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

JAN 14 1983

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of all data to determine carcinogenic potential of thiodicarb. (re: 264-GUE, 264-GUR; PP#0F2413, OH5275; Larvin. Petition proposing tolerances in or on cottonseed/hulls and soybeans/hulls and straw for residues of thiodicarb). Caswell 900AA.

TO: Jay Ellenberger, PM-12
Registration Division (TS-767C)

THRU: Christine Chaisson, Section Head C.I. Chaisson EFP 1/12/83 1/12/83
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Questions concerning the cancer assessment of studies submitted with the petition request referenced above were raised by Ed Gray (OGC). This special request is an update and review of the information submitted and the previous analysis by Toxicology Branch. Special concern was focused on acetamide, a metabolite of thiodicarb, which was reported to cause animal cancer at high dose levels.

Four acceptable cancer studies using thiodicarb and methomyl were found which are negative for oncogenicity. Methomyl is a key metabolite of thiodicarb in plants and animals. . Thiodicarb when administered to animals, is rapidly metabolized, with 90 percent of the administered radioactivity being excreted or exhaled within 72 hours and most of the remaining radioactivity being incorporated into the carbon pool, primarily in liver.

Acetamide is one of several metabolites which is part of the biotransformation pathway of thiodicarb and methomyl. At expected levels in feed of 0.1 ppm or up to 30 ppm (300 times expected worst case levels), acetamide is not found in milk or muscle of beef. At 100 ppm or 1000 times expected feeding levels, acetamide was found at 4 ppb, representing a level of 0.1 ppb when adjusted down to the expected maximum feeding rate of 0.1 ppm.

An NCI cancer study from the literature (Weisburger, J.H. et al. Prevention by arginine glutamate of the carcinogenicity of acetamide in rats. Tox. Appl. Pharm. 14: 163-175 (1969)) was reported as causing cancer when pure

acetamide was administered in the diet of rats at a rate of 2.5% (25,000 ppm).

The Union Carbide request resulted in the following review by Dykstra:

1) Memorandum from William Dykstra to Jay Ellenberger, EPA Reg. # 264-GUE; 264-GUR; PP#OF2413, OH5275; Larvin, Thidicarb; Petition proposing tolerances in or on cottonseed/ hulls and soybeans/hulls and straw for residues of thiodicarb, Dimethymyl N,N'-|thiobis|(methylimino)carbonyloxy|| bis |ethan-imidothioate| CASWELL#900AA; Accession #099581-96; 099598.

Dykstra's review included two oncogencities studies using thiodicarb:

Document 47: UC-571762; Chronic Oncongenicity Feeding Study in Mice (Carnegie-Mellon Institute of Research Project Report 43-10; January 25, 1980 (pages 60-64) of Dykstra's review.

Document 48. UC-51762; Chronic Toxicity and Oncogenicity Feeding Study in Fischer 344 Rats (Carnegie-Mellon Bushy Run Research Center Project Report 431-18; March 24, 1980), pages 64- 77 of Dykstra's report.

Both of these studies were identified as supplementary at the time however the Company submitted requested additional information which allowed Dykstra to rule that the studies were now acceptable (Memorandum from Dykstra to J. Ellenberger dated 4/28/82. The rat and mouse were both negative for oncogencity at 10 mg/kg/day (HDT). A notice of intent to approve the requested tolerance was published in the Federal Register (FR:47 page 16012, April 14, 1982).

Later, Dykstra discovered the NCI report an performed the above mentioned risk assessment (Memo from Dykstra to Ellenberger July 8, 1981).

Two other oncogencity studies using methomyl were also found as reported in:

Memorandum from Dykstra to Ellenberger PP#1H5320; Methomyl in/on Imported Tea at 0.5 ppm Caswell #549C. Accession # 070341-2, 079246-7. dated October 13, 1981.

A rat study was negative for oncogenicity at 400 ppm (HDT) and a mouse study was negative at 800 ppm (HDT).

The review of the detailed metabolic and residue studies on thiodicarb and methomyl by Union Carbide was provided in a memorandum from Alfred Smith to J.S. Ellenberger, dated January 21, 1981. Although the report by Smith was quite adequate, this Reviewer wanted to have additional information on the mass balance for the metabolism studies and more detailed

information on the amount of acetamide that could be expected from the use of cottonseed and soybean crops as feed. To expedite this, the Reviewer spoke to Union Carbide's residue chemist Dr. Richard Heintzelman on 1/6/82 who indicated that that cattle which received 7.2 mg/kg or 100 ppm radiolabeled thiodicarb lost 66% of the activity to carbon dioxide, 5% C^{14} in the urine, 11.4% in the feces; 4.6% in milk (they could not detect any acetamide in milk) and 10.1% was retained in the liver, thus accounting for 97.1% of the radiolabel administered. Such information was provided in the submitted studies.

Based on USDA estimates for feeding cottonseed and soybean products (which Heinzelman discussed in detail), one would at maximum expect cattle to receive about 0.1 ppm of the carbamates in feed (in contrast to the 100 ppm used in this experiment.

Dr. Ray Kent of the Residue Chemistry Branch, using the data provided the summary shown the attached table dated 1/7/83 taken from the Union Carbide report by Feung et al. "Studies on the Disposition of ^{14}C-Thiodicarb in Lactating Cows", Feb. 13, 1980, Proj. No. 814C50, File No. 27350 (reviewed and cited in Smith's review). At the 0.1 ppm level given by Smith (page 18) and at the 10 and 30 ppm levels in Kent's table, no acetamide residues in muscle were found. At 100 ppm (1000 times expected maximum feeding rates) the muscle contained 0.04 ppm or 0.1 ppb adjusted to the 0.1 ppm expected maximum feeding rate. Liver, at the 100 ppm resulted in 1.1 ppb maximum residues for acetamide.

A search of the Toxicology Data Bank, EMIC, ETIC, etc. did not provide new cancer studies on the four chemicals.

Conclusions

In view of the four validated negative carcinogenicity studies which are more directly applicable to our concerns and in view of the insignificant amounts of acetamide formed from the expected use of thiodicarb, the NCI study is not relevant to this application and thiocarb will not be considered an oncogen.

Stanley B. Gross 1/12/82

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Toxicology Branch (TS-769C)

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Ray Kent 1/11/83
Residue Chemistry

ESTIMATED MAXIMUM ACETAMIDE CONCENTRATIONS IN MILK AND TISSUES OF RUMINANTS INGESTING RESIDUE ~~COTTON~~ BEARING COTTONSEED AND SOYBEAN BYPRODUCTS.

(BASED ON ^{14}C-THIODICARB LACTATING COW FEEDING STUDY)

	FEEDING LEVEL					
	10		30		100	
TISSUE	FOUND (PPM)	ADJUSTED* (PPB)	FOUND (PPM)	ADJUSTED* (PPB)	FOUND (PPM)	ADJUSTED* (PPB)
LIVER	0.143	2.3	0.166	0.9	0.67	
KIDNEY	0.005	0.1	0.044	0.2	0.061	0.1
SPLEEN	0.004	0.1	0.017	0.1	0.022	<0.1
BACK MUSCLE	N/D	—	0.007	0.0	0.04	0.1
UDDER	0.016	0.3	0.073	0.4	0.084	0.1
MILK	N/D	—	ND	—	TRACE	—

* IT is estimated that consumption of residue-bearing cottonseed and soybeans will result in a maximum Thiodicarb dietary intake of 0.16 ppm for sheep and goats and 0.10 ppm for cattle. The figure of 0.16 ppm has been used in the calculation of adjusted residue.

$$\frac{0.16 \text{ ppm}}{\text{FEEDING LEVEL}} \times \text{RESIDUE FOUND} \times 1000 = \text{ADJUSTED LEVEL (PPB)}$$

900AA

NOTE TO THE FILES

SUBJECT: Special assignment on Thiodicarb

FROM: Stanley Gross
Toxicology Branch (TS-769C)

1/12/83

cc: Christine Chaisson

A meeting with was called by Doug Campt with Ed Gray (OGC), Jay Ellenberger from RD, John Malone (HED), Gene Paynter and others from Toxicology Branch, and Dick Schmidt and others from Residue Chemistry Branch on December 21, 1982 to discuss questions raised by Ed Gray concerning a risk assessment by William Dykstra of Toxicology Branch and residue analyses by Residue Chemistry made by Alfred Smith. The focus was the concern for possible exposures to acetamide, one of many low level metabolites of thiodicarb and methomyl and whose presence was found in animal feeding studies when the agents were administered at high dose levels. Dykstra had accepted the data from the literature because even at the given levels of 25,000 ppm of pure acetamide, the calculated a risk was only 10^{-8}. Ed Gray felt that this approach placed thiodicarb in a Delaney admendment situation and wanted to know if Union Carbide had methods for assuring that acetamide residues would be at or below a risk level of 10^{-6} (the "zero level" accepted by FDA as allowed by the DES amendment of the Delaney clause. Dick Schmidt and Alfred Smith indicated that the acetamide levels of 2 ppb were based on radiactivity analyses and that the company did not currently have methods of detecting acetamide at 2 ppb or at the 10^{-6} risk level. John Malone instructed Toxicology Branch (Christine Chaisson) to review and update the situation and report the findings to Registration Division.

Since I had already been assigned the task of reviewing Union Carbides more recent requests for tolerances on field and sweet corn and soybeans, I was also asked to update information on any cancer studies involving thiodicarb, methomyl, acetamide and acetonitrile and to re-review the stated concerns.

This assignment was completed with the submission of my memo to Jay Ellenberger:

> Review of all data to determine carcinogenic potential of thiocarb. (re: 264-GUE, 264-GUR; PP#0F2413, OH5275; Larvin. Petition proposing tolerances in or on cottonseed/hulls and soybeans/hulls and straw for residues of thiodicarb). Caswell 900AA.
> Dated 1/12/82

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