



12-21-88

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin - TAS Analysis of Proposed Section 18
Exemption for Use on Celery (#89-FL-08).

FROM: Susan L. Stanton *Susan L. Stanton* 12/21/88
Tolerance Assessment Program
HED/RCB (TS-769C)

THRU: R. Bruce Jaeger *RBJ* 12/22/88 *FE* 12/24/88
Head, Special Analysis and Outreach Section
HED/SACB (TS-769C)

TO: D. Stubbs/L. Pemberton, PM Team 41
Registration Support Branch
Registration Division (TS-767C)

Action Requested

Provide an analysis of dietary exposure to avermectin in conjunction with the proposed new use on celery. The Florida Department of Agriculture and Consumer Services has requested a Section 18 emergency exemption for the use of avermectin to control spider mites on celery. Tox consideration permitting, DEB has no objections to this Section 18 request (memo Suhre to L. Pemberton, 12/06/88).

Discussion

I. Analysis of Chronic Dietary Exposure:

1. The reference dose (PADI) used in the analysis was 0.00012 mg/kg body weight/day, derived from a NOEL of 0.12 mg/kg body weight/day from a 2-generation rat reproduction study with an uncertainty factor of 1000. The high uncertainty factor is due to the serious nature of the effects seen in the critical study and to existing data gaps. As new studies are submitted and reviewed in TOX Branch, the reference dose may change.

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2. Currently, there are no permanent tolerances established for avermectin. The food uses evaluated in the analysis were the published temporary tolerances (citrus, cottonseed, milk, & cattle) and the proposed use on celery. At the request of the Emergency and Minor Use Section (L. Pemberton) exposure from the recently granted emergency use on tomatoes was also included in calculations of the current TMRC. The residue value used for celery was 0.05 ppm (memo Suhre to L. Pemberton, 12/06/88). A complete listing of residue information is provided in Table 1.

3. The TAS routine chronic analysis estimates the Theoretical Maximum Residue Contribution (TMRC) for the U.S. population and for each of 22 population subgroups and compares this exposure estimate to the acceptable daily intake (Provisional ADI in this case). The results are presented in Table 2 and may be summarized as follows for the U.S. population and the two most highly exposed subgroups, non-nursing infants and children, ages 1-6:

	<u>Published Tolerances^a</u>	<u>Sec. 18 (Celery)</u>	<u>Total</u>
U.S. Population	0.000046 ^b (38.2%) ^c	0.000003 (2.5%)	0.000049 (40.7%)
Non-Nursing Infants	0.000111 (91.8%)	0.000001 (0.98%)	0.000112 (92.8%)
Children, 1-6 yrs.	0.000107 (89.0%)	0.000004 (3.3%)	0.000111 (92.3%)

^aIncludes established temporary tolerances and the emergency tomato use (Section 18 exemption).

^bTheoretical Maximum Residue Contribution (TMRC) in mg/kg/day.

^cExposure as percent of the PADI.

4. The chronic analysis was conducted using tolerance level residues and assumes that 100% of crops are treated. Since only a limited number of acres are treated under the EUPs and emergency exemption uses, actual exposure and risk would likely be somewhat lower.

Also, as mentioned above, the reference dose of 0.00012 mg/kg/day is provisional and may change as new studies are evaluated in TOX Branch.

II. Analysis of Acute Dietary Exposure:

1. 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 (See Table 1).

The TAS Detailed Acute Exposure Analysis calculates the distribution of single-day exposure for consumers in various subgroups. In this case the population of interest was the subgroup of females 13 years of age and older, the TAS subgroup most closely approximating women of child-bearing age. The theoretical average Margin of Safety (MOS) for developmental effects was calculated by dividing the NOEL by the mean single-day exposure. The following results were obtained:

	Average Daily Exposure (mg/kg body wt)	Average MOS
Established Uses	0.000033	1818
Established Uses + Celery	0.000036	1667

In addition, the distribution of exposure to avermectin showed that 98% of females 13 years of age and older would have a MOS of at least 500 from all established uses and the proposed use on celery and that no members of this subgroup would have a MOS less than 250 (See Table 3).

4. Both the chronic and acute exposure analyses are based on tolerances rather than actual residues. This conservative approach likely overestimates exposure significantly in each case, since it is unlikely that tolerance level residues would be encountered on foods as eaten or that all crops would be treated.

CC: Stanton (SACB), TAS File, TOX, DEB (Loranger), Caswell #063AB, RF, Jaeger (SACB).

Table 1

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

DATE: 12/12/88

PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES		DATA GAPS/COMMENTS		STATUS
			PAOI	SF			
02001AA	2uen reprod- rat	Decreased pup survival		-->1000	Chronic feeding- rat		HED complete 07/11/90
Caswell #063AB	NOEL= 0.1200 mg/kg	and body weight, increase	OTF RED= 0.000120		Chronic feeding- dog		HED reassess 06/12/97
02002AA	0.00 ppm	in incidence of retinal	EPA RED= 0.000000		UF of 1000 due to serious		EPA not scheduled
CAS No 65135-55-3	LEL= 0.4000 mg/kg	abnormalities. Doses by			effects in critical study		
A.I. CODE: 122804	0.00% ppm	gavage. No oncogenicity			and data gaps.		
CFR No 180	ONCO: Undetermined	data available			Mouse teratogen.		

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM)	
			NEW	PUBLISHED
02001AA	CITRUS CITRON	7G3468		0.005000
02002AA	GRAPEFRUIT-UNSPECIFIED	7G3468		0.005000
02002AA	GRAPEFRUIT-PULP	7G3468		0.005000
02002AA	GRAPEFRUIT-JUICE	7G3468		0.005000
02003AA	KUMQUATS	7G3468		0.005000
02004AA	LEMONS-UNSPECIFIED	7G3468		0.005000
02004AA	LEMONS-PULP	7G3468		0.005000
02004AA	LEMONS-PEEL	7G3468		0.005000
02004AA	LEMONS-JUICE	7G3468		0.005000
02005AA	LIMES-UNSPECIFIED	7G3468		0.005000
02005AA	LIMES-PULP	7G3468		0.005000
02005AA	LIMES-PEEL	7G3468		0.005000
02005AA	LIMES-JUICE	7G3468		0.005000
02006AA	ORANGES-UNSPECIFIED	7G3468		0.005000
02006AA	ORANGES-PULP	7G3468		0.005000
02006AA	ORANGES-PEEL	7G3468		0.005000
02006AA	ORANGES-JUICE	7G3468		0.005000
02007AA	TANGELOS	7G3468		0.005000
02008AA	TANGERINES	7G3468		0.005000
02008AA	TANGERINE-JUICE	7G3468		0.005000
11005AA	TOMATOES-WHOLE	89-FL01		0.005000
11005AA	TOMATOES-JUICE	89-FL01		0.005000
11005AA	TOMATOES-PUREE	89-FL01		0.005000
11003TA	TOMATOES-PASTE	89-FL01		0.005000
11005VA	TOMATOES-CATSUP	89-FL01		0.005000
13002AA	CELERY	89-FL08	0.050000	
13015AA	FENNEL	89-FL08	0.050000	
27003AA	COTTONSEED-OIL	6G3320		0.005000
27003AA	COTTONSEED-MEAL	6G3320		0.005000
50000BB	MILK-NON-FAT SOLIDS	7G3468		0.001000
50000FA	MILK-FAT SOLIDS	7G3468		0.001000
50000SA	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)	05/89		0.010000
53001KA	BEEF (ORGAN MEATS)-KIDNEY	EXP. 05/89		0.010000
53001LA	BEEF (ORGAN MEATS)-LIVER	EXP. 05/89		0.010000
53001MA	BEEF (BONELESS)-LEAN (W/O REMOVABLE FAT)	7G3468		0.010000

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Table 2

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 12/10/89

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CHEMICAL INFORMATION		STUDY TYPE		EFFECTS		REFERENCE DOSES		DATA GAPS/COMMENTS		STATUS	
Average	2gen reprod- rat	NOEL=	0.1200 mg/kg	Decreased pup survival	IPADI SF	0.0001000	Chronic feeding- rat	HED complete 07/11/86			
Coswell #63AR	NOEL=	0.00 ppm	0.00 ppm	and body weight; increase	OPP RfD=	0.000120	Chronic feeding- dog	HED reassess 06/12/87			
CAS No 65195-55-3	LEL=	0.4000 mg/kg	0.4000 mg/kg	in incidence of retinal abnormalities. Doses by	EPA RfD=	0.000000	UF of 1000 due to serious effects in critical study	EPA not scheduled			
A.I. COFF- 122804		0.00 ppm	0.00 ppm	gavage. No oncogenicity			and data gaps.				
CFR No 180	ONTO: Undetermined.			data available.			Mouse teratogen.				
POPULATION SUBGROUP		TOTAL TMRC (MG/KG BODY WEIGHT/DAY)		NEW TMRC**		NEW TMRC AS PERCENT OF PED		DIFFERENCE AS PERCENT OF RFD		EFFECT OF ANTICIPATED RESIDUES	
		CURRENT TMRC*								ARC	
U.S. POPULATION - 48 STATES		0.000046		0.000049		40.727500		2.549167			
U.S. POPULATION - SPRING SEASON		0.000045		0.000048		39.858333		2.646667			
U.S. POPULATION - SUMMER SEASON		0.000045		0.000048		40.379167		2.546667			
U.S. POPULATION - FALL SEASON		0.000047		0.000050		41.430833		2.465000			
U.S. POPULATION - WINTER SEASON		0.000046		0.000049		41.211667		2.500833			
NORTHEAST REGION		0.000050		0.000053		44.330000		2.827500			
NORTH CENTRAL REGION		0.000047		0.000050		41.670000		2.523333			
SOUTHERN REGION		0.000040		0.000043		35.546667		1.962500			
WESTERN REGION		0.000048		0.000052		43.428333		3.179167			
HISPANICS		0.000058		0.000061		50.673333		2.466667			
NON-HISPANIC WHITES		0.000046		0.000049		40.723333		2.700833			
NON-HISPANIC BLACKS		0.000041		0.000042		35.319167		1.428333			
NON-HISPANIC OTHERS		0.000052		0.000056		46.691667		3.510833			
NURSING INFANTS (< 1 YEAR OLD)		0.000035		0.000035		29.000833		0.203333			
NON-NURSING INFANTS (< 1 YEAR OLD)		0.000110		0.000111		92.808333		0.977500			
FEMALES (13+ YEARS, PREGNANT)		0.000035		0.000038		31.328333		2.041667			
FEMALES 13+ YEARS, NURSING		0.000038		0.000042		34.774167		3.485000			
CHILDREN (1-6 YEARS OLD)		0.000107		0.000111		92.310000		3.330000			
CHILDREN (7-12 YEARS OLD)		0.000070		0.000074		61.717500		3.030833			
MALES (13-19 YEARS OLD)		0.000048		0.000050		41.720000		2.075000			
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)		0.000039		0.000042		34.854167		2.095833			
MALES (20 YEARS AND OLDER)		0.000033		0.000036		29.900000		2.266667			
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)		0.000032		0.000035		28.993333		2.631667			

*Current TMRC does not include new or pending tolerances.

**New TMRC includes new, pending, and published tolerances.

TABLE 3

DETAILED ACUTE ANALYSIS: ALL STATISTICS BASED ON USEP'S DAILY CONSUMPTION 10:53 WEDNESDAY, DECEMBER 21, 1988 12

NAME: AVERMECTIN STUDY RDV NOEL SF STUDY TYPE SPECIES EFF. LEV. CORE GRADE DOC. NO.

CASELL NO: 063AB CFR NO: CFR A 00000.0012 000100 Reprductn Rat Systemic

CAS NO: 65195-55-3 SHAUGHNESSY NO: 122804 B C

STATUS CODES:

REV INFO: The NOEL for developmental effects is 0.06 MG/KG of BODY WEIGHT

FILE INFO: NEW ACTION: User Modifications APPROVED: Data NOT Used PUBLISHED: Data Used

SUMMARY OF ANALYSIS FOR FEMALES, 13 YEARS AND OLDER:

FEMALES (13+ YRS)

ESTIMATES BASED ON		ESTIMATED % OF POTENTIAL PERSON DAYS THAT ARE USER-DAYS	MEAN DAILY EXPOSURE MG/KG BODY WEIGHT/DAY	AVERAGE MOS
PRIOR TOLERANCES:	99.73		0.000033	1818
NEW TOLERANCES:	99.73		0.000036	1667

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
100	1	0	0	0	0	0	0	0	0	0	0
100	2	0	0	0	0	0	0	0	0	0	0
CORRESPONDING MOS:											
	500	250	167	125							