



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

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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*
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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:

$$\begin{aligned}\text{Average MOS} &= \text{NOEL} / \text{Exposure} \\ &= 0.06 \text{ mg/kg body weight} / 0.000038 \text{ mg/kg body} \\ \text{weight} & \\ &= 1579\end{aligned}$$

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

PAGE: 1

DATE: 04/10/89

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

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

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM)	
			NEW	PUBLISHED
02001AA	CITRUS CITRUS	7G3468		0.005000
02002AA	GRAPEFRUIT-UNSPECIFIED	7G3468		0.005000
02002AB	GRAPEFRUIT-PULP	7G3468		0.005000
02002JA	GRAPEFRUIT-JUICE	7G3468		0.005000
02003AA	KUMQUATS	7G3468		0.005000
02004AA	LEMONS-UNSPECIFIED	7G3468		0.005000
02004AB	LEMONS-PULP	7G3468		0.005000
02004JA	LEMONS-PEEL	7G3468		0.005000
02005AA	LEMONS-JUICE	7G3468		0.005000
02005AB	LIMES-UNSPECIFIED	7G3468		0.005000
02005JA	LIMES-PULP	7G3468		0.005000
02005JA	LIMES-PEEL	7G3468		0.005000
02006AA	LIMES-JUICE	7G3468		0.005000
02006AB	ORANGES-UNSPECIFIED	7G3468		0.005000
02006JA	ORANGES-PULP	7G3468		0.005000
02006JA	ORANGES-PEEL	7G3468		0.005000
02007AA	ORANGES-JUICE	7G3468		0.005000
02008AA	TANGELLOS	7G3468		0.005000
02008JA	TANGERINES	7G3468		0.005000
04003AA	TANGERINE-JUICE	7G3468		0.005000
04003AA	PEARS-FRESH	89-WA06		0.025000
04003DA	PEARS-DRIED	89-WA06		0.025000
11005AA	TOMATOES-WHOLE	89-FLO1		0.005000
11005JA	TOMATOES-JUICE	89-FLO1		0.005000
11005RA	TOMATOES-PUREE	89-FLO1		0.005000
11005TA	TOMATOES-PASTE	89-FLO1		0.005000
11005UA	TOMATOES-CATSUP	89-FLO1		0.005000
13002AA	CELERY	89-FLO8		0.050000
13016AA	FENNEL	89-FLO8		0.050000
27003AA	COTTONSEED-OIL	6G3320	0.005000	
27003AA	COTTONSEED-NEAL	6G3320	0.005000	
500000B	MILK-NON-FAT SOLIDS	7G3468		0.001000
50000FA	MILK-FAT SOLIDS	7G3468		0.001000
50000FA	MILK SUGAR (LACTOSE)	7G3468		0.001000
53001BA	BEEF-MEAT BYPRODUCTS	7G3468		0.010000
53001BB	BEEF (ORGAN MEATS)-OTHER	7G3468		0.010000
53001DA	BEEF-DRIED	7G3468		0.010000
53001FA	BEEF (BONELESS)-FAT (BEEF TALLOW)	7G3468		0.010000
53001KA	BEEF (ORGAN MEATS)-KIDNEY	7G3468		0.010000
53001LA	BEEF (ORGAN MEATS)-LIVER	7G3468		0.010000

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Table 1, continued

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DATE: 04/10/89

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

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

FOOD CODE	FOOD NAME	PETITION NUMBER	NEW	TOLERANCE (PPM)	
				PENDING	PUBLISHED
53001WA	BEEF (BONELESS)-LEAN (W/O REMOVABLE FAT)	763468			0.010000

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Table 2

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 04/10/89

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

EFFECT OF ANTICIPATED RESIDUES

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

<u>MEAN DAILY RESIDUE CONTRIBUTION PER USER-DAY</u>																
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
100	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Women of Child-Bearing Age:																
Margin of Safety:																
500 250 167																