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

APR 26 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chronic and Acute Dietary Exposure Analyses for the Use of Avermectin on Cotton, 7E3500

FROM: J. Robert Tomerlin, Ph.D. J R Tomerlin 4/24/89
Tolerance Assessment System Staff
HED/SACB (H7509C)

THROUGH: R. Bruce Jaeger RBJ 4/26/89
Head, Special Analysis and Outreach Section
HED/SACB (H7509C)

TO: George T. LaRocca, PM 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Action Requested

Provide estimates of dietary exposure resulting from the proposed use of avermectin on cotton. Both chronic and acute toxic effects are considered.

Discussion

1. Toxicology Endpoint: The routine chronic TAS analysis used a reference dose (ADI) of 0.0004 mg/kg body weight/day, based upon a NOEL of 0.12 mg/kg body weight/day and an uncertainty factor of 300 from a two generation rat reproduction study. This value has been approved by HED (3/30/89) and Agency (4/20/89) reference dose committees.

2. Residue Information: Food uses evaluated included the proposed use on cotton, which is not expected to result in secondary residues in meat or milk (F. Boyd memo, 4/21/89). There are not any published tolerances for avermectin at this time. Temporary tolerances on citrus with secondary residues in meat and milk are scheduled to expire in May of 1989. These tolerances, as well as tolerances on celery, pears, and tomatoes from Section 18 requests, were included in the analysis in the "published" category because permanent tolerances are pending for each of these uses. A summary of the residue information used in the analysis is attached as Table 1.

3. Chronic Exposure Analysis: The TAS chronic exposure analysis uses tolerance level residues and 100 per cent crop treated to

estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. The TMRC for the overall U.S. population is calculated as 0.000052 mg/kg body weight/day, which represents 13% of the ADI. The two most highly exposed population subgroups, non-nursing infants and children aged 1 to 6, have estimated TMRCs of 0.000151 mg/kg body weight/day (38% of the ADI) and 0.000118 mg/kg body weight/day (29% of the ADI), respectively. For any population subgroup, the proposed action on cotton results in an increased exposure of less than 0.000001 mg/kg body weight/day, representing less than 0.1% of the ADI. A complete TMRC summary is shown in Table 2.

4. Acute Exposure Analysis: A detailed acute exposure analysis was conducted using a NOEL of 0.06 mg/kg body weight for developmental effects. The food uses evaluated were the same as those evaluated in the chronic exposure analysis (Table 1).

The TAS acute exposure analysis estimates the distribution of single-day exposures for the overall U.S. population and certain population subgroups. The analysis evaluates the individual food consumption, as reported by respondents in the 1977-78 USDA Food Consumption Survey, and accumulates exposure to avermectin for each food consumed for which a tolerance is being evaluated. Each analysis assumes that avermectin residues are present at tolerance level in all foods consumed.

The toxicologic endpoint pertains to developmental toxicity. The TAS subgroup of interest in this analysis is women aged 13 and above, which is the TAS subgroup most closely approximating women of child-bearing age. The Margin of Safety (MOS) for the average consumer may be calculated according to the following relationship:

Average MOS = NOEL / Exposure

= 0.06 mg/kg body weight / 0.000038 mg/kg body weight

= 1579

An examination of the exposure distribution (Table 3) shows that none of the target population is expected to have an MOS less than 250.

Attachments

cc: TAS (Tomerlin, SACB), DEB, Tox, Caswell #063AB, B. Jaeger, Dykstra (TOX-IRS)

Table 1

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB DATE: 04/10/89 PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Avermectin Caswell #063AB CAS No. 65195-55-3 A.I. CODE: 122804 CFR No. 180.	2gen reprod- rat NOEL= 0.1200 mg/kg 0.00 ppm LEL= 0.4000 mg/kg 0.00 ppm ONCO: Negative- 2 species.	Incr retinal folds in weanlings, decr viability & lactation indices; decr pup body wt; incr of dead pups at birth. No evidence of oncogenicity.	ADI SF -->300 OPP RfD= 0.000400 EPA RfD= 0.000400	No data gaps. UF of 300 due pup deaths in critical study & maternal developmental toxicity in teratology studies. Mouse teratogen.	HED complete 07/11/86. HED reassess 06/12/87. HED reassess 03/30/89. EPA verified 04/20/89.

FOOD CODE	FOOD NAME		PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
02001AA	CITRUS CITRON	EXP. 05/89	7G3468			0.005000
02002AA	GRAPEFRUIT-UNSPECIFIED	EXP. 05/89	7G3468			0.005000
02002AB	GRAPEFRUIT-PULP	EXP. 05/89	7G3468			0.005000
02002JA	GRAPEFRUIT-JUICE	EXP. 05/89	7G3468			0.005000
02003AA	KUMQUATS	EXP. 05/89	7G3468			0.005000
02004AA	LEMONS-UNSPECIFIED	EXP. 05/89	7G3468			0.005000
02004AB	LEMONS-PULP	EXP. 05/89	7G3468			0.005000
02004HA	LEMONS-PEEL	EXP. 05/89	7G3468			0.005000
02004JA	LEMONS-JUICE	EXP. 05/89	7G3468			0.005000
02005AA	LIMES-UNSPECIFIED	EXP. 05/89	7G3468			0.005000
02005AB	LIMES-PULP	EXP. 05/89	7G3468			0.005000
02005HA	LIMES-PEEL	EXP. 05/89	7G3468			0.005000
02005JA	LIMES-JUICE	EXP. 05/89	7G3468			0.005000
02006AA	ORANGES-UNSPECIFIED	EXP. 05/89	7G3468			0.005000
02006AB	ORANGES-PULP	EXP. 05/89	7G3468			0.005000
02006HA	ORANGES-PEEL	EXP. 05/89	7G3468			0.005000
02006JA	ORANGES-JUICE	EXP. 05/89	7G3468			0.005000
02007AA	TANGELOS	EXP. 05/89	7G3468			0.005000
02008AA	TANGERINES	EXP. 05/89	7G3468			0.005000
02008JA	TANGERINE-JUICE	EXP. 05/89	7G3468			0.005000
04003AA	PEARS-FRESH		89-WA06			0.025000
04003DA	PEARS-DRIED		89-WA06			0.025000
11005AA	TOMATOES-WHOLE		89-FL01			0.005000
11005JA	TOMATOES-JUICE		89-FL01			0.005000
11005RA	TOMATOES-PUREE		89-FL01			0.005000
11005TA	TOMATOES-PASTE		89-FL01			0.005000
11005UA	TOMATOES-CATSUP		89-FL01			0.005000
13002AA	CELERY		89-FL08			0.050000
13016AA	FENNEL		89-FL08			0.050000
270030A	COTTONSEED-OIL		6G3320	0.005000		
27003WA	COTTONSEED-MEAL		6G3320	0.005000		
50000DB	MILK-NON-FAT SOLIDS	EXP. 05/89	7G3468			0.001000
50000FA	MILK-FAT SOLIDS	EXP. 05/89	7G3468			0.001000
50000SA	MILK SUGAR (LACTOSE)	EXP. 05/89	7G3468			0.001000
53001BA	BEEF-MEAT BYPRODUCTS	EXP. 05/89	7G3468			0.010000
53001BB	BEEF(ORGAN MEATS)-OTHER	EXP. 05/89	7G3468			0.010000
53001DA	BEEF-DRIED	EXP. 05/89	7G3468			0.010000
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	05/89	7G3468			0.010000
53001KA	BEEF(ORGAN MEATS)-KIDNEY	EXP. 05/89	7G3468			0.010000
53001LA	BEEF(ORGAN MEATS)-LIVER	EXP. 05/89	7G3468			0.010000

Table 1, continued

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

DATE: 04/10/89 PAGE: 2

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Avermectin Caswell #063AB CAS No. 65195-55-3 A.I. CODE: 122804 CFR No. 180.	2gen reprod- rat NOEL= 0.1200 mg/kg 0.00 ppm LEL= 0.4000 mg/kg 0.00 ppm ONCO: Negative- 2 species.	Incr retinal folds in weanlings, decr viability & lactation indices; decr pup body wt; incr of dead pups at birth. No evidence of oncogenicity.	ADI SF -->300 OPP RfD= 0.000400 EPA RfD= 0.000400	No data gaps. UF of 300 due pup deaths in critical study & maternal developmental toxicity in teratology studies. Mouse teratogen.	HED complete 07/11/86. HED reassess 06/12/87. HED reassess 03/30/89. EPA verified 04/20/89.

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)	7G3468			0.010000

Table 2

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 04/10/89

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Avermectin Caswell #063AB CAS No. 65195-55-3 A.I. CODE: 122804 CFR No. 180.	2gen reprod- rat NOEL= 0.1200 mg/kg 0.00 ppm LEL= 0.4000 mg/kg 0.00 ppm ONCO: Negative- 2 species.	Incr retinal folds in weanlings, decr viability & lactation indices; decr pup body wt; incr of dead pups at birth. No evidence of oncogenicity.	ADI SF -->300 OPP RfD= 0.000400 EPA RfD= 0.000400	No data gaps. UF of 300 due pup deaths in critical study & maternal developmental toxicity in teratology studies. Mouse teratogen.	HED completé 07/11/86. HED reassess 06/12/87. HED reassess 03/30/89. EPA verified 04/20/89.

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	%RFD
U.S. POPULATION - 48 STATES	0.000052	0.000052	12.985000	0.025750		
U.S. POPULATION - SPRING SEASON	0.000050	0.000050	12.616500	0.026250		
U.S. POPULATION - SUMMER SEASON	0.000051	0.000051	12.782750	0.025750		
U.S. POPULATION - FALL SEASON	0.000053	0.000053	13.339000	0.025750		
U.S. POPULATION - WINTER SEASON	0.000053	0.000053	13.193000	0.025500		
NORTHEAST REGION	0.000057	0.000057	14.204500	0.024250		
NORTH CENTRAL REGION	0.000053	0.000053	13.288250	0.025500		
SOUTHERN REGION	0.000045	0.000045	11.169000	0.025500		
WESTERN REGION	0.000056	0.000056	14.033000	0.027750		
HISPANICS	0.000064	0.000064	16.056500	0.024500		
NON-HISPANIC WHITES	0.000052	0.000052	13.028250	0.026250		
NON-HISPANIC BLACKS	0.000044	0.000044	11.006500	0.022750		
NON-HISPANIC OTHERS	0.000060	0.000060	15.025750	0.023250		
NURSING INFANTS (< 1 YEAR OLD)	0.000069	0.000069	17.322750	0.002750		
NON-NURSING INFANTS (< 1 YEAR OLD)	0.000151	0.000151	37.705250	0.007500		
FEMALES (13+ YEARS, PREGNANT)	0.000039	0.000039	9.747750	0.018500		
FEMALES 13+ YEARS, NURSING	0.000046	0.000046	11.581500	0.024500		
CHILDREN (1-6 YEARS OLD)	0.000117	0.000117	29.331250	0.046250		
CHILDREN (7-12 YEARS OLD)	0.000078	0.000078	19.587500	0.039000		
MALES (13-19 YEARS OLD)	0.000052	0.000052	12.986750	0.027750		
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000043	0.000044	10.875250	0.024500		
MALES (20 YEARS AND OLDER)	0.000038	0.000038	9.409000	0.021750		
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000037	0.000037	9.174250	0.020000		

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

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Table 3: Avermectin Acute Exposure Analysis

MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY

PERSON DAYS THAT ARE USER-DAYS	MG/KG BODY WEIGHT/DAY	AVERAGE MOS
99.7	0.000038	1759

ESTIMATED % OF POPULATION USER-DAYS WITH RESIDUE CONTRIBUTION EXCEEDING X UG/KG, FOR X=

	0	.12	.24	.36	.48	.60	.72	.84	.96	1.08	1.2	1.8	2.4	3.0	6.0	9.0	12.0
Women of Child-Bearing Age:	100	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Margin of Safety:		500	250	167													