7-26-84

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 26 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: PP#4F3013/4H5421: Thiodicarb in tomatoes. Evaluation of residue data and analytical method. Accession #072236

FROM: V. Frank Boyd, Chemist
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU: Charles L. Trichilo, Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

TO: Jay S. Ellenberger (PM# 12)
Insecticide-Rodenticide Branch
Registration Division (TS-767)

and

Toxicology Branch
Hazard Evaluation Division (TS-769)

Union Carbide Corporation, Agricultural Products Company, Inc. proposes tolerances for combined residues of the insecticide thiodicarb, dimethyl-N,N'[thiobis[(methylimino)carbonyloxy]] bis[ethanimidothioate], and its metabolite methomyl, S-methyl-N[(methylcarbamoyl)0xy] thioacetimidate on tomatoes at 3.0 ppm.

A food additive tolerance of 5.0 ppm on tomato paste is proposed in this submission under FAP#4H5421.

Temporary tolerance for the above commodity is proposed at the same level (PP#4G3014/4H5422).

A permanent tolerance is established on sweet corn, kernels plus cob, at 2.0 ppm (§180.407). Other tolerances have been proposed on cottonseed at 0.4 ppm, soybeans at 0.1 ppm soybean straw at 0.2 ppm, cottonseed hulls at 0.8 ppm and soybean hulls at 0.4 ppm (PP#0F2413).

The metabolite of thiodicarb, methomyl, is an insecticide with established tolerances on many commodities including tomatoes at 1.0 ppm.

Conclusions:

1a) The major residues of concern for thiodicarb on plants have been considered to be thiodicarb, per se, methomyl and methomyl oxime. It has recently come to our attention, however, that the carcinogen, acetamide, may also be a metabolite. Residue data for acetamide on tomatoes are needed.

1b) In livestock and poultry, the metabolic pathway would include residues of thiodicarb, methomyl, methomyl oxime, acetamide and acetonitrile. TOX has expressed concern over residues of acetamide and acetonitrile in meat, milk, poultry and eggs.

We defer to the toxicology Branch on the toxicological significance of acetamide and acetonitrile in these commodities and their need to be regulated.

1c) A C^{14}-acetonitrile study in the rat is included with this petition. The study shows that 5.72% of the administered thiodicarb is degraded to acetonitrile, with only 1.9% of the administered dose, maximally, becoming acetamide.

(2a) An adequate analytical method is available for enforcement purposes for thiodicarb and its metabolites methomyl and methomyl oxime.

2b) A validated analytical method is needed for the determination of residues of acetamide in/on tomatoes.

2c) If TOX concludes that acetamide and acetonitrile need to be regulated in meat, milk, poultry and eggs, then validated analytical methods will be needed for animal products.

(3a) Residues of thiodicarb, methomyl and methomyl oxime in tomatoes are not expected to exceed the proposed tolerance of 3.0 ppm, under the proposed conditions of use, provided a 1-day PHI is imposed on the label. (This is the shortest interval for which there is residue data).

(3b) The adequacy of the food additive tolerance of 5.0 ppm, for tomatoes paste, as proposed, cannot be substantiated by the processing study because of the low residue level (0.13 ppm) in the tomatoes used for processing. A study using tomatoes containing residues at or near the proposed 3.0 ppm level is required. Analysis should be conducted for paste, puree, catsup and dried pomace.

(4a) A cattle feeding study conducted at levels of 0.1 ppm to 150 ppm was submitted with PP#3F2773. We are withholding our conclusions with respect to residues in meat and milk until the questions raised in conclusion 3, above, are resolved. (See 3b above).

(4b) There will be no problem of secondary residues in poultry and eggs since tomato pomace is not a significant poultry feed item.

(4c) The metabolites of thiodicarb will occur in meat and milk. We defer to TOX on the toxicological significance of the metabolites, acetamide and acetonitrile. Their estimated levels in meat and milk cannot be determined at this time but will be based on the residue level in dried tomato pomace (See conclusion 3b above).

(5) A Codex sheet is attached. There are no Codex, Mexican or Canadian tolerances for thiodicarb on tomatoes.

Recommendations

We recommend against the proposed tolerance. A favorable recommendation is contingent upon resolution of the questions raised in Conclusions 1a, 1b, 2b, 2c, 3a, 3b, 4a and 4c. TOX should respond to our deferrals in conclusions 1b and 4c above.

Detailed Considerations

Manufacturing Process and Formulations

The manufacturing process of thiodicarb was delineated in PP# OF2413/FAB# OH5275, memo of A. Smith, 1/21/81. [redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

The impurities in technical thiodicarb are not likely to produce a residue problem.

Two new formulations are presented with this petition. LARVIN® 80DF is an 80% dry flowable formulation and LARVIN 3.2 AF is a 34% aqueous flowable or 3.2 lbs./gal liquid formulation of thiodicarb. All ingredients in these formulations are cleared for preharvest use under §180.1001.

3

Proposed Use:

Thiodicarb insecticide is applied on tomatoes at rates of 0.4 to 1.0 lb. ai/A for infestation of lepidopterous larvae. The lower rate is used on smaller and/or fewer larvae, while the higher rate should be reserved for larger larvae and/or greater numbers of larvae. Applications are repeated as needed.

Nature of the Residue:

Metabolism in plants

The metabolism of thiodicarb has been studied in several plants, including tomatoes, and was considered adequately delineated in connection with PP#OF2413, #9G2152, #3G2782 and 3F2773, 4/11/83.

C^{14}-thiodicarb was not appreciably translocated when applied to leaves of carrots. However, upon stem injection in corn, soybeans, wheat, cabbage and tomatoes the C^{14}-Thiodicarb is translocated and extensively degraded to naturally occurring plant constituents by volatilization as acetonitrile and carbon dioxide. Some detoxification occurs by way of conjugation and/or binding with plant structural components.

Rapid cleavage of the N-S-N linkage results in two molecules of methomyl from one molecule of thiodicarb. Thiodicarb and methomyl comprise the majority (96-98%) of the free (>50%) residue components in plants. Methomyl is degraded to methomyl oxime through sequential sulfoxidation to the sulfoxide and hydrolysis to methomyl methylol. Approximately 2% of the residue is methomyl metabolite conjugated, about 10% of the residue is bound non-hydrolyzable conjugates and the remaining 35% residues are lost as volatiles.

A metabolism study in tomatoes (Union Carbide Project No. 814C50, File #26055, 3/1/79) was presented in this petition. C^{14}-acetaldehyde-labeled thiodicarb was applied at 1.0 lb. ai/A as an aqueous brushing to the upper-leaf surface of greenhouse tomato plants at flowering. Approximately 50% of the radioactivity was volatilized as carbon dioxide and acetonitrile. Only 0.5% of the activity was found in the fruit, and 49.3% of the activity in the leaves (non-translocated). The residues in leaves was mainly parent (80%) and free methomyl metabolites (6.5%) with 14.5% conjugated and/or bound.

TOX has recently expressed concern over the possibility of acetamide as a plant metabolite of thiodicarb and methomyl.

The reason for the concern over possible residues of acetamide lies in the fact that this carcinogen has been found to be a metabolite of thiodicarb in cattle. Thiodicarb is prepared by reacting methomyl with sulfur dichloride. The residue of concern for thiodicarb on plants consists of that insecticide plus its metabolites methomyl and methomyl oxime. In cattle tissues, carbamate residues weren't found (except in liver) but the radiolabel was in the form of acetamide, acetonitrile and naturally occurring components such as lipids.

We have reexamined the plant metabolism studies for thiodicarb to determine if acetamide is a component of the residue. In none of these reports have we been able to find acetamide identified as part of the radiolabel on crops. Since both $^{14}CO_2$ and $CH_3{}^{14}CN$ were found in the volatiles from the treated plants, it is very likely that acetamide is involved in the degradation as it is one of the expected intermediates on the pathway from acetonitrile to carbon dioxide. Being much less volatile than acetonitrile, (b.p. = 82 °C versus 222°C for acetamide) we would not be surprised it acetamide were found on plants. It's level would be determined by its relative rates of formation and degradation, probably to acetic acid. From the data available at this stage we can not obtain an estimate as to what this concentration of acetamide could be on plants. It appears that in the above studies the petitioners were not specifically searching for acetamide. However, it is possible this metabolite was not found simply due to it not being present at measurable levels. Residue data using a validated method are needed for acetamide on tomatoes treated with thiodicarb at the maximum proposed rate.

The major components of the plant residues appear to be the parent compound and a very small amount of the oxime metabolite, S-methyl-N-hydroxythiacetimidate. In the absence of data on the carcinogenic metabolite acetamide, it is our judgement that the fate of methomyl on plants is not adequately understood for purposes of this petition.

Metabolism in Animals

The metabolism of thiodicarb in animals has been studied in the rat, cow and poultry and previously evaluated in connection with PP#OF2413, 3F2773 and 3G2782.

In rats approximately 66% of the radioactivity was recovered from distribution throughout the body, with the greatest quantity present in the digestive system. The residues consisted of parent and methomyl with lesser quantities (<2.0% each) of methomyl oxime, methomyl sulfoxide, methomyl sulfoxide oxime and 4 undidentified metabolites. The remaining (30%) radioactivity was considered to be volatilized as acetonitrile and CO_2.

In the cow 66% of the radioactivity was eliminated as CO_2 and acetonitrile within 72 hours after dosing. The remainder of the C^{14}-activity was found in urine (4%), feces (11%), milk (5%) and tissues (10%), primarily in the liver (primarily thiodicarb 9%). In the cow tissues thiodicarb is metabolized to methomyl, then methomyl oxime, and subsequently to acetonitrile. The acetonitrile is metabolized to acetamide, then acetic acid, which enters the normal tricarboxylic acid pathway for production of normal body constituents.

Milk contained no parent nor methomyl, but rather, acetonitrile, acetamide and natural components containing reincorporated C^{14}, i.e., lactose, lactalbumin, lipids and casein. Radioactivity levels plateaued in milk and tissue within 6 days and dissipated rapidly after last feeding.

In poultry the metabolism is like the cow with residues of acetonitrile and acetamide in eggs and tissues, but declining rapidly after the last feeding. No parent compound or carbamoyl residues were found in tissues or eggs. At seven days no residues were found (0.002 ppm).

The nature of the residue in animals is adequately understood. The parent, methomyl and methomyl oxime are toxicologically significant residues, but are not reported in meat, (with exception of liver) milk, poultry and eggs. Quantities of the more water soluble metabolites, acetonitrile and acetamide, are found in milk and eggs, and some other tissues in the C^{14}-studies.

Metabolism in the rat is similar to that occurring in plants. A difference in dosing of rats as compared to dosing of cows and chickens may be more responsible for less complete metabolism (less water-soluble, non-carbamoyl metabolites) in the rat. Published data using C^{14}-methomyl 1/ indicates that metabolism of acetonitrile to acetamide and acetic acid occurs in the rat also.

Details of acetonitrile metabolism in the rat is included in the 12/5/83 report entitled "Acetonitrile metabolism in the Rat", submitted with this petition. A single dose of 1-C^{14}-acetonitrile was administered to the rat by intubation at 0.3 mg./kg. C^{14} activity was largely eliminated in the respiratory gases, 65 to 75%, as acetonitrile and CO_2 in a ratio of 85:1. About 11% of the activity was eliminated via urine and feces with about 16% remaining in the body tissues after 3 days. Since a minimal amount of CO_2 (0.8%) was produced from acetonitrile, this corroborates the work of Huhtanen and Dorough 1/ concerning the production of acetonitrile and CO_2 from syn and anti isomers of methomyl in rats. syn methomyl is metabolized to CO_2 with anti methomyl resulting in acetonitrile, primarily. According to Beckman rearrangement, the production

1/ Huhtanen, K. and Dorough, A.W., Pest. Biochem & Physiol. 6, 57-583 (1976).

Of:

acetonitrile ----->acetamide----->acetic acid

↓

Tricarboxylic Acid Cycle

occurs primarily from <u>anti</u>-methomyl, but the <u>syn</u> isomer is formed from thiodicarb. This indicates that a maximum of 2% (w/w), see Table VI-6 hour sample (12/5/83 Project Report 804R10), acetamide could result from the thiodicarb dosed, providing all acetonitrile is degraded to acetamide.

Experimentally, thiodicarb feeding studies have shown estimated residues in tissues, eggs or milk as high as 0.6 ppm acetonitrile in milk and 0.5 ppm acetamide in beef liver from feeding 100 ppm thiodicarb; since tomato pomace is not generally used in poultry feed, poultry tissues and eggs are not involved in this tolerance proposal.

Analytical Methodology

Residues of thiodicarb, methomyl and methomyl oxime are determined as the methomyl oxime, by extraction of tomatoes with acetone: water, 9:1(v/v), partitioning in methylene chloride followed by hydrolysis to the oxime. Cleanup is accomplished by liquid-liquid partition (water and methylene chloride). Quantitation is achieved with GC/FPD in the sulfur mode.

Method sensitivity is 0.02 ppm with an average recovery of 95% in the fortification range of 0.02 to 10.0 ppm, and the extraction efficiency of the method for tomatoes is 98%. Stability of thiodicarb in frozen storage (-30°C) is proven by fortification of each set of field samples at 0.05, 0.1, 0.25, 0.5, 1.0, 1.5, 2.0, 5 or 10 ppm and analysis at 45 days to 6 mos. giving recoveries of 74 to 114%. The analytical method is considered adequate for enforcement. A successful method trial was performed in cotton and soybeans (PP2413, A. Smith, 11/4/82).

Residue Data

Thirteen field trials were reported from 9 tomato growing states (NC, MS, CA, IA, IN, AL, OH, NJ and FL). All control values ranged from <0.02 to <0.05 (depending on method sensitivity in particular laboratory) except for a single value of 0.18 ppm found in a check sample from the North Carolina trial.

Following 6 to 8 application of Larvin 500, 3.2 AF or 80 DF at 1.0 lbs ai/A, samples taken at 1, 3, 7 and 14 days, PHI showed no difference in residues due to formulation or PHI. No clear pattern of degradation occurs over 14 days following the last of multiple applications according to the data presented. Combined residue level for thiodicarb, methomyl and methomyl oxime ranged from <0.05 to 2.2 ppm at a 14 day PHI or <0.02 to 0.63 ppm at a 1 day PHI. It is recommended that the label include a statement requiring a PHI of 1-day, since this is the shortest period for which data is presented to support a 3.0 ppm tolerance.

A processing study was performed using tomatoes bearing a residue of 0.13 ppm on the rac. No concentration of residue was found in the juice, puree, wet pomace or dry pomace. A concentration of 1.6 X was found in tomato paste (0.13 ppm to 0.21 ppm). Since the tolerance proposed is 3.0 ppm for the rac and the highest residue found was 2.2 ppm, the use of tomatoes bearing a residue level of 0.13 ppm on the rac is considered inadequate for determining the potential for concentration of residues due to processing.

A processing study using tomatoes bearing residues at or near the proposed tolerance level is needed. Analyses should be conducted on puree, paste catsup and dried pomace.

Meat, Milk, Poultry and Eggs

No livestock feeding studies were submitted in this petition. The feed item involved is tomato pomace.

Cattle and poultry feeding studies were previously submitted and discussed in detail in connection with PP#OF2413/FAP#OH5275 (memo of A. Smith January 21, 1981).

In the cattle feeding study, lacatating cows were fed acetyl-1-^{14}C thiodicarb daily for 21 days at dietary levels equivalent to 0.1, 10, 30 and 100 ppm. Analysis for thiodicarb residues showed no carbamate residues in milk and tissues (except liver); i.e., no thiodicarb, methomyl, methomyl metholyl, methomyl sulfoxide, or methomyl oxime sulfoxide. However, activity in the form of acetonitrile was detected in milk at levels of 0.001, 0.051, 0.263 and 0.814 ppm, respectively, with trace amounts (<0.01 ppm) of acetamide found only at the highest feeding level of 150 ppm. Also, measurable levels of acetamide and acetonitrile were detected in liver and kidney, only at the 10, 30 and 100 ppm; and in the muscle, only at the 30 and 100 ppm feeding levels as shown in the following table:

	Feeding Level (ppm)					
	10		30		100	
TISSUE	Acetamide	Acetonitrile	Acetamide	Acetonitrile	Acetamide	Acetonitrile
Liver	0.143	0.002	0.166	0.014	0.677	0.625
Kidney	0.005	0.002	0.044	0.013	0.061	0.036
Muscle	-	-	0.007	0.004	0.04	0.047

The presence of acetamide and acetonitrile in the adipose tissue (fat) was not reported. However, assuming the presence of these metabolites in the fat tissue, their level was calculated based on the relative activity detected in fat to those in the muscle tissue as follows (in ppm): 0.002, 0.001; and 0.03, 0.036 acetamide, acetonitrile at the 30 and 100 ppm feeding levels, respectively. As with muscle tissue, no acetamide or acetonitrile are expected to be detected at the lower feeding levels of 0.1 and 10 ppm.

We defer to TOX on the toxicological significance, if any, of the acetamide and acetonitrile components and whether they need to be regulated. If regulation is required and potential residues may be present in meat and milk, then an enforcement method for these metabolites will be required.

If we feed a hypothetical diet of:

25% - tomato pomace - 5.0 ppm proposed

We would be feeding 1.25 ppm thiodicarb residues. Using the 10 ppm feeding level from the above study, we would find a maximum of:

Cattle Product	Acetonitrile (ppm)	Acetamide (ppm)
milk	0.01	-
liver	0.001	0.02
kidney	0.001	0.001
muscle	-	-
fat	-	-

No carbamate residues would be found.

These values are estimates only, since the presented data from the tomato processing study are considered inadequate for establishing a tolerance level for tomato pomace (see discussion under Residue Data, above). Conclusions regarding meat and milk residues must be deferred until an adequate processing study is evaluated.

Since tomato pomace is not used as poultry feed, secondary residues are not expected to occur in poultry and eggs from the proposed use of thiodicarb on tomatoes.

Other Considerations: An International Residue Limit Status Sheet is attached. No international tolerances have been established for thiodicarb.

TS-769:RCB:F.Boyd:vg:CM#2:Rm810:X77324:7/25/84
cc: R.F., Circu., Thompson, FDA, TOX, EEB, EFB, PP#4F3013/4H5421
RDI: Quick, 7/13/84; Schmitt, 7/17/84

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Thiodicarb

CCPR NO. ____

PETITION NO. 4F3013
4/24/84 Boyd
J. dee 4/25/84

Codex Status

[✓] No Codex Proposal Step 6 or above

Residue (if Step 9): ____

Crop(s)	Limit (mg/kg)

Proposed U.S. Tolerances

TOMATOES — 3 PPM
(FAT) TOMATO PASTE — 5 PPM

Residue: Thiodicarb & methomyl as methomyl oxime

Crop(s)	Tol. (ppm)
Tomatoes	3.0

CANADIAN LIMIT

Residue: ____

Crop	Limit (ppm)
none	

MEXICAN TOLERANCIA

Residue: ____

Crop	Tolerancia (ppm
none	

NOTES:

Page 1 of 1