3-7-83

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

MAR 7 1983

EXPEDITE

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: PP#3F2793/FAP3H5378: Thiodicarb in Soybeans. Evaluation of residue data and analytical method

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and

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Hazard Evaluation Division (TS-769)

The Union Carbide Agricultural Products, Inc., proposes tolerances for combined residues of the insecticide thiodicarb, dimethyl N,N'-[thiobis[[(methylimino)carbonyl]oxy]] bis[ethanimidothioate], and its metabolite methomyl, N-[(methylcarbamoyl)oxy]thioacetimidate, in or on soybeans at 0.2 ppm and soybean hulls at 0.8 ppm.

There are no permanent tolerances established for thiodicarb. Permanent tolerances were proposed for soybeans at 0.1 ppm, soybean straw at 0.2 ppm, soybean hulls at 0.4 ppm, cottonseed at 0.4 ppm, and cottonseed hulls at 0.8 ppm (PP#OF2413/FAP#OH5275. The usage on soybeans in the petition permits higher application rates than was permitted in PP#OF2413. Permanent tolerances are also pending for corn grain at 0.05 ppm, corn forage and fodder at 60 ppm, and sweet corn kernels plus cobs at 1.5 ppm (PP#3F2773).

The metabolite of thiodicarb, methomyl, is an insecticide with established tolerances on a variety of commodities at levels of 0.1-40 ppm (§180.253). These Tolerances include 0.2 ppm for soybeans and 10 ppm for soybean forage.

Conclusions

1(a). The nature of the residue is adequately delineated. The significant components of plant and animal residues are the parent compound thiodicarb and its metabolite methomyl.

1(b). Animal tissues also contain the metabolites acetonitrile and acetamide. Acetamide is suspected of being a carcinogen. We defer to the Toxicology Branch on the toxicological significance of these components and if they need to be regulated.

2(a). An adequate analytical method is available for enforcement purposes for residues of thiodicarb and methomyl.

2(b). If TOX concludes that acetonitrile or acetamide needs to be regulated, then validated analytical methods will be needed.

3. The label permits an unlimited number of applications. We can conclude that residues in soybeans and its byproducts (meal, oil, soapstock) or soybean hulls are not likely to exceed the proposed tolerances provided the label is revised to limit use to 4 applications per season.

4. The metabolites of thiodicarb (acetonitrile and acetamide) will occur in eggs, milk, and meat of livestock [§180.6(a)(1)]. We defer to TOX on the toxicological significance of these metabolites and if such components need to be regulated. The estimated acetamide levels are as follows.

Meat of cattle and horses	0.9 ppb*
Eggs; meat of hogs	0.5 ppb
Milk	<0.2 ppb
Meat of poultry	0.4 ppb
Meat of goats and sheep	3 ppb

*(ppb = parts per billion)

No carbamate-type residues are expected in eggs, milk or meat (i.e., thiodicarb, methomyl, methomyl oxime, methomyl oxime sulfoxide, methomyl methylol).

5. A Codex sheet is attached. There is no conflict with Codex, Mexican or Canadian tolerances.

Recommendation

We recommend against the proposed tolerances. A favorable recommendation is contingent upon resolution of the questions raised in Conclusions 1(b), 2(b), 3 and 4.

Detailed Considerations

Proposed Uses

Larvin ®Thiodicarb Insecticide 75% Wettable Powder (75% active ingredient - a.i.) and Larvin ®500 Thiodicarb Insecticide (an aqueous flowable containing 43% a.i.) are proposed for aerial or ground foliar applications on soybeans when insects appear. Repeat applications are to occur as needed.

Apply at rates of 0.25 - 0.75 lb act/A depending on the level of infestation. Forage, hay or straw is not to be fed to livestock. No application is to occur less than 28 days before harvest (PHI, 28 days).

There is no restriction on the number of applications permitted. Because the data reflect a maximum of 4 applications and residue up to 0.19 ppm are reported, the label should restrict use to 4 applications per season.

Methomyl is registered for use on soybeans with ground or aerial foliar applications at 0.22 - 0.45 lb act/A. A PHI of 14 days is imposed.

The combined thiodicarb and methomyl uses could result in residue levels in beans and hulls greater than the proposed thiodicarb tolerances or the established methomyl tolerances. However, this situation may be appropriately handled as in §180.3 (i.e., tolerances for Related Pesticide Chemicals). This has been fully discussed in #PP#OF2413.

The manufacturing process for technical thiodicarb has been fully discussed in reviews of PPs 9G2152 and OF2413. The impurities are not likely to produce a residue problem. The inert ingredients are cleared for use under §180.1001.

Nature of the Residue

The nature of the residues resulting from metabolism and/or degradation of thiodicarb has been fully discussed in our reviews of PP#9G2152 and PPOF2413. Thiodicarb is absorbed, metabolized, and translocated by plants (cotton, soybeans, corn, wheat, cabbage, carrots). The chemical is extensively degraded and/or metabolized and eliminated from the plant as the volatile compounds carbon dioxide and acetonitrile. The chemical is, to some extent, completely degraded, and its elements reincorporated into naturally-occurring plant constituents. A minor pathway for detoxification is conjugation and/or binding with plant constituents.

The major components of plant residues are the parent compound thiodicarb and its metabolite methomyl. The metabolites methomyl oxime, methomyl sulfoxide, and hydroxymethyl methomyl appear as minor components of plant residues and usually less than 10% of the residues. The metabolites appear in the free and conjugated and/or bound forms which usually represent less than 10% of the plant residues.

The significant components of plant residues are the parent thiodicarb and its metabolite methomyl.

Thiodicarb is rapidly absorbed, metabolized, and excreted by animals (rats, cattle, poultry). Some residues are retained in eggs, milk, and meat.

In animals thiodicarb is metabolized step-wise to methomyl, followed by hydrolysis to the methomyl oxime which is subsequently metabolized to acetonitrile. The acetonitrile is then metabolized to acetamide which is hydrolyzed to acetic acid. The acetic acid then enters the intermediary metabolism cycles of the animal. This ultimately results in the production of carbon dioxide which is expired.

The residues of meat, milk, and eggs contained no thiodicarb or its metabolites methomyl, methomyl oxime, methomyl oxime sulfoxide, and methomyl methylol. The metabolites acetonitrile and acetamide were present in milk, eggs, and meat and declined rapidly after the end of the feeding period. A large portion of the ingested dose was present as reincorporated atoms in naturally-occurring components.

The nature of the residue in animals is similar to that in plants. The parent compound thiodicarb and its metabolite methomyl are components of toxicological concern. However, the metabolite acetamide is also present in eggs, milk and meat. The Toxicology Branch has indicated that acetamide could be a carcinogen. We defer to TOX on the toxicological significance of a acetamide and if its residues need to be regulated. We also defer to Toxicology Branch on the significance of acetonitrile residues and whether they need to be regulated in meat, milk and eggs.

Analytical Method

A ground soybean seed sample is extracted by blending with an acetone/methanol mixture. The sample mixture is filtered and concentrated to remove the acetone.

The concentrate is taken up with acetonitrile and washed with hexane. The acetonitrile phase contains the thiodicarb residues and is evaporated to dryness.

The residue is taken up with and refluxed in dilute aqueous sodium hydroxide. (The alkaline reflux coverts thiodicarb residues to the methomyl oxime.) The refluxed mixture is cooled, acidified and buffered, and the oxime is partitioned into methylene chloride. The solvent is evaporated, and the residue is taken up in acetone.

The residue is determined by gas chromatography using a detector which is sensitive to sulfur. The results are expressed as thiodicarb residues.

Sulfur-containing pesticides with registered uses on soybeans were tested with the residue method. No interferences with the determination of thiodicarb residues were noted.

Untreated (control) samples of soybean seed had <0.02-0.07 ppm thiodicarb-equivalent residues. Control samples, fortified with thiodicarb and methomyl at levels of 0.02-2.0 ppm, had recoveries of 64-93%.

Control samples of soybean straw had <0.02-0.36 ppm thiodicarb equivalent residues. Control soybean forage samples (whole immature green plants) had <0.02-0.43 ppm thiodicarb equivalent residues, and control samples of soybean hay had <0.02-0.78 ppm thiodicarb-equivalent residues.

Control samples of straw, hay, and forage were fortified with thiodicarb residues at levels of 0.1-400 ppm. Recoveries were 62-92%. Two aberrant values of 133% (24 ppm) and 172% (10 ppm) wre noted.

The residue method has been successfully tested with soybeans and thiodicarb and its metabolite methomyl at levels of 0.1 ppm and 0.2 ppm (PP#OF2413, memo 11/4/82).

An adequate analytical method is available for enforcement of the proposed tolerances for thiodicarb and its metabolite methomyl.

However, if TOX determines that residues of acetamide or acetonitrile must be regulated, then validated analytical methods which determine such residues will be necessary.

Residue Data

Samples were collected from crops grown in Mississippi, Iowa, North Carolina, Illinois, Okalahoma, Alabama, Maryland, Ohio, missouri, Arkansas, and South Carolina. The crops had been treated by ground (30-40 gallons spray per acre) or simulated aerial (3-5 gallons spray per acre) applications and harvested at various intervals following the last application.

Soybean seed had residues of <0.05-0.19 ppm at 26-32 days following the last of 2-4 applications at the maximum proposed rate of 0.75 lb act/A.

We conclude that residues in or on soybean seed are not likely to exceed the proposed tolerance of 0.2 ppm from the proposed use.

Soybean byproducts

Data were submitted in PP#OF2413 which showed that residues in the soybean are not concentrated in the byproducts (i.e., meal, oil, soapstock). Thus, residues in these byproducts will be adequately covered by the tolerance level for the bean.

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Figure 1

Metabolic pathways of UC 51762 in plants

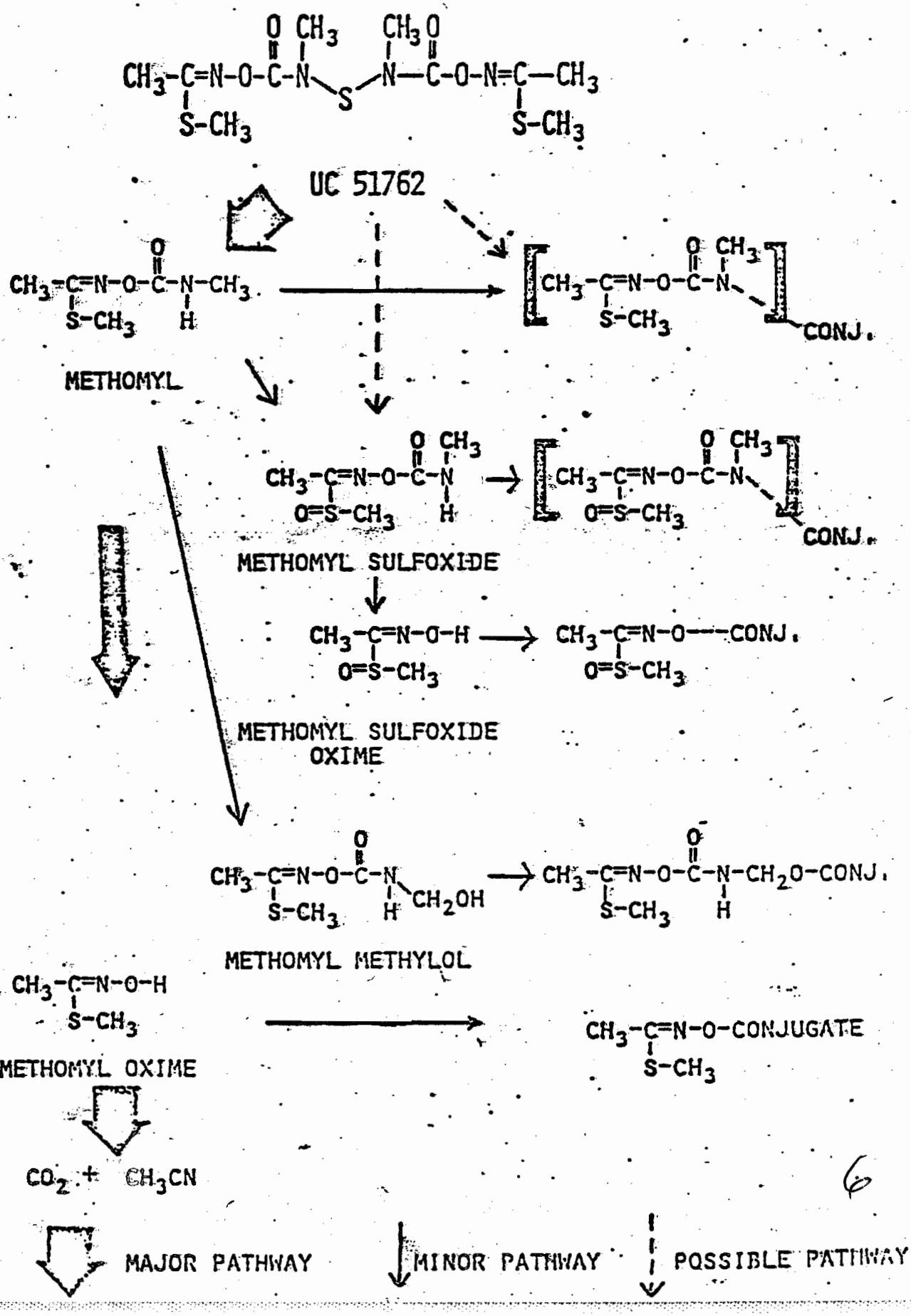
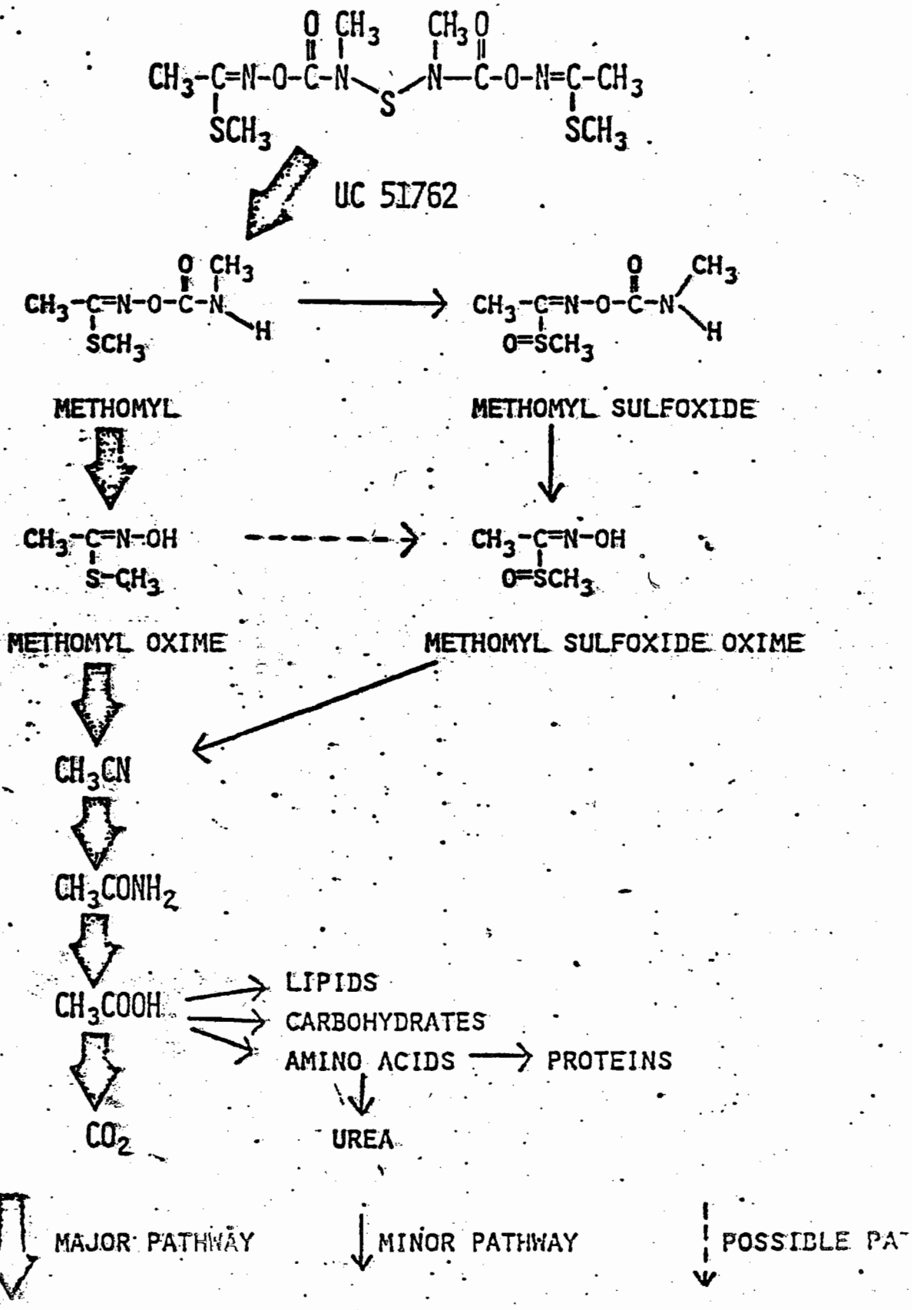


Figure 2

Metabolic pathway of UC 51762 in animals



However, the data showed that residues are concentrated in the hull and by a factor of 4X. As a result, the proposed tolerance of 0.8 ppm will adequately cover residues in the soybean hull.

Soybean forage and fodder

Samples of soybean forage (whole green plants before maturity) were collected from crops treated once at 0.75 lab act/A. Residues were <0.02-76 ppm at 7 days after application.

Samples of soybean hay (green plants cut 7 days after application and air-dried for 3 days) were collected from crops which had received one application at 0.75 lb act/A. Residues were <0.05-300 ppm at 10 days after treatment.

Samples of soybean straw (mature plants with seed removed) were collected from crops which had received 3 and 4 applications at 0.75 lb act/A. Residues were <0.02-16 ppm at intervals of 26-32 days after the last treatment.

The residue levels for the forage, hay, and straw are quite variable and very high in some cases. This data supports the proposed label restrictions on the feed use of the forage, hay, and straw.

Feeding studies

Cattle

Lactating cows were fed radiolabelled C^{14}-thiodicarb daily for 21 days at levels equivalent to 0.1, 10, 30, and 100 ppm in the diet. Milk samples were collected for analysis at regular intervals. Tissue samples were collected for analysis on the 1st day of feeding and 7 days later.

No carbamate residues were noted in samples of milk or tissues. The metabolites acetonitrile and acetamide were found in milk and meat. Radioactivity in milk plateaued at about 6 days, and residues decreased rapidly after the last feeding. Residues of thiodicarb in milk and tissues (liver, kidney, spleen, back muscle, udder, ovary) are tabulated below. Residue were generally highest in liver.

	Feeding Levels (PPM)			
	0.1	10	30	100
Milk	0.001	0.051	0.263	0.814
Tissues		0.004-0.145	0.011-0.267	0.059-1.302

Poultry (PP#OF2413)

Laying hens were fed radiolabelled C^{14}-thiodicarb in the daily diet at a level of 15 ppm for 21 days. (The petitioner contends that 3 dosage levels wre fed: the 15 ppm level and two additional levels of 29 ppm and 102 ppm. The 29 ppm and 102 ppm levels were formed by the addition of radiolabelled C^{14}-thiodicarb and unlabelled thiodicarb. The combined quantities were then expressed as ppm thiodicarb. All feed levels were then treated as if only radiolabelled C^{14}-thiodicarb had been fed. The resulting radioactivity in eggs, meat, and excreta from each feeding level was counted and expressed as being derived from levels of 15, 29, and 102 ppm C^{14}-thiodicarb. This is misleading since the same quantitity of C^{14}-thiodicarb was fed at each level. The results merely show the same amount of radioactivity which has been diluted or concentrated to reflect different concentrations. Therefore, only the 15 ppm level is evaluated here since it represents total C^{14}-thiodicarb.)

Egg samples and feces samples were collected daily during the feeding period and for 7 days after the end of the feeding period. Tissue samples were collected and analyzed at 6 hours, 3 days, and 7 days after the ending of the feeding period. All samples were analyzed for C^{14}-radioactivity. Total radioactivity in eggs plateaued at 2-10 days. (Radioactivity was not expressed on the whole egg; residue were expressed only on the shell, white, or yolk.)

Thiodicarb is ingested, metabolized, and excreted by chickens with some deposition of residues in eggs and tissues. No residues were noted of the parent compound, thiodicarb, or its metabolites: methomyl, methomyl oxime, methomyl oxime sulfoxide, and methomyl methylol. The metabolites acetonitrile and acetamide were present in eggs and tissues and declined rapidly after the end of the feeding period. Much of the radioactivity in eggs and meat were present as reincorporated C^{14} in naturally-occurring components. The tissue (liver, breast, thigh) activity levels were 0.03-0.05 ppm from the 15 pm feeding level at 6 hours after the end of feeding. At 7 days, no residues were noted (<0.002 ppm).

Residue levels of equivalent thiodicarb (radioactivity) for eggs were expressed separately on the shell, yolk, and white. The yolk had a maximum of 0.024 ppm thiodicarb residues at 21 days, and the white had 0.046 ppm at 14 days. The residue level can be calculated for the whole egg by considering the yolk as 32.75% of the whole egg and the white as 57.01% of the whole egg (Mercia, L.S., "Raising Poultry The Modern Way," Charlotte, Vermont, 1978, p. 24). With these values, the whole egg contains 0.073 ppm (due to yolk) and 0.081 ppm (due to white) as a result of the 15 ppm feeding level.

Summary of Residues Found in Feeding Studies

Metabolite		Residues (ppm) noted at feeding levels (ppm)				
		0.1	10	15	30	100
Acetamide	cattle liver		0.143		0.166	0.677
	milk					<0.01
	eggs			0.02		
	poultry liver					0.060
Acetonitrile	cattle liver		0.002		0.014	0.625
	milk	0.001	0.051		0.263	0.814
	eggs			0.07		
	poultry liver			0.047		0.445

Meat, Milk, and Eggs

Soybeans, soybean meal and soapstock, and soybean hulls may be fed to livestock. Forage, hay, or straw is not to be fed to livestock.

The maximum likely ingestion levels, based on the proposed tolerance levels of 0.2 ppm (soybeans) and 0.8 ppm (soybean hulls), are as follows: cattle and horses (0.16 ppm); goats and sheep (0.24 ppm); hogs (0.08 ppm); poultry (o.1 ppm).

Using the estimated ingestion levels and the cattle and poultry feeding studies, the level of residues likely to result in eggs, milk, and meat can be calculated. (The components of the residues are acetamide and acetonitrile. See discussion under nature of the Residue.) The estimates are as follows:

	Acetonitrile	Acetamide
Meat, fat, and meat byproducts of cattle and horses	0.03 ppb*	0.9 ppb*
milk	<2 ppb	<0.2 ppb
Meat, fat, and meat byproducts of poultry	0.3 ppb	0.06 ppb
Eggs	0.5 ppb	0.1 ppb
Meat, fat, and meat byproducts of hogs	0.02 ppb	0.5 ppb
Meat, fat, and meat byproducts of goats and sheep	5 ppb	3 ppb

*(ppb = parts per billion)

TS-769:RCB:ASmith:vg:CM#2:Rm810:X77377:3/1/83
cc: RF, Circ., Smith, Thompson, FDA, TOX, EEB, EFB, PP#3F2793/FAP3H5378
RDI: Quick 2/22/83; Schmitt, 2/25/83

SMITH, A.

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL THIODICARB

PETITION NO. 3F2793/3H5378

CCPR NO.

Codex Status

/ X / No Codex Proposal Step 6 or above

Proposed U.S. Tolerances

DIMETHYL N,N'[THIOBIS[(METHYLIMINO) CARBONYLOXY]bis[ETHANIMIDOTHIOATE]

Residue (if Step 9):

Residue: AND ITS METABOLITE METHOMYL

Crop(s)	Limit (mg/kg)

Crop(s)	Tol. (ppm)
SOYBEANS	0.2 ppm
SOYBEAN HULLS	0.8 ppm

CANADIAN LIMIT

Residue:

Crop	Limit (ppm)
NONE	

MEXICAN TOLERANCIA

Residue:

Crop	Tolerancia (ppm)
NONE	

Notes: