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

FEB 11 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: An Interim Assessment Analysis of Oncogenic Dietary Risk on the Chemical Thiophanate-Methyl.

To: Amy Rispin, Ph.D.
Science Integration Staff
Hazard Evaluation Division

From: Charles Frick C. Frick 2/8/88
Tolerance Assessment Program
Residue Chemistry Branch, HED

Thru: Karl Arne, Ph.D.
Branch Senior Scientist
Residue Chemistry Branch, HED

Please find attached the Tolerance Assessment System (TAS) tolerance assessment, which was conducted on request from Dr. Gary Burin, Science Integration Staff, HED, to evaluate the dietary/ oncogenic risk for the published tolerances of Thiophanate-methyl. This is in compliance with the policy established in HED that TAS will be used for all Registration Standards, Special Reviews, and on new chemicals.

It should be noted that there are in-house, pending tolerances for Thiophanate-methyl. These pending tolerances have not been included in this analysis.

This TAS analysis must be considered an interim assessment- see memorandum from Gary Burin to Phil Hundeman, attached to this report.

TOLERANCE ASSESSMENT

CHEMICAL: THIOPHANATE-METHYL

1. The Reference Dose (RFD) for this chemical is 0.08 mg/kg/day (PADI). This value has been approved by the Toxicology Branch and Agency Reference Dose Committees.

2. The potency estimate Q^* has been calculated as 3.9×10^{-3} $(mg/kg/day)^{-1}$ for the metabolite of Thiophanate-methyl, MBC. This value is used for the dietary risk assessment for Thiophanate-methyl- See Burin memo.

3. The food uses evaluated by the Tolerance Assessment System (TAS) are published tolerances. Where data is available these tolerances have been factored by the percent of crop treated with Thiophanate-methyl. This data submitted to TAS by BUD, memorandum Edward Brandt to Lois Rossi, 1/14/88.

4. A comparision of these published tolerances to the PADI was conducted using the TAS Routine Chronic Analysis. The TAS analysis estimates the potential dietary exposure for the U.S. population average and for 22 subgroups (A summary table is appended). The Theoretical Maximum Residue Contribution (TMRC) for the U.S. population is 0.0157 mg/kg/day, which is equal to 19.7% of the PADI.

5. The subgroup with the highest calculated exposure was non-nursing infants (0.0974 mg/kg/day, 121.7% of the PADI).The majority of the exposure to this subgroup comes from milk products (0.0649 mg/kg/day, 81% of the PADI). No data were available to assess the actual residues of Thiophanate-methyl in milk products.

6. An assessment of the oncogenic risk follows on the next page.

DIETARY RISK ASSESSMENT (ONCOGENICITY)

1. The following risk assessment is based on the Q^* value 3.9×10^{-3} $(mg/kg/day)^{-1}$* and the TMRCs generated by the TAS analysis of the published tolerances of Thiophanate-methyl factored by the percent of crop treated. Risk was calculated only for the U.S. population in accordance with current HED policy. This value was calculated by the relationship:

$$RISK = EXPOSURE \times Q^*$$

The risk was therefore calculated as:

Total Diet - $0.0157 \times (3.9 \times 10^{-3}) = \underline{6.1 \times 10^{-5}}$

Milk Products - $0.0105 \times (3.9 \times 10^{-3}) = \underline{4.1 \times 10^{-5}}$

* As noted this is the Q^* value for MBC a metabolite of Thiophanate-methyl.

Attachment

cc. TAS File
Thiophanate SF
Reading File
C. Frick (RCB)
S. Rathman (TOX)
Circ.
PMSD

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Thiophanate-methyl Caswell #375A CAS No. 23564-05-8 A.I. CODE: 102001 CFR No. 180.371	2yr feeding- rat NOEL= 8.0000 mg/kg 160.00 ppm LEL= 32.0000 mg/kg 640.00 ppm ONCO: Negative rat, mouse.	Decreased body weights, decreased spermatogenesis hyperthyroidism.	PADI 100 OPP RfD= 0.080000 EPA RfD= 0.080000 WHO RfD 0.080000 Type: ADI	Rabbit teratology.	TOX complete 2/21/86. ORD verified 3/11/86. WHO last reviewed 1977.

POPULATION SUBGROUP	TOTAL TMRC (MG/KG BODY WEIGHT/DAY) CURRENT TMRC*	NEW TMRC**	NEW TMRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC (MG/KG/DAY)	%RFD
U.S. POPULATION - 48 STATES	0.024003	0.024003	30.003578	0.000000	0.015751	19.688898
U.S. POPULATION - SPRING SEASON	0.022354	0.022354	27.942176	0.000000	0.014828	18.534953
U.S. POPULATION - SUMMER SEASON	0.026139	0.026139	32.673809	0.000000	0.017051	21.313485
U.S. POPULATION - FALL SEASON	0.023930	0.023930	29.912443	0.000000	0.015762	19.702406
U.S. POPULATION - WINTER SEASON	0.023596	0.023596	29.494699	0.000000	0.015372	19.214399
NORTHEAST REGION	0.026120	0.026120	32.650144	0.000000	0.016372	20.464433
NORTH CENTRAL REGION	0.023962	0.023962	29.952506	0.000000	0.015958	19.947195
SOUTHERN REGION	0.019967	0.019967	24.958545	0.000000	0.013553	16.941638
WESTERN REGION	0.028206	0.028206	35.257074	0.000000	0.018429	23.036241
HISPANICS	0.028875	0.028875	36.094238	0.000000	0.019984	24.980061
NON-HISPANIC WHITES	0.024367	0.024367	30.458967	0.000000	0.015833	19.790699
NON-HISPANIC BLACKS	0.019163	0.019163	23.954115	0.000000	0.013109	16.386017
NON-HISPANICS OTHER	0.025537	0.025537	31.920869	0.000000	0.016792	20.989656
NURSING INFANTS (<1 YEAR OLD)	0.083196	0.083196	103.995141	0.000000	0.030675	38.344056
NON-NURSING INFANTS (<1 YEAR OLD)	0.173703	0.173703	217.128285	0.000000	0.097420	121.774825
FEMALES (13+ YEARS, PREGNANT)	0.017182	0.017182	21.477411	0.000000	0.011845	14.806546
FEMALES 13+ YEARS, NURSING	0.021293	0.021293	26.615712	0.000000	0.014615	18.268389
CHILDREN (1-6 YEARS OLD)	0.066420	0.066420	83.024391	0.000000	0.042182	52.727441
CHILDREN (7-12 YEARS OLD)	0.037043	0.037043	46.303813	0.000000	0.025439	31.798627
MALES (13-19 YEARS OLD)	0.020733	0.020733	25.916585	0.000000	0.015372	19.215109
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.017795	0.017795	22.243330	0.000000	0.012463	15.579154
MALES (20 YEARS AND OLDER)	0.013519	0.013519	16.898723	0.000000	0.009312	11.639446
FEMALES (20 YEARS AND OLDER)	0.013883	0.013883	17.353195	0.000000	0.009024	11.279594

*Current TMRC does not include new or pending tolerances.
**New TMRC includes new, pending, and published tolerances.

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MEMORANDUM

SUBJECT: Thiophanate-Methyl Dietary Risk Assessment

FROM: Gary J. Burin, D.A.B.T.
Science Integration and Policy Staff
Hazard Evaluation Division (TS-769C)

TO: Phil Hundeman, PM-21
Insecticide-Rodenticide Branch
Registration Division (TS-767C)

THRU: Amy S. Rispin, Chief
Science Integration and Management Staff
Hazard Evalaution Division (TS-769C)

I have conferred with Toxicology Branch and Residue Chemistry Branch regarding the risk assessment for Thiophanate-methyl that will be presented in the Registration Standard. There is a consensus that risk be approached as follows:

1. The fungicidal activity of thiophanate-methyl depends on its conversion to MBC (as is the case with benomyl, another fungicide with similar uses). Therefore, the application of thiophanate-methyl will result in MBC residues in or on plants. The amount of MBC residue will be no more than one half the thiophanate-methyl residue based on molecular weight considerations.

2. There is a limited amount of evidence that dietary exposure to the metabolite MBC poses an oncogenic risk. MBC was classified as a Group C oncogen (based on the Agency's Cancer Assessment Guidelines) which is defined as a possible human oncogen, based on the following:

   (a) MBC has been shown to cause liver tumors in two closely related strains of mice (CD-1 and SPF Swiss), whereas no liver tumors were produced by MBC in another strain of mice (NMRKf SPF-71).

(b) MBC interferes with cell division and DNA precursor biosynthesis in fungi. MBC produces weak mutagenic effects consistent with spindle poison activity rather than gene mutations or DNA damage and repair.

(c) MBC showed no oncogenic response in ChR- CD rats.

3. Thiophanate-methyl did not show any positive effect in oncogenic studies in the rat and mouse. The absence of a maximum tolerated dose (MTD) in the mouse oncogenicity study requires that a new study be conducted with mice. This study has been requested and is underway.

4. The weight of evidence places thiophanate-methyl in Class D- inadequate testing for oncogenic potential. A final assessment of the risks associated with thiophanate-methyl is not possible at this time.

5. An applicator risk assessment may be conducted after receipt of the mouse oncogenicity study. The weight of evidence will and the need for quantitative risk assessment be revisited at that point.

6. An interim assessment of oncogenic dietary risk can now be made by assuming complete conversion of thiophanate-methyl to MBC with a cancer potency for MBC based on the positive mouse oncogenicity studies. That risk estimate will be revisited when adequate oncogenicity testing of thiophanate-methyl is available. The risk assessment should eventually be based on potency estimates and actual residues for both MBC and thiophanate-methyl.

A Tolerance Assessment Evaluation will be sent to you shortly (the RCB contact for this has been out sick for the last several days). The TAS risk estimate adjusts for the percentage of crop treated (based on the January 14, 1988 memorandum of Edward Brandt) and readily available actual residue information. The upper bound risk estimate prior to consideration of actual residues was in the low 10^{-5} range.

cc: J. Hauswirth
C. Frick