125 mg/kg (3 ppm)

Temik Sulfone (ASO₂)

Rats	0.6 mg/kg (12 ppm)
Dogs	0.6 mg/kg (24 ppm)

In PP# OF1008, reviewed by Dr. G. E. Whitmore 4/6/71, the petitioner submitted an acute human study. These data showed that man was no more acutely sensitive to oral ingestion of aldicarb than the rat. Dr. Whitmore concluded that an infant receiving 1000 cc of milk per day, milk containing 0.002 ppm, would have a total intake of 0.002 mg/day. This study demonstrated a ChE no-effect level for adult human males as 0.025 mg/kg.

No new data were submitted with PP# 2H1188.

Data submitted with this petition are in reference to the toxicity of Temik 10GV and 15GV, the two formulations involved in this petition.

Rats oral LD₅₀ - 7.07 mg/kg of Temik 10GV
 Rats Dermal LD₅₀ - 2.5 gm/kg of Temik 10GV
 6.2 gm/kg of Temik 15GV

A skin penetration study was made with Temik 10GV and Temik 15GV in comparison to 5 other pesticide formulations. The test was made on 5 rats per dose level with application of the pesticide to the slipped skin of the belly area for 4 hours. The following table show the results of the study.

<u>Formulation</u>	<u>Physical form</u>	<u>LD₅₀</u>
Diazinon, 14G	granular	> 12.8 gm/kg
Di-syston, 15G	granular	> 12.8 gm/kg
Galecron, 5P	solid	> 12.8 gm/kg
Temik, 10GV	granular	4.58 gm/kg
Temik, 15GV	granular	6.32 gm/kg
Meta-systox R	liquid	1.49 ml/kg
Vapor (Vapona)	liquid	2.99 ml/kg

A 2-year feeding study was submitted to show a comparison of the NEL's of aldicarb (A), aldicarb sulfoxide (ASO), aldicarb sulfone (ASO₂) and a 1:1 mixture of ASO:ASO₂. These materials were fed to 20 male and 20 female Green Acres Laboratory Controlled Flora rats per dose level. Levels fed were 0.6 and 0.3 mg/kg (ASO); 2.4 and 0.6 mg/kg (ASO₂); 1.2 or 0.6 mg/kg of a 1:1 mixture of ASO:ASO₂, and 0.3 mg/kg aldicarb (A). Additional groups of 16 male and 16 female per level were kept in parallel for serial sacrifice. Four of each sex were killed after 6 months and the remainder after 12 months to determine organ weight and histological effects. The following table shows the maximum dosage levels that the rats received in their diets for 2 years without ill effects:

<u>Material Fed</u>	<u>No Ill Effect</u>	<u>Levels Fed</u>
1:1 of ASO:ASO ₂	0.6 mg/kg (12 ppm)	0.6 or 1.2 mg/kg
ASO	0.3 mg/kg (6 ppm)	0.3 or 0.6 mg/kg
ASO ₂	2.4 mg/kg (48 ppm)	0.6 or 2.4 mg/kg
A	0.3 mg/kg (6 ppm)	0.3 mg/kg

These results are considerably different from those previously reported (see page 2). Groups of rats were killed after 6 months, 1 year and 2 years for gross and microscopic examinations of their tissues. A considerable number of tumors were found with the most frequent type being adenomas of the pituitary and thyroid or pheochromocytoma of the adrenal. However, the similar percentage was

found in the controls consequently were considered not to be dose-related. This conclusion was also concurred with by K. J. Davis, D.V.M. 9/20/73 (see Sec. C, No. 5 of the present petition).

In summary of the ChE inhibition at the end of the 2-year study the data show the following.*

	0.6 ASO:ASO ₂ ΔOD	0.3 ASO ΔOD	0.6 ASO ₂ ΔOD	0.3 A ΔOD	0.0 Control ΔOD
Male Source					
Plasma	0.86	0.88	1.06	0.81	1.09
RBC	0.58	0.59	0.51	0.54	0.56
Brain	0.68	0.67	0.67	0.64	0.65
Female Source					
Plasma	2.69	2.22	1.96	2.14	2.10
RBC	0.57	0.53	0.54	0.54	0.56
Brain	0.77	0.74	0.71	0.77	0.88

These data show that at the lowest levels given for 2 years there is only a slight ChE depression in the plasma of the male rats while all other levels are statistically insignificant. This indicates that the metabolites when fed together at 1:1 are approximately 3X less toxic than the parent compound.

A 7-day dog feeding study was completed where 2 male and 2 female beagles per group were fed aldicarb at levels of 0.7, 0.3 or 0.2 mg/kg/day. It was reported that there were no deleterious effects noted in the criteria examined; mortality, appetite, body weight changes, plasma and RBC ChE inhibition and liver and kidney weights. Brain ChE activity significantly depressed but was considered not to be dose related.

* ChE determinations were made using DTNB (5,5'-dithio-bis-(2-benzoic acid) based on modification of colorimetric method of Carry & Routh, Clin. Chem. 11, 91-96 (1963). Heparinized blood samples were centrifuged at room temperature, plasma removed, rbc made to original volume with cold 0.9% saline and used immediately. Brains were homogenized and diluted with 0.25M sucrose.

Conclusions

About the only thing the newly submitted data have established is that the metabolites A. sulfoxide and A. sulfone are less toxic than the parent compound when fed in a 1:1 combination.

Previously submitted data indicated that both the ChE NEL and systemic for aldicarb per se based on the 2-year rat study is 0.1 mg/kg or 2 ppm. Therefore the maximum residue that could be safely supported by these data is 0.2 ppm on edible crops such as potatoes. Since peanut hulls are not an edible commodity a residue of 0.5 ppm would be considered safe as it would not be transferred to meat or milk when used as for fiber in cattle or poultry feed. Peanuts make up only 0.6% of the total 1500 gm diet consequently would not make a significant contribution to the total intake. The amount received from potatoes at 0.2 ppm would be 0.021 mg which is below the 0.03 maximum calculated by Dr. Whitmore.

If we use the reasoning in Dr. Whitmore's memo of 3/28/67 (re PP# 3G0473, 7F0573) that the safe ADI for aldicarb per se is 0.03 mg, we cannot support 1 ppm of aldicarb on potatoes. However, CB has concluded (memo of D. V. Reed, 1/24/72, PF# 2F1188) that "the past plant metabolism studies, the residues present at harvest are comprised of aldicarb sulfoxide, aldicarb sulfone. . . and possible traces of the parent compound." Since the NEL for a mixture of the sulfoxide and the sulfone was shown to be 0.6 mg/kg then conservatively using the 1/100 fold safety factor instead of the usual 1/10 for ChE inhibition, a value of 0.006 mg/kg or 0.36 mg could be supported in the total diet of a 60 kg man. With potatoes at 10% of the total dietary, at a 1 ppm tolerance the amount of the sulfoxide-sulfone (in a ratio of 3:1) contributed daily would be 0.15 mg. This is less than the ADI, and would be safe.

Further assurances of safety are based upon petitioner's statement in Section G that residues of aldicarb and its ChE inhibiting metabolites are further lowered by cooking.*

Recommendation

Chemistry Branch considerations permitting, TB finds the proposed tolerance for residues of aldicarb and its cholinesterase inhibiting metabolites at 1 ppm on potatoes is safe.

* We defer to CB for concurrence with petitioner's claim.

Robert P. Schmidt 9/27/73

Robert P. Schmidt, D.V.M.
Toxicology Branch, ABPR

cc: CB
EEB
Division File
Branch Reading File
PP# 3F1414

R/D Init:CHWilliams:9/26/73

RPSchmidt:sss:9/26/73

Init:CHWilliams

*CHW
9/28/73*

4 Aldicarb (Temik) residue tolerance request: 0.2 ppm (sugarcane fodder and forage; 0.02 ppm sugarcane stalk; 0.02 ppm sweet potatoes.

March 20, 1972 11A

007611

Mr. Drew H. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2F1158

Toxicity data (5 April 1971, PP# 1008 memorandum) supporting the safety of established aldicarb residues demonstrated the following:

2 ppm no effect in rats diets fed for two years and in a 3-generation rat reproduction study.

3.3 ppm no effect in dog diets fed for two years.

Adult human males, 0.025 mg/kg as a non-ChE inhibiting dose.

Conclusion

These data are adequate to support the safety of the requested residue tolerances of this petition.

Discussion

CB's 24 Jan., 1972 memorandum discusses some toxic aspects of feeding experiments as presented in Sec. C. They specifically refer to an acute (7 day) mouse feeding experiment demonstrating the fed material was more toxic as related to other reported mouse feeding experiments.

TB has taken due note of this same information and rates it unimportant in respect to our safety responsibilities. The study that CB is concerned about is acute toxicity data, providing about the same information as an LD₅₀ determination. The difference recorded between two 7 day trials on a few mice is actually within an experimental error range.

In answer to a CB specific question (24 Jan., 1972 memo) relative to the above toxicity information, TB is of the opinion it isn't necessary for the petitioner to furnish more complete chemical characterization of samples used in past toxicity studies. We believe the petitioner has adequately explained the noticed difference in the mouse acute toxicity studies.

Page 2 - PP No. 2F1188

When it has been determined that plants and animals (cow & rat) metabolism is similar (24 Jan., 1972 CB memo) the various plant metabolites decrease in significance since they would have been developed in the animal and the sum total toxic reaction in the test animal would reflect exposure to the parent compound and its developed metabolites. TB's long standing policy for such a situation is that safety consideration of possible plant residues can be adequately supported without detailed toxicity data information about the metabolites. With but few exceptions, metabolites are less toxic to fed animals than the parent compound. Those metabolites that have been found to be more toxic than the parent compound aren't more toxic by several degrees. To be significant, the metabolites would have to be as toxic or more so than the parent and present in the same amount or in a greater amount than the parent compound.

The above discussion is in response to Conclusions 1(a), 1(b), 1(c) in CB's 24 Jan., 1972, PP No. 2F1188 memorandum.

George E. Whitmore, D.V.M.
Section Chief
Toxicology Branch
Pesticides Tolerances Division

cc:

CGFitzhugh
JGCummings
PRD/EPA
Perrine Branch
Atlanta Branch (CLewis)
Division Reading File
Branch Reading File
PP No. 2F1188

GEMhitmore/ccw 3/22/72
Init: CMWilliams

Memorandum

PUBLIC HEALTH SERVICE

CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE

Food and Drug Administration

SEP 10 1969

007611

DATE: September 9, 1969

TO : Dr. Thomas H. Harris
 Division of Pesticide Registration
 Office of Product Safety, (PS-300)

FROM : J. K. Kirk *J. K. Kirk*
 Associate Commissioner for Compliance (CC-1)

SUBJECT: Aldicarb-Pesticide Petition 9H2418

Your memorandum of August 25, 1969 gives us concern. We have looked at the previous objection which you raised on this product -- which didn't mention a dust problem -- and now it would appear that because a dust problem has been eliminated you are willing to withdraw your objections.

May we have further discussion from you as to just what the facts are, and, if the product may be safely used, just why?

Attachment:
 File (to be returned)

cc:
 CC-10 Mr. Jester
 SC-13



VP Inhalation 3/11/69
Temik 11/10/67

TEMIK

July 28, 1969

007611

- Acute Rat Dermal (10.3%)(#31-137)(4 hrs.) : LD₅₀= 44.9 mg/kg of active ingredient. Only summary available.
- Acute Rabbit Dermal (10.3%)(#31-137)(4 hrs.) : LD₅₀= 200 mg/kg of active ingredient only available.
- Acute Inhalation with Saturated Vapors (10G-V)(#31-173) : No effects noted.
- Acute Rat Dermal (4 hrs)(10%) : LD₅₀= ~0.2 gms/kg (wet)
LD₅₀= >1.6 & <6.4 gms/kg (dry)
- Acute Rabbit Dermal (4 hrs)(10%) : LD₅₀= >1.6 & <3.2 gm/kg (wet)
- Acute Rabbit Dermal (10G)(1 hr) : LD₅₀= 141 mg/kg (dry).
Report No. 28-78, table No. 28-62.
- 14 Day Rabbit Dermal (10.3%)(#31-137)(10-G-V) : Levels tested were 50 and 100 mg/kg. The formula was wetted while in contact with the skin. The 100 mg/kg level showed body wt loss and muscular fasciculation.
- 5 Day Rat Saturated Vapor Inhalation (10-G-V)(#31-173) : No effects noted.
- 15 Day Rabbit Dermal (10.5%) : The 0.2 and 0.1 gm/kg levels caused depressed body wt gain.
- Subacute Exposure on Topsoil (10G)(28 day) : Soil was treated with the equivalent of 100 and 500 lbs per acre. No adverse effects were noted.
- Human Poisoning : See Ref Nos. 41,42,43,44,45 and 46.

RDCOBEPLY:am 6/3/69

TEMIK

- Seven Day Rat Feeding (Sulfoxide) : Levels tested were 0.8 and 0.4 mg/kg. The no effect level is 0.4 mg/kg.
- Seven Day Rat Feeding (Sulfone) : Levels tested were 0.4, 1.0, 2.5, 5.0 and 20 mg/kg. The no effect level is ~0.4 mg/kg.
- Seven Day Rat Feeding (Temik) : Dosage levels tested were 3.2, 1.6, 0.8, 0.4 mg/kg. Results are questionable.
- Acute Rat Dermal (99%) : LD₅₀ = 3.15 mg/kg in first study.
LD₅₀ = 7.0 mg/kg in second study.
- Potentiation Study : No potentiation was noted.
- Comparative Behavioral Effect in Rat (Tech) : Lowest effect dose was 0.266 mg/kg by ip route.
- Effective Therapy for Overdoses of Temik (Rat) : The effect of Temik was shown to be principally peripheral. Atropine was effective.
- Antidotal Therapy in Rats : Atropine plus decamethonium ^{Br?} was very effective.
- Guinea Pig Sensitizing Potential : NO sensitization response was noted.

Derivation Potential In Chickens : No overt ataxia or limb paralysis noted.

Metabolism Study : Major route is to Sulfoxide and then to Sulfoxide Oxime. Elimination of Temik from the rat, dog, and cow is virtually complete in 5 to 7 days with 96 to 98% of the radioactivity accounted for.

From 64 to 83% of the metabolites are excreted in the first day, nine of the rat, dog and cow.

Acute Rat Oral (Sulfone) : LD₅₀ = 25 mg/kg at a 0.1% conc. in corn oil.

(Sulfoxide) : LD₅₀ = 0.88 mg/kg at a 0.1% conc. in corn oil.

(Temik Oxime) : LD₅₀ = 2380 mg/kg at a 90% conc. in corn oil.

(Sulfoxide Oxime) : LD₅₀ = 8.0 gm/kg as a 10% aqueous solution.

(Sulfoxide Nitrite) : LD₅₀ = 4.0 gm/kg as undiluted.

(Sulfone Oxime) : LD₅₀ = 1590 mg/kg as a 5% in corn oil.

(Sulfone Nitrite) : LD₅₀ = 350 mg/kg as 1% in polyethylene glycol 400.

Acute Rabbit Dermal (Sulfoxide) : LD₅₀ = 5.0 mg/kg.

Acute Rabbit Eye (Sulfoxide) : 100 mg of dry powder produced death in thirty minutes. A 1% solution in propylene glycol caused no corneal injury or death.

- Acute Rat Inhalation (50 WP) : A dust cone of 13.33 mg/m³ produced 5/6 deaths at 30 minutes (or 6.7 mg/m³ of A.I.)
- Plant Metabolites : Metabolites are much less toxic than the parent chemical.
- Radio-Activity Study in Rats (Sulfone) : Chemical was readily absorbed and excreted within 7 days.
- Radio-Activity Study in Dogs (Temik) : Elimination required eleven days. Metabolites are listed in report.
- Metabolism in Rat and Dog (Temik Sulfone) : Three metabolites were recovered probably containing the sulfone grouping.
- Six Month Rat Feeding (Sulfoxide) : Levels tested were 0.125, 0.25, 0.5, and 1.0 mg/kg. Ch.I noted at all levels.
- Seven Day Rat Feeding (Sulfoxide) : Ch.I noted at seven days at 1.0 mg/kg. No ch.I noted at same level when animal was tested one day after last treatment.
- Ninety Day Rat Feeding (Sulfoxide) : Levels tested were 0.0625, 0.125, 0.25, and 0.5 mg/kg. Body wt. inhibition noted at 0.5 mg/kg. No other real effects were in evidence.
- Six Month Rat Feeding (Sulfone) : Levels tested were 0.2, 0.6, 1.8, 5.4, and 16.2 mg/kg. Ch.I noted at 1.8, 5.4 and 16.2 mg/kg.
- Seven Day Rat Feeding (Sulfone) : Level tested was 5.4 mg/kg. Ch.I noted at seven days. Complete recovery was noted when animals were tested for Ch.I 24 hrs. after last treatment.

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Ninety Day Rat Feeding (Sulfone) : Levels tested were 0.2, 0.6, 1.2, 1.8, 5.4, and 16.2 mg/kg. CH. I noted at 1.8, 5.4 and 16.2 mg/kg. Complete recovery was noted when animals were tested for CP.I. 24 hrs. later.

Ninety Day Dog Feeding (Sulfone) : Levels tested were 0.2, 0.6, 1.8 and 5.4 mg/kg. Some body weight inhibition was noted at 5.4 mg/kg. Plasma CH. I was noted at 5.4 mg/kg.

Acute Rat Dermal (10.3%) (#31-137) : LD₅₀ = 44.0 mg/kg of active ingredient. Only summary available.
(4 hrs.)

Acute Rabbit Dermal (10.3%) (#31-137) : LD₅₀ = >200 mg/kg of active ingredient. Only summary was presented for review.
(4 hrs.)

14 Day Rabbit Dermal (10.3%) (#31-137) : Levels tested were 50 and 100 mg/kg. The formula was wetted while in contact with the skin. The 100 mg/kg level showed body wt. loss and muscular fasciculation.
(10-G-V)

Acute Inhalation With Saturated Vapors (10-G-V) (#31-173) : No effects noted.

Five Day Rat Saturated Vapor Inhalation:
(10-G-V) (#31-173) : No effects noted.

Air Sampling At Formulation Plant : Site was considered as being hazardous.

Human Case Report : One person (a formulator) showed a 57% reduction in cellular CH.F and some tightness of the chest.

Rossi Case (Human Poisoning) : See ref. No. 41

Pittsburgh Case (Human Poisoning): See ref. No. 42

English Case (Human Poisoning) : See ref. No. 43

Toxicity of Treated Mint and Lettuce: Both the mint and lettuce took up and retained the toxin. The mint appears to be more toxic than the lettuce.

Wenatchee Poisoning (Human) : See ref. No. 45

Waddell Poisoning (Human) : See ref. No. 46

Usare Contact (Human) : Highest contact would be app. 4 mg of active ingredient per day per man. Values can be taken two ways. I do not agree with the presentation.

T I M I NAcute Rat Oral (Sulfone)

The oral LD₅₀ = 25 mg/kg. The test material was given as a 1% solution in corn oil.

Acute Rat Oral (Sulfoxide)

The LD₅₀ = 0.88 mg/kg.

Seven Day Rat Feeding (Sulfoxide)

Five males and five females were tested per dosage level of 0.4, and 0.8 mg/kg.

Results: The 0.8 mg/kg dosage level produced a reduction in body weight and erythrocyte cholinesterase depression. The no effect level in this study appears to be 0.4 mg/kg.

Seven Day Rat Feeding (Sulfone)

Five males and five females were tested per dosage level of 0.4, 1.0, 2.5, 5.0, and 20 mg/kg.

Results: The dosage levels between 1.0 and 20 mg/kg cause a decrease in the brain cholinesterase activity. The 20 mg/kg level also produces a decrease in body weight and decrease in the plasma and erythrocyte cholinesterase activity. The no-effect level appears to be 0.4 mg/kg.

Seven Day Rat Feeding (Chemic)

Five males and five females were tested per dosage level of 0.4, 0.8, 1.6, and 3.2 mg/kg.

Results: The chemical depressed the body weights of the male and female rats at 3.2 mg/kg but did not affect liver or kidney weights. Plasma cholinesterase was depressed among males and females at this level but only in erythrocytes among males. Brain cholinesterase showed no inhibition in either sex. At the lower dosage levels there were no statistically significant deviation from control values.

Comments: Although the high dosage level used in the study is three or four times the acute oral LD₅₀, no deaths were reported. This plus the lack of outstanding organic phosphate poisoning symptoms makes me hesitant to accept this test as being completely valid.

Acute Rat Dermal (99%)

The test material was given as a solution in dimethylphthalate. The contact time was 24 hours. In the first study, the rats were kept in restraining cages and in the second study aluminum foil was used to hold the test material in place.

Results: The rats which were kept in restraining cages showed an LD₅₀ of 3.5 mg/kg. These animals showed slight fasciculations at one to two hours following treatment. At 24 hours the surviving rats of the highest dosage level were weak. Deaths occurred between

7 and 22 hours. Recovery required one to three days.

The animals which had the dose held in place by the aluminum foil showed an LD_{50} = 7.0 mg/kg. Fasciculations appeared one to five hours after the application, and were followed by semi-collapse, lacrimation, and salivation. At 24 hours, the survivors were irritable and a few were weak. Deaths occurred between seven and thirty hours. Recovery required one to four days.

Potentiation Study

The test material was tested in equiconcentration solutions with the following cholinesterase inhibitors; diazinon, dipterex, EPN, guthion, malathion, methyl parathion, sevin, and trithion.

Results: The results are considered to be in the range of simple additive effect. The ratios ranged from 0.19 to 1.83. As indicated above, these ratios are considered additive if they fall between 0.5 and 2.0.

Comparative Behavioral Effect In Rat (Technical)

Discrete or noncontinuous avoidance behavior was studied in 10 male harlan rats, weighing between 400 and 500 gms. Studies were performed in a ten compartment rat shock box. Each compartment was supplied with one lever with an operating pressure of 12 gms, a cue light consisting of a 24 volt light bulb, and an individual grid floor to which 3 milliamperes of current was delivered by a grid scabler. The two chemicals tested were Tamik and sulfoxide.

The chemicals were injected intraperitoneally using either ethyl alcohol or distilled water as solvents. The animals were tested for six hours.

Results: Effects of Temik and the sulfoxide during the six hours indicated that a dose of 0.266 mg/kg was the lowest dose effective throughout the six hour period. The dose of 0.133 mg/kg appeared to be somewhat effective during the first 3 hour period but not significantly so during the second period.

The intraperitoneal $LD_{50}=0.57$. Thus, the ratio between the lowest effective dose of (0.266 mg/kg) and the intraperitoneal LD_{50} (0.57 mg/kg) gives a ratio of 2.

Effective Therapy for Overdoses of Temik in the Rat

Temik and its metabolites sulfoxide and sulfone were dosed orally at 1 and 2 times their respective oral LD_{50} to male rats and an attempt was made to identify possible sites of reaction.

Results: These chemicals produced a strong muscarinic action at exocrine, excretory, bronchial, and cardiac nerve sites. In addition a nicotinic effect was showed to occur at the myoneural junctions. The effect of Temik was shown to be principally peripheral with little or no central nervous system effects in the rat. Atrazine was shown to be the antimuscarinic drug of choice and capable of completely blocking the muscarinic effects noted at 2 times the LD_{50} of the test material and its metabolites.

Results indicate that there is no action on the autonomic plexus and that all nicotinic effects are exerted on the neuromuscular junction.

Antidotal Therapy in Rats

Terik was dosed at 6 and 8 times the oral LD₅₀ followed within 3 to 4 minutes by intravenous atropine sulfate at several different dosages which were then followed within one minute by intravenous decamethonium. When multiple doses were given, the antidotes were injected as soon as the effect being blocked reoccurred. In other studies 2-PAM was administered intramuscularly at 15.0 mg/kg alone or in combination with atropine sulphate at 5.0 mg/kg intraperitoneally within three to four minutes after two or three times the intraperitoneal LD₅₀ of Terik.

Results: While 8 times the oral LD₅₀ dose of Terik could not be effectively blocked, 6 times the LD₅₀ dose could be controlled when atropine sulfate and decamethonium were used in combination. PAM in combination with atropine sulfate appeared no better than atropine in controlling the effects of 2 and 3 times the intraperitoneal LD₅₀ dose.

Sensitizing Potential in the Guinea Pig

Twenty-two young adult guinea pigs were injected intradermally with 0.05 ml of an 0.1% solution of Terik in 0.85% saline.

Starting 48 hours after the initial injection, a series of 7 interdermal sensitizing injections of 0.1 ml of the Temik solution were given at the rate of 3 injections per week. Each injection was given into an untreated site.

The animals were then allowed a three week incubation period and then were given a challenge interdermal injection of 0.05 ml of the Temik solution.

Results: No albino male guinea pig of the group showed any sensitization response.

Demyelination Potential in Chickens.

Six chickens were tested per dosage level of 9.0, 4.5, and 2.25 mg/kg. All solutions were made up in corn oil once each week and orally administered daily for 30 days. At the conclusion of dosing, the animals were observed for an additional 30 days in order to detect any delayed signs of ataxia or hind limb paralysis.

Metabolism Study

Several metabolism studies in animals showed the major pathway of degradation to be by oxidation to Temik sulfoxide which in turn was degraded to sulfoxide oxime which in turn was conjugated. Other pathways included hydrolysis and nitrile series.

These studies showed that the elimination of the test material from the rat, dog, and cow is virtually complete in 5 to 7 days with 96 to 98% of the radioactivity accounted for. Most of the

Temik metabolites (64 to 83%) are excreted in the first day urine of the three species and only moderate amounts are found in the feces. One investigator found no radioactivity in the rat carcass 4 days after dosing with labelled Temik. This may indicate that the compound is not stored in the tissues.

Direct metabolic studies were the two toxic metabolites (Temik sulfide and sulfone, had been performed in the rat where 97% and 87% respectively of dosed compounds were excreted in 7 to 11 days. Post-mortem examination of the carcasses and gastro-intestinal tract of these rats showed no detectable residue radioactivity 7 days after ingestion. Urinary excretion of Temik sulfone by the dog which was dosed at 1 mg/kg was reported to be about 76% in 7 days.

Acute Rabbit Dermal (Sulfoxide)

The test material was applied to the test animals as a 5% solution in propylene glycol.

Results : The LD_{50} = 5.0 mg/kg.

Acute Rabbit Eye

The instillation of less than 100 mg of the dry powder Temik sulfoxide caused death in a rabbit in 30 minutes. An excess of a 1% solution in propylene glycol did not produce corneal injury nor death.

Acute Rat Inhalation (50 hr)

Sixty male rats were exposed to a dust concentration of 13.33 mg/m³ of the formulation.

Results: At 15 minutes, no deaths were noted. At 30 minutes 5 of the 6 females were dead. Autopsy findings revealed tetechial hemorrhage of the lungs and traces of blood in the intestines. Typical anticholinesterase symptoms were observed after the one-half hour inhalation.

Toxicity of Plant Metabolites

These data indicate that the plant metabolites of Terik are much less toxic than the parent compound. The oral LD₅₀ for rats are 8.0, 1.6, 4.0, and 0.35 gm/kg for the oxime sulfoxide, oxime sulfone, nitrile sulfoxide and nitrile sulfone. Rats were the most tolerant of all species studied with the exception of nitrile sulfone for which rabbits had a greater tolerance.

It was established by means of purified enzyme preparations that these probable non-carbamate metabolites were not cholinesterase inhibitors.

Radioactivity Study in Rats (Sulfone)

S-methyl-C¹⁴ (22.5 µc/mg) Terik sulfone dissolved in polyethylene glycol 400 was administered to rats by stomach intubation.

- 9 -

During this study, the animals were housed individually in all glass metabolism cages which permitted the simultaneous and separate collection of urine, feces, and respiratory CO_2 . At the termination of the study (7 days) the animals were killed and the carcasses of 2 animals were analyzed for residual C_{14} .

Results: The sulfone is readily absorbed and excreted by the rat with an average of 74% in the urine, 10% in cage washings, 1.8% in feces and 0.60% in respiratory CO_2 . No radioactivity could be detected in the gastrointestinal tract nor in the carcass after 7 days.

Radioactivity in Dogs (Temik)

Nonlabeled Temik at a dose of 0.75 mg/dog/day was added to the food of 3 female beagle dogs maintained in individual metabolism cages for 20 days. On the 21st day only, a methyl labeled C_{14} was substituted for the nonlabeled compound. After this single exposure, the dogs were continued on nonlabeled Temik for the remainder of the study. Urine from each dog was collected and analyzed for radioactivity each day by liquid scintillation counting techniques.

Results: The elimination from the dogs by way of the urine required 11 days. The rate of excretion had become less than 2% of the dose after the 2nd day and less than 1% of the dose after the 3rd day. Elimination by way of the urine averaged 74% of the dose for the 3 dogs.

A urinary metabolic profile as determined by silica gel chromatography led to the identification of Temik sulfone nitrile, Temik sulfone oxime, Temik sulfone, Temik sulfoxide oxime, and Temik sulfoxide. These compounds account for 44.5% of the activity from the column. Temik, Temik nitrile, or Temik oxime cannot be detected.

Metabolism in the Rat and Dog (Temik Sulfone)

Urinés from Temik sulfone orally dosed rats obtained in the material balance study reported earlier was used to obtain a profile.

Results: The metabolic profile obtained by silica gel chromatography with urine from dogs fed labeled Temik gave a chromatogram with 10 distinguishable areas. Profiles developed from urines of dogs and rats dosed with labeled sulfone indicated six of these areas probably contained compounds with sulfone grouping. Individual peak components were verified by thin layer chromatography. Temik sulfone nitrile, Temik sulfone oxime, and Temik sulfone were identified in urines from the dogs dosed with Temik sulfone. These components plus sulfoxide nitrile, sulfoxide oxime, and Temik sulfoxide comprised the known organo-soluble fractions generally reported.

Six Month Rat Feeding (Sulfoxide)

Fifteen males and fifteen females were tested per dosage level of 0.125, 0.25, 0.5, and 1.0 mg/kg.

Results: All rats survived the 1.0 mg/kg level. No more than one rat of either sex died at any of the lower dosage levels during the first three months, and only one of 96 rats died during the last three months of the study.

The overall diet consumption of the male rats at the 1.0 mg/kg level was slightly but significantly depressed at 3 months, but not at 6 months. The male animals at this dosage level also showed a reduction in body weight gain as compared to the control animals. The male animals in the two lower dosage levels also showed a reduction in body weight gain.

Plasma cholinesterase was significantly inhibited in the males and the females at 0.5, and 1.0 mg/kg. It was also significantly inhibited at 0.25 and 0.125 mg/kg in the males at 3 months of dosing. However, it was not inhibited at 6 months.

Erythrocyte cholinesterase was inhibited at 1.0 mg/kg at 3 months; and at 1.0, 0.5, and 0.25 mg/kg at 6 months. No significant inhibition of erythrocyte cholinesterase was found at 0.125 mg/kg in either sex at 3 or 6 months in the males.

Brain cholinesterase was significantly lower than the control value in the males at 1.0 mg/kg at 3 months and in the females at 1.0 and 0.5 mg/kg at 6 months.

No gross or microscopic lesions were observed.

Seven Day Rat Feeding (Sulfoxide)

Part I Five males and five females were tested at a dosage level of 1.0 mg/kg for 7 or 8 days. Cholinesterase values were determined at the end of this period.

Results: This level produced significantly depressed erythrocyte and plasma cholinesterase values.

Part II Five males and five females were tested at a dosage level of 1.0 mg/kg for 7 days plus 1 day on control feed.

Results: The cholinesterase values which were noted in the prior part of this study were not obvious in this section. Depressions of as much as 80% which were noted in the other study were completely reversed in this study. This data indicates that the chemical is rapidly metabolized within the body.

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TEMPNinety Day Dog Feeding (Sulfoxide)

Three male and three female beagle dogs were tested per dosage level of 0.0625, 0.125, 0.25, and 0.5 mg/kg/day.

Prior to the first day of feeding and at 11 weeks the following were determined - blood urea nitrogen, blood glucose, bilirubin, SGOT, SCPT, serum alkaline phosphatase, total red blood cell and white blood cell, differential white blood cell count and hemoglobin.

The plasma and erythrocyte cholinesterase were determined prior to the first dose and at 1.5 weeks and at 1, 2, and 3 months of dosing. The brain cholinesterase value were also determined at the termination of the study.

Results: The 0.5 mg/kg animals showed a significant retardation of body weight gain during the first week of the study. After this point the weight was not significant but it was definitely lower than the corresponding control animals. No mortality occurred during the entire study.

The biochemical and hematological determinations made in this study appeared to be within a normal range. There were some sporadic significant differences in the alkaline phosphatase and SGOT however none of them appeared to be indicative of a detrimental effect exhibited by the chemical.

Six Month Rat Feeding (Sulfone)

Fifteen males and fifteen females were tested per dosage level of 0.2, 0.6, 1.8, 5.4, and 16.2 mg/kg. Five rats of each sex were randomly selected and killed after 3 months of dosing. Cholinesterase levels, liver and kidney weights and microscopic appearance of the cranial, thoracic and abdominal viscera were made at this point. The surviving animals were sacrificed at 6 months.

Results: The mortality rate, diet consumption, and liver and kidney weights of the test animals were statistically similar to the control values. Body weight changes of the rats at the highest dosage level (16.2 mg/kg) were significantly lower than that of the control animals for the first 27 & 5 days for the males and females respectively. At a later date the males again showed a significant body weight inhibition.

Plasma, erythrocyte and brain cholinesterase were all significantly depressed at the dosage levels of 5.4 and 16.2 mg/kg at 3 and 6 months. Plasma cholinesterase was also depressed in the males at 3 months and in the females at 6 months at a dosage level of 1.8 mg/kg; erythrocyte cholinesterase was also lower in these rats at this level as well as in the males at 6 months. Brain cholinesterase was lower in the females at 6 months at the dosage level of 1.8 mg/kg. No depression of cholinesterase values was noted at the 0.6 mg/kg dosage level.

No gross or microscopic lesions were noted in any tissue or organ at the 3 or 6 months interval period.

Seven Day Rat Feeding (Sulfone)

I. Five males and five females were fed the dosage level of 5.4 mg/kg until after 7 or 8 days of dosing.

II. A similar group was started on the same date but the test material was removed 24 hrs. prior to the termination of the study.

Ninety Day Rat Feeding (Sulfone)

I. Five males and five females were tested per dosage level of 0.2, 0.6, 1.2, 1.8, 5.4, and 16.2 mg/kg.

II. An identical group was tested at the same dosage levels and the same protocol with the exception that the animals did not receive any test material during the final 24 hrs. before termination of study.

Results: The significant plasma and erythrocyte cholinesterase depression at 16.2 and 15.4 mg/kg and brain cholinesterase depression at these levels and 1.8 mg/kg (female only for brain) after 3 months of dosing was reversed in the second study after only 24 hrs. on control diet.

Ninety Day Dog Feeding (Sulfone)

Three males and three females were tested per dosage level of 0.2, 0.6, 1.8, and 5.4 mg/kg/day.

Plasma and erythrocyte cholinesterase and hematocrit were determined prior to the first dose and at 1.5 weeks and at 1, 2, and 3 months.

Results: The body weight gain of the 5.4 mg/kg/day dosage level was lower than the corresponding test and control animals. This difference was not considered significant.

No mortality was noted during the study. The individual liver and kidney weights were comparable to the corresponding control values. The individual and mean values of the biochemical test and hematological determinations showed only a significant difference in the serum glutamic-oxalacetic transaminase at the 0.6 mg/kg level but not at the 1.8 or 5.4 mg/kg.

Acute Rat Dermal (Four hours)(Ten C-V)(10.3%)(No.31-137).

Only a summary of these data are presented and they indicate that a four hour test was conducted with the chemical on rats. The chemical was in granular form which was placed under the tape and were wetted at frequent intervals with physiological saline.

Results: The acute LD50=44.9 mg of active ingredient per kg.

Acute Rabbit Dermal(Four hours)(10.3%)(#31-137)(10-C-V)

The test material was placed under the adhesive tape in the dry form.

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Results: No mortality resulted among the four animals dosed at 200 mg/kg of active ingredient. Only a summary of the data was presented.

Fourteen Day Rabbit Dermal (10.37) (#1-137) (10-G-V)

Five rabbits were tested per dosage level of 0.05 and 0.10 gm/kg. The 0.05 group was started two days later than the 0.10 gm/kg group. The test material was applied in the form of granules under a 4x4" gauze pad which was retained in place by a fiberglass screening. The rabbits were immobilized for six hours each day, and the gauze wetted with 2 ml of water every 45 minutes, eight times per day.

Results: The body weight of ^{the} 0.1 gm/kg group was significantly depressed throughout the first week of testing. Recovery was noted during the second week. One rabbit receiving the 0.05 gm/kg dosage level lost a considerable amount of weight 637 gms by the end of the study. If this animal's values were extracted from the results the results would be considered normal. If the results of this animal were included they would show a mean body weight loss of 0.023 gms at the end of fourteen days.

Acute Inhalation With Saturated Vapors (10-G-V) (#31-173)

Six female rats were placed into a chamber which had previously been heated in a room to 106° F with 18.56 gm of Temik 10-G-V granules in it which had been wetted. Length of exposure for the rats was eight hours.

The exact procedure and specifications are listed in the report. I do not feel that every aspect of the procedure should be reported here.

Results: The rats which were killed immediately after the eight hour exposure showed no significant depression of the cholinesterase values of the RBC and plasma.

Five Day Rat Saturated Vapor Inhalation(10-G-V) (#31-173)

The protocol employed for this study was identical to the protocol used for the acute inhalation with the saturated vapors with the exception that the length of the study was extended from one to five consecutive days.

Results: The results obtained from these rats indicated no significant depression of the RBC and plasma cholinesterase.

Air Sampling At Formulation Plant

The formulation of 484 lbs of the formulation (10-G) showed the following findings: the dryer did not control the vapors, mists, and possible fine particles given off during the drying process; the large area in which the dryer was located contained concentrations of the test material considered hazardous to the health of unprotected personnel; unknown quantities of methylene chloride and the test material were exhausted to the atmosphere; the work with the test material was difficult

to isolate from other agricultural chemical operations being performed in the area by unprotected Chemical Formulators personnel.

Huran Case Report

This case involves one person, a Chemical Formulator which showed a 57% reduction in cellular cholinesterase after exposure to the test material. His plasma cholinesterase level was within the normal range. Two days later the cellular level cholinesterase value had returned to within the normal range. The exposure consisted of operation of a mechanical bagging machine during the morning working period.

The man also complained of being tired and having a tightness in his chest.

Toxicity of Treated Mint and Lettuce

I. Under field conditions the test material was applied to established mint and lettuce plants at the rates of 30 lbs. active ingredient per acre broadcast and 3 lb. active ingredient per acre sidedress for the mint and lettuce respectively. The crops were picked seven days after treatment. These plants were then presented to rabbits which have been fasted for 24 hours. The amount of the plants consumed within a 24 hour period was calculated.

II. Laboratory grown mint and lettuce were treated in the laboratory with the test material at the rate of 20 lbs. of active ingredient per acre broadcast. The plants were picked seven days after treatment.

Results: Plants grown under field condition showed a total residue level of 49.83 ppm in the mint and 18.68 ppm in the lettuce seven days after treatment. Metabolic products detected in these plants were qualitatively similar to those previously reported in other plant species. The test rabbits did not rapidly consume the quantities of food presented to them. The highest amount of plant material which was consumed by the rabbits during the 24 hour period resulted in a dosage level of 1.3 and 0.6 mg/kg of Temik plus Temik sulfoxide for the mint and lettuce respectively. No mortality was noted.

In the laboratory portion of the study the treated mint contained 43.54 ppm and the lettuce had 54.24 ppm of total C¹⁴-Temik equivalents seven days after treatment. The plants were then homogenized for the purpose of oral feeding to rats. The 14 day rat LD⁵⁰ level of this homogenite was 13.1 gr /kg for the mint and greater than 32 gr /kg for the lettuce.

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Usage Contact In Cotton (In Human)

The highest concentration of Temik and its toxic metabolites found in cotton when the pesticide is used at recommended dosage is about 186 ppm. During the time when cotton scouts may be expected to be examining the cotton crop for insect infestation the pesticide level will be about 42 ppm. In examining the plants some of the leaves will be pinched off and/or crushed, thus permitting contact with plant juices. Estimates from knowledgeable persons placed the volume of plant juices contacted at a level probably not exceeding 20 ml in a workday.

If we assume a concentration of 200 ppm of Temik and its toxic metabolites in the cotton juices, each ^{LITER} ~~liter~~ of plant juice will contain 200 mg of active ingredient. If a man contacts 20 ml of this plant juice he will contact and absorb 4 mg of ~~the~~ pesticide.

The report goes on to say that if we now assume a man response like a rabbit insofar as ^{dermal} ~~transdermal~~ absorption we find the following: The skin penetration LD⁵⁰ in a rabbit of an aqueous solution of Temik is 19.8 mg/kg (?). In a 70 kg man this would mean the LD⁵⁰ dose for him would be 19.8x70 or 1,386 mg. If we now apply a factor of safety of 100 we arrive at a dose of 13.8 mg of pesticide. The report states that this is still 3 times more than the 4 mg to which the man could theoretically be exposed.

There are two things wrong with this report so far as my knowledge of the chemical goes. First the rabbit LD⁵⁰ which is presented in the earlier books received from the company indicates that the LD⁵⁰ is approximately 5.0 mg/kg and not 19.8 mg/kg as stated in this section of the book. This alteration in value replaces the 13.8 mg mentioned in this section with a value of 3.5 mg. As you can readily see the 3.5 mg is below the theoretical exposure level of 4 mg.

Secondly the person writing this book (Dr. Haines) has calculated from the acute dermal LD⁵⁰ rather than the acute dermal LD⁰. In essence he is saying that the man who receives this exposure has a 50% chance of dying which is further reduced by a safety factor of 100.

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TABLE II

TOXICOLOGY OF ALDICARB METABOLITES IDENTIFIED
IN TOBACCO AND SMOKE PYROLYSIS PRODUCTS
AND SAFETY FACTORS FOR CALCULATED EXPOSURE

Compound	Rat Oral LD ₅₀ mg/kg	7-Day Rat Dietary NIEL, mg/kg	Calculated Daily Exposure mg/kg/day, from 40 Cigarettes per day ⁸	Safety Factor Rat NIEL mg/kg/day ÷ Daily Exposure mg/kg/day
Acetone sulfide	0.9 ²	0.5 ⁴	0.00013	3,800
Acrolein alcohol	11,300 ¹	1,000 ¹	0.00010	2,500,000
Acrolein oxide	16,000 ¹	-	0.00010	-
Acrolein nitrile	4,000 ³	100 ³	0.00073	170,000
Acrolein oxime	8,000 ³	125 ³	<0.00007	>1,800,000
Aldicarb sulfone	25 ²	5 ⁵	0.00010	25,000
Allyl alcohol	11,300 ¹	-	0.00017	-
Allyl oxide	11,300 ⁶	>4,000 ⁶	0.0013	>2,200,000
Allyl nitrile	350 ³	72 ³	0.0006	20,600
Allyl oxime	1,590 ³	50 ³	0.00033	150,000
Allyl aldehyde	n.a. ⁷	n.a. ⁷	0.00033	-

1. J. Ag. Food Chem 10 (3) 446 1970, Farley, W. J., et al.

2. Federal Register 970792, Section C, Part II, Reference 2

3. EPA, Reference 20

4. EPA, Reference 24 (90-day study)

5. EPA, Reference 25 (90-day study)

6. Data not available to EPA

7. Data not available

8. Calculated from data assuming each cigarette contains 0.8 mg nicotine.

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TABLE I

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PYROLYSIS PRODUCTS IN CIGARETTE SMOKE AND
 METABOLITE RESIDUES IN CURED AND GREEN TOBACCO
 GROWN IN S-METHYL C-14 ALDICARB TREATED SOIL

Product	$\mu\text{g/g}$ (cured weight basis)		
	Green ⁽¹⁾	Cured	Smoke
Aldicarb sulf oxide	24.3	8.1	<u>0.2</u>
Sulf oxide alcohol	1.3	0.9	0.6
Sulf oxide oxide	7.6	11.0	0.9
Sulf oxide nitrile	1.2	6.0	1.1
Sulf oxide ester	1.2	1.0	ND
Aldicarb sulfone	32.1	16.3	<u>0.3</u>
Sulfone alcohol	ND	1.0	1.0
Sulfone oxide	12.6	10.0	2.7
Sulfone nitrile	6.6	3.8	5.2
Sulfone ester	1.4	1.6	0.5
Sulfone aldehyde	ND	0.4	0.5
Polyn	29.6	33.6	0.8
Residue	7.5	5.0	-
Total	125.4	98.7	15.0

(1) Data are based on fresh weight residues.

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Mr. Frank T. Sanders

February 25, 1976

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The large magnitude of the safety factors demonstrate the lack of hazard. The three products where safety factors could not be calculated are all minor components of the tank with very low toxicity expected. Although the safety factors are based on dietary studies, the latter do give an indication of inhalation toxicity. This, coupled with the large magnitude of the safety factors, leads to the conclusion that there is no reasonable expectation of effect or hazard from inhalation, and no need for a separate inhalation test.

Very truly yours,

R. L. Meeker

R. L. Meeker
Group Leader
Pesticide Registration
Chemistry

RLM:jl

Attachments

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Caswell No 1,19A

DATE: September 6, 1978

SUBJECT: EPA # 1016-TO, Standak WP75. Sulfocarb on Tobacco.

007611

FROM: H.W. Spencer, Ph.D.
Toxicology Branch/RD

TO: F. Sanders, PM #12

Registrant: Union Carbide Corp.
7825 Baymeadows Way. P.O. Box 17610
Jacksonville Florida, 32216

Conclusions and Recommendations

1. Label for use should indicate pounds of WP 75/acre
2. Supply the following data to support the registration request:
 - a. Oral Toxicity LD 50 - rat, female (WP 75)
 - b. Dermal Irritation - individual scores using the moistened
 - c. Inhalation LC 50, rat, female (WP 75, dust)
 - d. Individual eye irritation data for study II 38-87.
3. The use of the pesticide should be delineated as to the type and use of tobacco, especially since curing of tobacco by methods other than heating, i.e. "flue cured" does not tend to lower the residues as well as the flue curing method since residue data on tobaccos such as Maryland (barn-cured) were not presented for review.

Toxicity Data Summary Considered

1. Oral LD 50 (technical) 21.4 (14.5-31.7) mg/kg rat, male
2. Oral LD 50 (WP 75) 23.3 (15.8-34.5) mg/kg rat, male
3. Dermal LD 50 (technical) 1000 (472-2090) mg/kg rat, male
4. Inhalation (WP 75) dust 1 hour LC 50 \approx 0.8 mg/L rat, male
5. Inhalation (WP 75) dust 4 hour LC 50 \approx 0.5 mg/L rat, male
6. Eye irritation (WP 75) rabbit Not irritated
7. Neurotoxicity - hen - negative at 250 mg/kg
8. 18-month feeding - mouse - negative for oncogenic survey. NEL = 9.6 mg/kg/day.
9. Oral LD 50 1.5 (0.97-2.59) g/kg (sulfocarb oxime) rat, male
10. Oral LD 50 0.35 g/kg sulfocarb nitrite rat, male.
11. Oral LD 50 (0.146-0.54) ml/kg (methane sulfonic acid (undiluted) rat, male.
12. 3-generation rat -(technical) NEL = 9.6 mg/kg
13. teratology - rat - no terata formed at 9.6 mg/kg
14. 56 day feeding - rat CHE NEL = 2.4 mg/kg/day.
15. Inhalation 9 day x 6 hour/day at 0.018 mg/L (WP 75) NEL for CHE in RBC, plasma in rat females at 0.006 mg/L

The 9 day 6 hr/day NOEL for CHE Inhibition of 0.006 mg/L was used in assessing the safety of the residue intake for man.

Data submitted indicated that the actual weight percent respired into the lungs was not 70% but was instead only 10.2% of the actual weight. However, that smaller weight represented 70% of the number of particles (1.5 to 4.5 microns). The material in the lungs, with exception of the clay, could be assumed to be rapidly absorbed into the blood stream. Other particles also inhaled, but filtered on to the mucous membranes may be variably absorbed.

Adding a safety factor of 10X the figure of 0.0006 mg/L was used in the succeeding calculations.

0.0006 mg/L inhaled X 4 ml per breath X 50 times/minute = 0.2L/min. X .0006 mg/L

.00012 mg/minute
.14 kg= wt of rat
0.000857 mg/min/kg
X 60 min/hr
0.051426 mg/kg/hr. or 51.4 μg/kg/hr.

Assuming 3.23/hr of tobacco is smoked, then the smoker inhales 4.8 μg/g of tobacco. This represents 15.5 μg/hr or 0.0155 mg/hr. of residue or 0.26 μg/kg/hr and results in about a 200 X S.F. for Choline esterase inhibition.

The other metabolite appearing in highest proportion in the smoke is the sulfo carb nitrile with an oral LD 50 of 350 mg/kg calculations suggest that only about 2.1 μg/kg/hr. will be presented to the smoker. Assuming 6 cigarettes/hr. and in 16 hr. day, 34 μg/ of the nitrile would be exposed to the lungs of the smoker. A ratio of over 10,000 : 1 from the oral LD 50.

BD initial RE:8/14/78:lf

E 9/8/77

2 007614

Formulation: Temik 15% Granular

Active Ingredient

15% 2-methyl-2-(methylthio) propionaldehyde carbamoyl oxime

Inert Ingredient

Inert ingredient information not included.

*Cleared as inerts in 40 CFR 180.1001(d)

Toxicity Data

The following toxicity data were submitted with this report

Acute Rabbit Oral LD50 (Temik 10G) - 17.8 mg/kg

Four rabbits were used per level of 10, 20, and 40 mg/kg was administered via gelatin capsule.

Results

LD50 = 17.8 (8.38 to 37.9) mg/kg or 1.78 mg/kg of active ingredient. Tremors, salivation, pin point pupils, loose stools and diarrhea four hours were noted at all levels. The acute no effect level is less than 10.0 mg/kg. Gross pathology was unremarkable.

Acute Rabbit Oral LD50 (Temik 15G) - 10.6 mg/kg

Four rabbits was used per level of 6.67, 13.33, and 26.67 mg/kg

The test material was administered via gelatin capsule.

Results

LD50 = 10.6 (6.5 to 17.3) mg/kg or 1.59 mg/kg of active ingredient. Tremors, salivation, pin point pupils, loose stools were noted at all levels. The acute oral no effect level is less than 6.67 mg/kg formulation. Gross pathology was unremarkable.

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Acute Rabbit Dermal LD₅₀ (Dry Temik 10G) - >4.8 gm/kg

Four adult New Zealand white rabbits were tested at 4.8 gm/kg. The test material was applied dry on intact skin. Length of exposure was four hours.

Results

No mortality occurred. Signs, symptoms and gross pathology were unremarkable.

Acute Rabbit Dermal LD₅₀ (Dry Temik 15G) - >4.8 gm/kg

Four adult New Zealand white rabbits were tested at 2.4 gm/kg and one at 4.8 gm/kg. The test material was applied dry on intact skin. Length of exposure was four hours.

Results

No mortality occurred. Signs, symptoms and gross pathology were unremarkable.

Acute Rabbit Dermal LD₅₀ (Wet Temik 10G) - >4.8 gm/kg

Four adult New Zealand white rabbits were tested at 4.8 gm/kg and one at 2.4 gm/kg. The test material was applied wet on intact skin. Length of exposure was four hours.

Results

No mortality occurred. Tremors were observed among the high level rabbits. No symptoms were noted at 2.4 gm/kg. Gross pathology was unremarkable.

Acute Rabbit Dermal LD₅₀ (Wet Temik 15G) - 4.8 gm/kg

Four adult New Zealand white rabbits were tested per level of 2.4 and 4.8 gm/kg. The test material was applied wet on intact skin. Length of exposure was four hours.

Results

LD₅₀ = 4.8 (1.34 to 17.2) gm/kg. Typical cholinergic signs were evident at both levels.

Acute Male Rat Dermal LD₅₀ (Dry Temik 10G) - 2.10 gm/kg

Four adult male rats were tested per level of 1.25, 2.5, and 5.0 gm/kg. The test material was applied dry to intact skin for four hours.

Results

LD₅₀ = 2.10 (1.38 to 3.21) gm/kg. Typical cholinergic signs were noted at all levels. Gross pathology revealed petechial hemorrhages in lungs; stomach injected and congested kidneys and adrenals.

Acute Male Rat Dermal LD₅₀ (Dry Temik 15G) - 3.15 gm/kg

Four adult male rats were tested per level of 2.5 and 5.0 gm/kg. Length of exposure was four hours on intact skin.

Results

LD₅₀ = 3.15 (1.93 to 5.14) gm/kg Typical cholinergic signs were noted at both levels. Gross pathology revealed petechial hemorrhages in the lungs; stomach and intestine injected; and congested adrenals and kidneys.

Acute Female Rat Dermal LD₅₀ (Dry Temik 10G) 3.97 gm/kg

Four adult female rats were tested per level of 2.5 and 5.0 gm/kg. Length of exposure was four hours on intact skin.

Results

LD₅₀ = 3.97 (2.43 to 6.48) gm/kg. Typical cholinergic signs were noted at both levels. Gross pathology revealed petechial hemorrhages in the lungs and slightly congested adrenals and kidneys.

Acute Female Rat Dermal LD₅₀ (Dry Temik 15G) 3.97 gm/kg

Four adult female rats were tested per level of 2.5 and 5.0 gm/kg. Length of exposure was four hours to intact skin.

Results

LD₅₀ = 3.97 (2.43 to 6.48) gm/kg. Typical cholinergic signs were noted at both levels. Gross pathology revealed petechial hemorrhage in the lungs; mottled livers; injected stomachs and intestine; and slightly congested kidneys and adrenals.

Acute Male Rat Dermal LD₅₀ (Wet Temik 10G) 0.566 gm/kg

Four adult male rats were tested per level of 0.4 and 0.8 gm/kg. Length of exposure to the moistened test material was four hours on intact skin.

Results

LD₅₀ = 0.566 (0.347 to 0.924) gm/kg. Typical cholinergic signs were evident at both levels. Gross pathology revealed petechial hemorrhage in the lungs; stomach and intestine injected.

Acute Male Rat Dermal LD₅₀ (Wet Temik 15G) 0.566 gm/kg

Four adult male rats were tested per level of 0.4 and 0.8 gm/kg. Length of exposure to the moistened test material was four hours on intact skin.

Results

LD₅₀ = 0.566 (0.347 to 0.924) gm/kg. Tremors were noted at both levels. Gross pathology revealed petechial hemorrhage in the lung; intestine injected; and congested adrenals and kidneys.

Acute Female Rat Dermal LD₅₀ (Wet Temik 10G) - 0.673 gm/kg

Four adult female rats were tested per level of 0.4, 0.8, 1.6, and 3.2 gm/kg. Length of exposure to the moistened test material was 4 hours on intact skin.

Results

LD₅₀ = 0.673 (0.440 to 1.03) gm/kg. Gross pathology revealed petechial hemorrhage in the lungs; injected stomachs and intestines and congested adrenals and kidneys. Tremors were observed at all levels.

Acute Female Rat Dermal LD₅₀ (Wet Temik 15G) - 1.01 gm/kg

Four adult female rats were tested per level of 0.8, 1.6 and 3.2 gm/kg. Length of exposure to the moistened test material was four hours on intact skin.

Results

LD₅₀ = 1.01 (0.617 to 1.65) gm/kg. Tremors were noted at all levels. Gross pathology of survivors revealed slight lung congestion, mottled livers, and speckled kidneys.

Acute Rat Inhalation (Temik 10G)

Six rats were exposed to the test material in a sealed chamber for 8 hrs. Fifty grams of the material was placed on a shallow tray over which air was intermittently circulated. This chamber was prepared at least 16 hours prior to introduction of the rats.

007611

Results

No mortality or other toxic signs and symptoms were observed.

NOTE: The air concentration of the test material was not determined.

Acute Rat Inhalation (Temik 15G)

Six rats were exposed to the test material in a sealed chamber for 8 hrs. Fifty grams of the material was placed on a shallow tray over which air was intermittently circulated. This chamber was prepared at least 16 hours prior to introduction of the rats.

Results

No mortality or other toxic signs and symptoms were observed.

NOTE: The air concentration of the test material was not determined.

Human Monitoring Study (Temik 15G)

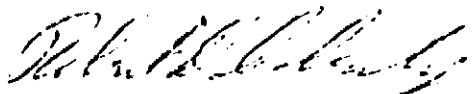
One human applied 3700 pounds of Temik 15G to 188 acres during a five day period (8-9 hours daily). Air and wipe samples were collected from both man and machine. Urine was also analyzed. An MD examined the subject daily.

Results

No apparent effects were observed.

CONCLUSION

These data will be added to our toxicity data file for this chemical.


Robert D. Coberly, Biologist
Toxicology Branch
Registration Division (HM-567)

cc: Division File, Branch File, PP No. 3F1414

RDCoberly/km 06-25-74

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Dr. Schmidt

007611

SUBJECT: Temik (Aldicarb) - Review of data submitted in support of the proposed 1 ppm aldicarb and its metabolite in potatoes. DATE: February 11, 1974

FROM:

TO: Mr. Lee TerBush
Acting Chief
Coordination Branch

Pesticide Petition No.: 3F1414 - Union Carbide Corporation
1730 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

In a conference with the petitioner January 11, 1974, Toxicology Branch agreed to reconsider the objections to granting the requested tolerances (COB letter of 12/19/73). Petitioner was requested to reiterate in writing the points discussed at the meeting. This has been done.

Materials now submitted are:

A. Attachment 1 - Interpretation by Mr. Carol Weil, Senior Fellow of Carnegie-Mellon University.

In his summary of data previously submitted for the long-term rat feeding studies, he states that "because the entire first two-year study was without effect, the level of 0.3 mg/kg aldicarb was fed in the second two-year study. Absolutely no male or female rats died during the entire first year of doses at 0.3 mg/kg (as contrasted to approximately 38 to 43% at 0.1 mg/kg in the 90-day study)." Mr. Weil argues thusly: "The only reasonable explanation for the reason for the mortality in the 90-day study was that the crystals of aldicarb were incorporated in the rats diets by rolling for 8 hours in a ball mill. This might not have crushed the crystals to so small a size that, perhaps, rats received crystals of aldicarb as portions of their dry diets. In subsequent --- studies, the aldicarb was incorporated in the diet by an efficient vertical mixer."

To corroborate these findings Mr. Weil cites a teratology study in which the highest dosage of aldicarb fed was 1.0 mg/kg/day from days one to seven of pregnancy, days 5 to 15, or throughout pregnancy, all produced negative results or mortality.

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The aforementioned (0.3 mg/kg level of aldicarb), two-year rat study was reviewed by Dr. B. Schmidt, 9/25/73. These data were part of a study to estimate the toxicity of the sulfoxide and sulfone metabolites of Temik. This study established a ChE-NEL of 0.3 mg/kg for aldicarb or 6 ppm.

B. Attachment 2

A letter from C. U. Dernehl, M.D. of Union Carbide to Dr. R. C. Back, Agricultural Products, Union Carbide. Dr. Dernehl describes human studies in which single acute doses of aldicarb were given at levels of 0.1, 0.05 and 0.025 mg/kg. All three groups showed effects on blood ChE levels. It was stated that "the method used to determine blood ChE measured the sum of effects on cholinesterase and pseudocholinesterase, and since aldicarb is known to bind the plasma ChE before it binds RBC-ChE, it is a reasonable conclusion that much of the observed ChE inhibition seen in human volunteers was due to bound plasma pseudocholinesterase."

This report of ChE effects at all levels fed is contrary to our evaluation (memo of G. E. Whitmore, PP# OF1008, 4/6/71) in which it was considered that 0.025 mg/kg of aldicarb was a "no-effect" level for ChE inhibition in this study with humans. Using a safety factor of 10 (to account for the very young and very old) a level of 0.0025 mg/kg aldicarb in the total dietary could be supported. This translates to 0.15 mg/day for a 60 kg man.

Setting aside the arguments of Dr. Dernehl, at a level of aldicarb of 1 ppm on potatoes a maximum of 0.150 mg aldicarb per se would be contributed to the daily human 1500 gm diet considering potatoes at 10% of the diet. This value is exactly equal to the ADI for aldicarb per se. It is highly unlikely that raw potatoes would constitute 10% of any individual's diet and the residues on cooked potatoes are below 1 ppm.

CB, however, has found that at harvest the residue on the raw potatoes consists of aldicarb sulfoxide and aldicarb sulfone with little, if any, aldicarb per se (memo of M.J. Nelson, PP# 3F1414). CB further concludes that residues in all processed commodities* are substantially less than in the raw potatoes per se.

* One exception was potato flakes where residues in reconstituted flakes are not expected to exceed the 1 ppm tolerance for potatoes per se.

TB has stated earlier (memo of R. P. Schmidt, 9/25/73, this PP) that the toxicity of aldicarb and aldicarb sulfoxide was similar and that the data would not support a 1 ppm where the residue of aldicarb sulfoxide might approach 1 ppm. To arrive at this conclusion we were equating the original 90-day "no-effect" level for aldicarb to aldicarb sulfoxide, when actually the observed "no-effect" level in the 2-year feeding of aldicarb sulfoxide was 6 ppm. In the 2nd 2-year feeding with aldicarb, the "no-effect" level was also 6 ppm, in contrast to the 90-day "NEL" of 2 ppm. The next highest fed level of aldicarb sulfoxide (12 ppm) demonstrated no effects on ChE inhibition in the females in either plasma, rbc, or brain and in the males the only effect was a lowering of the plasma ChE, not the rbc or the brain. Since this study was for 2 years, the actual NEL for ChE inhibition is closer to 12 ppm than to 6 ppm.

In our previous evaluations, TB has been concerned that for aldicarb per se there was such a narrow margin between a no-effect level at 0.1 mg/kg (2 ppm) in the subacute study and a high mortality at 0.5 mg/kg (10 ppm). This effect has not been borne out in any further studies with aldicarb -- long term, teratology and reproduction studies.

- C. Attachments 3 and 4 are in response to CB's questions.
- D. Attachment 5 is a revised Section F.

Conclusions

A reconsideration of the laboratory animal toxicity data for aldicarb indicates that the data can support a level of 1 ppm of aldicarb and its sulfoxide and sulfone on potatoes with an adequate margin of safety.

However, when human data are available these definitely afford more assurance as to the safety of the pesticide on the rac as ingested by man. This is particularly applicable in this instance where acute toxicity is of primary interest. The "no-effect" level for ChE

inhibition for man can support a tolerance of 1 ppm aldicarb on potatoes. Even though we have data on man, we have also used an additional 10-fold safety factor and have considered the residue on the whole raw potato. Actually the residues of aldicarb and the sulfoxide and sulfone are reduced in processed potatoes so an additional factor of safety is involved.

Recommendations

We recommend that the tolerances proposed in this petition be established, since the toxicity data presented support their safety.

Robert P. Schmidt 2/11/74

Robert P. Schmidt, D.V.M.
Toxicology Branch
Registration Division

cc: Division File
Branch Reading File
CB
EEB
PP# 3F1414

R/D Init:CHWilliams:2/8/74
RPSchmidt:sss:2/11/74
Init:CHWilliams

*Clear
2/11/74*

END