Dr. Schmidt

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Date: November 9, 1972

Reply to Attn of:

Subject: Dimethoate - The petitioner is requesting a standard residue tolerance for the pesticide dimethoate and its oxygen analog of 1 ppm in or on grapes.

To: Mr. Drew M. Baker, Jr., Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 3F1301

American Cyanamid Co.
Princeton, N. J. 08540

The petitioner had referred to Section C of petition numbers 0F0867, 3F0385, 8F0661, 7F0578, 9F0812, 0G1007, and FAP# 8H2278. No new toxicology data has been submitted with this new petition. Dr. M.L. Quaife reviewed the 0G1007 petition which requested a temporary tolerance of 1 ppm of dimethoate on grapes, and recommended for its establishment in her 6/27/72 memorandum.

TB now recommends for the establishment of the permanent tolerance of 1 ppm in or on the rac grapes based upon the safety data supplied in the previous petitions.

Robert P. Schmidt 11/10/72

Robert P. Schmidt, D.V.M.
Toxicology Branch
Pesticides Tolerances Division

cc: JGCummings
PRD/EPA
Atlanta Branch (CLewis)
Perrine Branch
Division Reading File
Branch Reading File
PP# 3F1301

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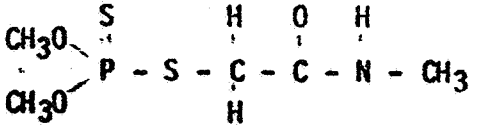
Chemical and Physical Properties

Name: Dimethoate

Chemical Name: O,O-dimethyl-S-methylcarbamoylmethyl phosphorodithioate

Chemical structure:



Molecular Weight: 229

Physical Form: White, crystalline solid

Melting Point: 52-52.5°C

Solubility: Approximately 3% in water; > 50% in most organic solvents; insoluble in petroleum ether.

Stability: Decomposes readily on heating above 170°C; hydrolyzes slowly in boiling water.

Purity: Better than 95%

Impurity: Major impurity is [redacted]

Use: Antimyiatic agent - control of insects and mites on ornamental plants - control of houseflies in dairy barns - control houseflies around homes, recreational areas, food processing plants.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Data Submitted and Reviewed

1. Chemical and Physical Data Sheet
2. Acute Rat Oral LD_{50} = 245 mg/kg
3. Acute Rat Dermal LD_{50} = > 800 mg/kg
4. Acute Guinea Pig Dermal LD_{50} = > 2000 mg/kg
5. Acute Rat Eye Irritation
6. Subacute Rat Study - 28 days
7. Potentiation Study - Rats
8. Subacute Dog Feeding (90 days)
9. Subacute Rat Feeding (90 days)
10. Metabolism Study
11. Acute Sheep Toxicity
12. Acute Cattle Toxicity
13. Acute Mice Toxicity
14. Chronic Cattle Toxicity
15. Tissue Residues in Cattle Using P^{32}
16. Metabolite Study in Sheep
17. Persistence of Dimethoate and Metabolites Following Foliar Application to Plants
18. Metabolic Pathway in Sheep

Acute Rat Oral (4% solution in corn oil)

Five male rats were used per level of 800, 400, 200, and 100 mg/kg.

Results - LD_{50} = 245 mg/kg (185-325). Most deaths occurred within several hours and were preceded by signs of toxicity characteristic of cholinesterase inhibition, i.e., excessive salivation, diarrhea, tremors, prostration, convulsions, etc. Such signs were observed at dosages of 200 mg/kg and above. Survivors of this level regained normal appearance and behavior at approx 18 hours post treatment.

Acute Rat Dermal

The product was applied as a solution in propylene glycol to the closely clipped backs of male albino rats at dosages ranging from 12.5 mg/kg to 800 mg/kg. Each animal was immobilized for a period of 4 hours at which time he was returned to his individual cage.

Results - No deaths occurred at any dosage level during the 7 day observation period, nor were gross signs of systemic toxicity observed in any case. No skin irritation was noted.

Acute Guinea Pig Dermal

Two groups of male albino guinea pigs, 5 animals per group, received a single application of a product as a 50% solution and diethyl succinate at dosages of 1000 mg/kg and 2000 mg/kg. The treatment area was not covered nor were the animals restrained.

Results - No gross signs of systemic toxicity were noted at either dosage level during the first seven days following the dose. At 24 hours post

treatment, blood was drawn by cardiac puncture from the animals of the 2000 mg/kg level, and plasma and erythrocyte cholinesterase activity determined.

A slight but significant decrease in mean plasma, cholinesterase activity was noted. A more pronounced decrease of cholinesterase activity was noted in the erythrocytes. One animal of the 2000 mg/kg group died on day 4 after an episode of diarrhea. The fatality is attributed to the effects of the dose, as this animal exhibited the greatest depression in cholinesterase activity. The dermal LD_{50} is equal to greater than 2000 mg/kg. Application of the chemical did not result in primary skin irritation.

Acute Rat Eye Irritation

Approximately 10 milligrams of the dry product was placed in the left eye of 5 albino rats. The eye was examined at 30 seconds and again at intervals over the next several days.

Results - No perceptible irritation resulted from this application.

Subacute Rat Feeding Study

10 males and 10 females were used per level of 50 ppm, 100 ppm, 200 ppm. In mg/kg/day these levels in males are equivalent to 5, 10, 18 mg/kg/day and 6, 12, 21 mg/kg for the females.

Results - No deaths occurred during this time and the gross appearance and behavior in the animals were comparable to those of the control. The male and female rats of the 200 ppm level showed a significant reduction in mean food intake and mean body weight gain. The males at the 100 ppm level also

showed a significant reduction in body weight gain. After 33 to 37 daily doses, blood was drawn for determination of cholinesterase activity and plasma and erythrocytes. Samples of brain tissue were removed for the same purpose. No gross pathology related to the ingestion of this product was found at autopsy. The results of the cholinesterase activity determinations showed a significant reduction of activity in plasma, erythrocytes and brain at all levels of administration. It should be noted that tissue was not removed from these animals for histopathological examination.

Potentiation Study (Rats)

Dimethoate was tested in combination with diazinon, EPN, guthion, malathion, methylparathion, parathion, phosdrin, Systox, tetram, thimet and trithion. Dimethoate was combined with each of the other phosphates in a two-component mixture of substantially equitoxic proportions. The observed result was compared with an "expected" result that was calculated by the addition of weighted reciprocals of the LD_{50}s of the individual components. The observed LD_{50} was numerically greater than the expected for trithion, thimet, methyl-parathion, malathion, and guthion. The remaining six mixtures had an observed LD_{50} lower than the expected LD_{50}. From these results one could safely assume that there is a degree of potentiation between dimethoate and the aforementioned 5 phosphates. Also that there was no significant potentiation in the remaining six phosphates.

Conclusion

It is the opinion of the reviewer that the equation used in determining the expected LD_{50} is inadequate. $\frac{\%\ \text{Component A}}{LD_{50}\ \text{of A} \times 100} + \frac{\%\ \text{Component B}}{LD_{50}\ \text{of B} \times 100} = \frac{1}{LD_{50}\ \text{of combinati}}$

Comments

The reviewer in an effort to establish whether or not potentiation did or did not take place, took the observed LD_{50} of each combination and determined how much of each of the chemicals was involved. This figure then was compared to the LD curve for that chemical. If the LD value for each of these figures was equivalent to the chemicals LD_0, the reviewer felt that potentiation was present. This method of review revealed the following findings:

1. Dimethoate in combination with parathion, phosdrin, Systox and tetram produced a degree of potentiation.
2. Dimethoate in combination with EPN and guthion produced slight potentiation.
3. The remainder of the chemicals tested showed no potentiation.

Subacute Dog Feeding (90 days)

One male and one female dog was used per level of 2, 10, 50 and 1500 ppm. The 1500 ppm level was gradually increased to 3000 ppm. Microscopic studies were conducted on sections of aorta, bladder, esophagus, gall bladder, intestines, mesenteric lymph node, salivary gland, skeletal muscle, stomach, thymus, tongue, trachea, adrenals, brain, gonads, heart, kidneys, liver, lung, pancreas, pituitary, spleen and thyroid was conducted for the 1500 ppm.

Results - The dietary level of 2 ppm produced no noticeable effects. The 10 ppm level produced a slight depression of the red blood cell cholinesterase activity. At 50 ppm the red blood cell cholinesterase activity was further decreased but the plasma cholinesterase activity remained essentially unchanged.

Food consumption of these animals was adequate. The 1500 ppm level produced a marked and rapid decline in the red blood cell and plasma cholinesterase activity. By the end of the first week these activities were reduced to approximately 25% of their normal value. As this dietary level was gradually increased to 3000 ppm a slight further inhibition of blood cholinesterase activity was noted. The male dog of this level showed few signs of cholinesterase inhibition and ate essentially all of the food offered while the female showed sporatic tremors, had diarrhea and refused approximately 10% of the total food offered. Neither dog showed any abnormal changes in blood urea nitrogen, blood glucose or bromsulfalein retention value. Results from the hemological studies were also within normal limits. No significant organ weight changes were noted. No pathology which could be related to the ingestion of dimethoate was observed.

Summary - The no-effect level of dimethoate to dogs appears to be in excess of 2 ppm with the minimal effective level being approximately 10 ppm. Signs of toxicity observed during this study are considered typical signs of toxicity associated with organic phosphates.

Subacute Rat Feeding (90 days)

Preliminary Studies - Preliminary experiments using 1000 ppm and 2000 ppm of dimethoate showed typical signs of cholinesterase inhibition with deaths between 7 and 11 days. A level of 500 ppm resulted in pronounced but less severe signs of cholinesterase inhibition. A level of 400 ppm produced some signs of muscular twitching. A level of 200 ppm appeared to be well tolerated by the animals. Weanling rats did not tolerate dimethoate as well as young adult males. Weanlings fed 250 and 500 ppm showed marked signs of cholinesterase inhibition with several deaths during the first week of feeding.

90 Day Feeding Study (Rats)

Ten males and ten females were used per level of 2, 8, 32, and 400 ppm of dimethoate. The mean dosage in mg/kg/day for the 2,8, 32 ppm is 0.16, 0.67, and 2.6.

Results - The dietary levels of 2, 8, and 32 ppm were well tolerated by both male and female rats without any signs of cholinesterase inhibition. Females of the 32 ppm level exhibited a marked reduction in mean liver weight. It should be noted that at the 400 ppm level females exhibited increased liver weights. When compared to the controls, the 400 ppm animals showed significant decreases in mean weight gain, plasma, erythrocyte and brain cholinesterase activities. These decreases ranged from slight to marked. Mean food intake was not affected. Among males the mean kidney weight was markedly increased and the mean liver weight was slightly but significantly increased. No hemological and pathological findings of significance were observed.

As the 32 ppm level provided no information as to the no-effect level, a 50 ppm level was instituted for 33 days. This level produced sharp decreases in plasma, erythrocyte and brain cholinesterase activities. Mean food intake, mean weight gain, mean kidney weight and mean liver weight was comparable to the control animals. Based on this study one would conclude that the no-effect level is in the range of 32 to 50 ppm.

Metabolism Study

Radioactive dimethoate was used in these investigations. After treatment the parent compound and breakdown products were isolated and identified by infrared spectra or chromatographic. The metabolism of dimethoate is very rapid in

both plants and animals. The breakdown products appear to be the same but quantitative differences have been noted. In animals the principle metabolic pathway is apparently through the carboxic derivative, $(CH_3O)_2$ $PSSCH_2COOH$. Dimethoate and its metabolites are weak inhibitors of cholinesterase. With the exception of the oxygen analogue, the metabolites show no increase in potency as antiesterases, have no appreciable mammalian toxicity, and are not inhibitors of cholinesterase.

Acute Sheep Toxicity

1. No toxicity in fat sheep given I.M. doses of 20, 40, 60 and 80 mg/kg.
2. Two of four cull sheep in poor physical condition given 40 mg/kg showed marked but not fatal toxic symptoms.
3. 192 lambs at 25 mg/kg I.M. gave no toxic reaction.
4. Four pregnant and four nursing ewes at 25 mg/kg I.M. produced no toxicity symptoms, no miscarriages and normal lambs were delivered.
5. I.M. doses of 75 and 100 mg/kg respectively killed 2 of 3 and 3 of 3 lambs.
6. Parenteral LD_{50} - single dose sheep equals approximately 60 mg/kg.
7. Single dose oral LD_{50} in sheep equals approximately 150 mg/kg.
8. 51 to 81% depression in red blood cells cholinesterase activity was evident between 1 and 5 days after an I.M. dose of 50 mg/kg in 16 sheep. Brain cholinesterase activity was considerably reduced.

Acute Cattle Toxicity

Oral or I.M. to calves showed no toxicity at 10 mg/kg, mild symptoms at 20 mg/kg, severe symptoms at 40 mg/kg and death at 80 mg/kg.

Acute Mice Toxicity

Acute Oral LD_{50} in mice is equal to approximately 133 mg/kg (range 112-154).

Chronic Cattle Toxicity

A dose of 0.2 to 0.5 mg/kg orally for 46 days in calves produced little or no depression of blood CHE.

Tissue Residue and Fate of Metabolites

Four sheep at 25 mg/kg showed no residue in fat, 3-12 ppb in muscle, 15 ppb in liver, and produced no signs of gross pathological effect.

Metabolites in Sheep

1. Carboxy derivative
   a. Acute oral LD_{50}, rats equal 2500 to 3000 mg/kg
   b. Not a cholinesterase inhibitor
2. Desmethyl derivative (2%)
   a. Not a cholinesterase inhibitor
   b. Oral LD_{50} in rats equals 1500 to 2000 mg/kg
3. Oxygen Analogue (2-6%)
   a. More toxic cholinesterase inhibitor
   b. Oral LD_{50} in rats equal to 55 mg/kg
   c. Major portion rapidly metabolized to oxycarboxy derivative
   d. Not present in animal after 24 hours.

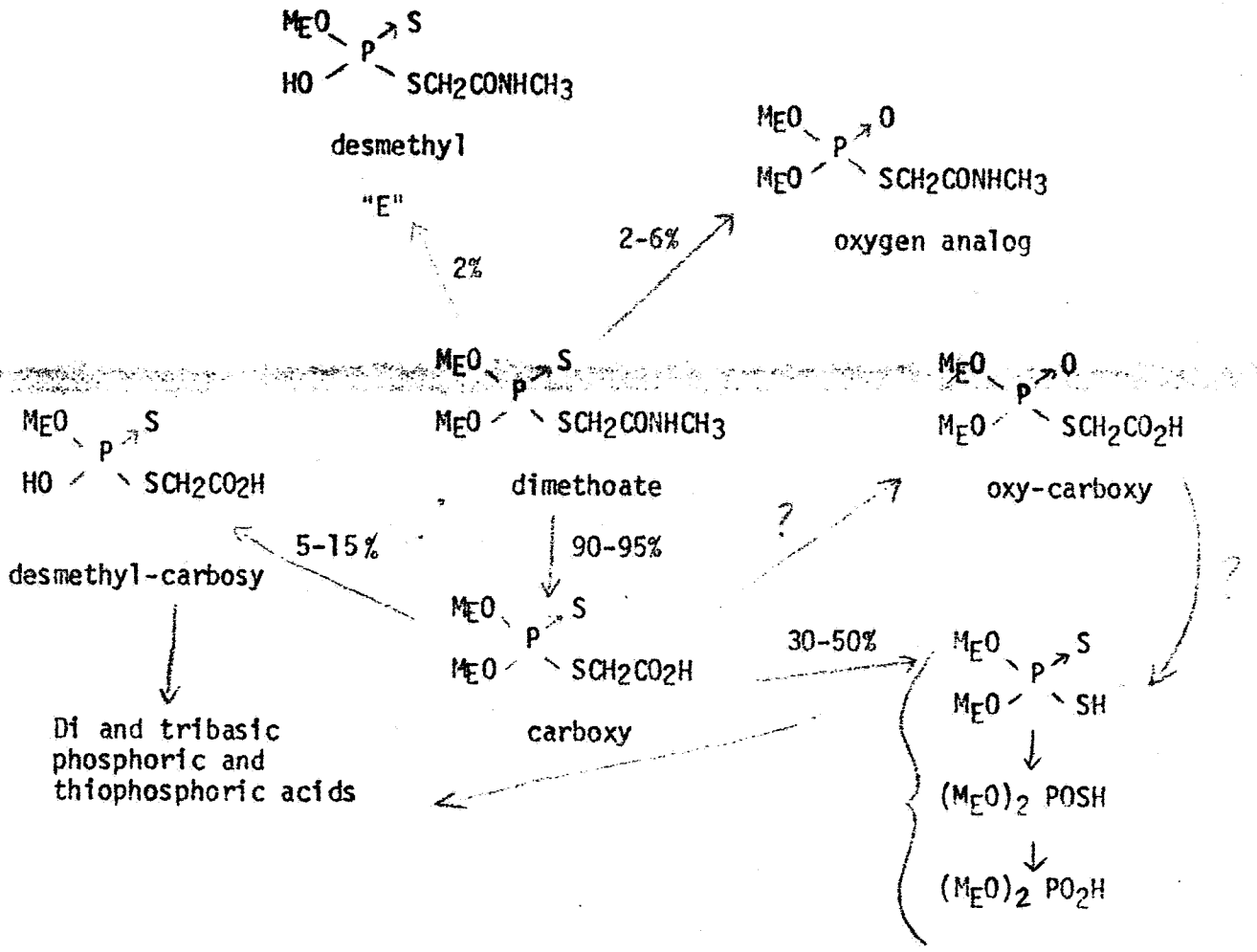
Tissue residues and blood excretion patterns using P^{32}

Four steers were dosed by capsule at 10 or 15 mg/kg with dimethoate labeled with P^{32}.

Results - Dose was well tolerated by 3 or 4 steers with no toxic symptoms. The fourth at 15 mg/kg refused food and water for a time. Approximately 89% was recovered in the urine; with 6-9% being recovered in the feces.

Metabolic Pathway in Sheep

A) Intramuscular Dimethoate in Sheep



General Summary

Based on the data reviewed as of November 1, 1966, Dimethoate can be classified among the lesser toxic organic phosphate insecticides. The acute oral and dermal LD_{50} values are approximately 200 mg/kg and > 800 mg/kg respectively. At least under short term contact, the chemical is not irritating to the eye.

Available data indicates that dimethoate in combination with several other organic phosphates exhibits a moderate degree of potentiation.

Cholinesterase inhibition of plasma and erythrocytes in rats occurs between 32 and 50 ppm. Erythrocyte cholinesterase inhibition is evident at 50 ppm; plasma cholinesterase activity is not effected at 2 ppm.

The feeding of high levels to both dogs and rats caused marked depression of cholinesterase actives but produced no significant variations in hematologic changes or anatomical pathology.