NOTE TO: George LaRocca, PM 15

SUBJECT: Corrections to the Avermectin TAS Analysis of 7/6/89

FROM: J. R. Tomerlin J R Tomerlin 7/7/89

I provided a TAS analysis for proposed avermectin tolerances on citrus dated 7/6/89. This analysis contained two errors which should be corrected. First, the RfD used in the chronic analysis is 0.0004 mg/kg body weight/day, not 0.004 mg/kg/day as indicated in the memorandum.

Secondly, the acute analysis I reported used the wrong study. The NOEL for the acute exposure analysis is in fact 0.06 mg/kg body weight from a mouse teratology study, not 0.12 mg/kg body weigh from the 2 generation mouse reproduction study. I misunderstood Bill Dykstra earlier and thought he said that the NOEL from the rat study was appropriate for the acute analysis, which is not what he told me.

The change in the acute NOEL changes the Margins of Safety I reported. The average MOS reported on page 3 of my 7/6/89 memo should be 1580, not 3160. The minimum MOS using tolerances is 125, not 250; and the minimum MOS using anticipated residues is 250, not 500.

I will correct the draft FR notice to be consistent with the proper NOELs that were used in the analysis.

cc: TAS, DEB, Caswell #063AB, Dykstra (TOX-IRSB)

DEBBIE
8F3592

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

JUL 6 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chronic and Acute Dietary Exposure Analysis for the Proposed Use of Avermectin on Citrus, PP#8F3592/FAP#8H5550

FROM: J. Robert Tomerlin, Ph.D. J.R. Tomerlin 7/6/89
Tolerance Assessment System Staff
HED/SACB (H7509C)

THROUGH: Reto Engler, Ph.D.
Chief, Science Analysis and Coordination Branch
Health Effects Division (H7509C)

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

Action Requested

Provide estimates of chronic and acute exposure to avermectin from published tolerances and the proposed use on citrus using anticipated residues where available.

Discussion

1. Toxicology Endpoint: The routine chronic TAS analysis used a reference dose (ADI) of 0.004 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 2 generation rat reproduction study. This value has been approved by HED (3/30/89) and Agency (4/20/89) reference dose committees.

corrected

The acute exposure analysis was conducted using the NOEL of 0.12 mg/kg body weight for developmental toxicity from the 2 generation rat reproduction study (personal communication, W. Dykstra).

2. Residue Information: Food uses evaluated were published tolerances from 40 CFR 180.449 and the proposed use on citrus. Anticipated residues were developed from processing studies using field trial data for citrus, citrus juice, cottonseed, and extrapolated from animal feeding studies for milk (V. F. Boyd memo, 6/29/89). A summary of the residue information used in the analysis is attached as Table 1.

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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. Using anticipated residues, it is possible to calculate the Anticipated Residue Contribution (ARC). TMRC and ARC exposure summaries for the overall U.S. population and all 22 TAS population groups are shown in Table 2. Exposure estimates calculated from anticipated residues (ARC) for the overall U.S. population and the two most highly exposed TAS population groups are summarized in the following table.

Avermectin Exposure Summary Using Anticipated Residues

	Overall U.S. Population	Non-Nurs. Infants	Children Aged 1 - 6
Published Tolerances	< 0.000001[a]	< 0.000001	< 0.000001
Cottonseed	< 0.1[b]	< 0.1	< 0.1
PP#8F3592	0.000115 28.8	0.000258 64.5	0.000298 74.6
TOTALS	0.000115 28.8	0.000258 64.5	0.000298 74.6

[a]Exposure estimate in mg/kg body weight/day.
[b]Exposure expressed in per cent of the ADI.

4. Acute Exposure Analysis: 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 individual food consumption, as reported by respondents in the 1977-78 USDA Nationwide Food Consumption Survey, and accumulates exposure to avermectin for each food consumed for which a tolerance has been established. Each analysis assumes that avermectin residues were uniformly present in the entire commodity supply.

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

Average MOS = NOEL / Exposure (ARC)

For avermectin, this would equate to:

Average MOS = ~~0.12~~ 0.06 mg/kg body weight / 0.000038 mg/kg body weight

= ~~3160~~ 1580

Even using tolerance level residues, no woman of child-bearing age is expected to ingest any more than 0.00048 mg/kg body weight of avermectin at one time, which translates to a <u>minimum</u> MOS of ~~250~~ 125. Using anticipated residues, the <u>minimum</u> MOS for women of child-bearing age is ~~500~~. 250

5. <u>Comments</u>: The proposed tolerance on citrus increases exposure from 21 to 114 per cent of the ADI using tolerances and from 19 to 74 per cent of the ADI using anticipated residues. The use of anticipated residue data resulted in exposure estimates that did not exceed the ADI for any TAS population group.

Even using tolerance level residues in the acute exposure analysis, no one in the appropriate population group is expected to have an MOS for developmental toxicity less than 250

Attachments

cc: TAS (Tomerlin, SACB), DEB, Caswell #063AB, Dykstra (TOX-IRSB)

Table 1

ANTICIPATED RESIDUE INFORMATION FOR CASWELL NUMBER 063AB

DATE: 07/03/89

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 UF -->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.

OOD CODE	FOOD	FOOD FORM	PET.#	TOLERANCE (ppm)	ANTICIPATED RESIDUE (ppm)	AR STATISTIC TYPE	% CROP TREATED	RES. VALUE USED IN TAS RUN (ppm)
2001AA	CITRUS CITRON	22 COOKED-FRESH-BAKED	8F3592	N 0.020000	0.012000		100.00	0.012000
2002AA	GRAPEFRUIT-UNSP	00 NOT SPECIFIED	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2002AB	GRAPEFRUIT-PULP	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2002AB	GRAPEFRUIT-PULP	21 COOKED-NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2002JA	GRAPEFRUIT-JUICE	15 RAW-FRESH OR CANNED	8F3592	N 0.020000	0.012000C	PROCESSING	100.00	0.006000
2002JA	GRAPEFRUIT-JUICE	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.006000C	PROCESSING	100.00	0.012000
2003AA	KUMQUATS	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2004AA	LEMONS-UNSPEC	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2004AA	LEMONS-UNSPEC	22 COOKED-FRESH-BAKED	8F3592	N 0.020000	0.012000		100.00	0.012000
2004AB	LEMONS-PULP	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2004AB	LEMONS-PULP	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.012000		100.00	0.012000
2004HA	LEMONS-PEEL	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2004HA	LEMONS-PEEL	21 COOKED-NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2004JA	LEMONS-JUICE	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.060000		100.00	0.060000
2004JA	LEMONS-JUICE	15 RAW-FRESH OR CANNED	8F3592	N 0.020000	0.060000		100.00	0.060000
2004JA	LEMONS-JUICE	21 COOKED-NFS	8F3592	N 0.020000	0.060000		100.00	0.060000
2004JA	LEMONS-JUICE	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.060000		100.00	0.060000
2005AA	LIMES-UNSPEC	00 NOT SPECIFIED	8F3592	N 0.020000	0.012000		100.00	0.012000
2005AB	LIMES-PULP	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2005HA	LIMES-PEEL	21 COOKED-NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2005JA	LIMES-JUICE	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.060000		100.00	0.060000
2005JA	LIMES-JUICE	15 RAW-FRESH OR CANNED	8F3592	N 0.020000	0.060000		100.00	0.060000
2005JA	LIMES-JUICE	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.060000		100.00	0.060000
2006AA	ORANGES-UNSPEC	00 NOT SPECIFIED	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006AB	ORANGES-PULP	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006AB	ORANGES-PULP	21 COOKED-NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006HA	ORANGES-PEEL	21 COOKED-NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006HA	ORANGES-PEEL	22 COOKED-FRESH-BAKED	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006HA	ORANGES-PEEL	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2006JA	ORANGES-JUICE	15 RAW-FRESH OR CANNED	8F3592	N 0.020000	0.061000C	PROCESSING	100.00	0.061000
2006JA	ORANGES-JUICE	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.061000C	PROCESSING	100.00	0.061000
2007AA	TANGELOS	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000		100.00	0.012000
2008AA	TANGERINES	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.012000	PROCESSING	100.00	0.012000
2008JA	TANGERINE-JUICE	15 RAW-FRESH OR CANNED	8F3592	N 0.020000	0.060000C	PROCESSING	100.00	0.060000
27003OA	COTTONSEED-OIL	18 PROCESSED OIL	6G3320	P 0.005000	0.001000	FLD TRIALS	100.00	0.001000
27003WA	COTTONSEED-MEAL	18 PROCESSED OIL	6G3320	P 0.005000	0.001000	FLD TRIALS	100.00	0.001000
50000DB	MILK-NON-FAT SOL	10 RAW-FRESH OR NFS	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000DB	MILK-NON-FAT SOL	21 COOKED-NFS	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000DB	MILK-NON-FAT SOL	51 COOKED-CANNED	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000FA	MILK-FAT SOLIDS	10 RAW-FRESH OR NFS	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000

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Table 1, continued

ANTICIPATED RESIDUE INFORMATION FOR CASWELL NUMBER 063AB

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 UF -->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	FOOD FORM	PET.#	TOLERANCE (ppm)	ANTICIPATED RESIDUE (ppm)	AR STATISTIC TYPE	% CROP TREATED	RES. VALUE USED IN TAS RUN (ppm)
50000FA	MILK-FAT SOLIDS	21 COOKED-NFS	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000FA	MILK-FAT SOLIDS	51 COOKED-CANNED	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000SA	MILK SUG (LACT)	21 COOKED-NFS	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
50000SA	MILK SUG (LACT)	51 COOKED-CANNED	8F3592	N 0.005000	0.001000	EXTRAP	100.00	0.001000
53001BA	BEEF-MEAT BYP	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001BA	BEEF-MEAT BYP	26 COOKED-FRESH-PICKLED,CORNED,OR CURED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001BB	BEEF-OTH ORGAN	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001BB	BEEF-OTH ORGAN	51 COOKED-CANNED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001DA	BEEF-DRIED	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	22 COOKED-FRESH-BAKED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	23 COOKED-FRESH-BOILED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	24 COOKED-FRESH-BROILED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001FA	BEEF-FAT	25 COOKED-FRESH-FRIED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001KA	BEEF-KIDNEY	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001LA	BEEF-LIVER	25 COOKED-FRESH-FRIED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001LA	BEEF-LIVER	31 COOKED-FRESH OR CANNED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001MA	BEEF-LEAN	10 RAW-FRESH OR NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001MA	BEEF-LEAN	21 COOKED-NFS	8F3592	N 0.020000	0.020000		100.00	0.020000
53001MA	BEEF-LEAN	22 COOKED-FRESH-BAKED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001MA	BEEF-LEAN	23 COOKED-FRESH-BOILED	8F3592	N 0.020000	0.020000		100.00	0.020000
53001MA	BEEF-LEAN	24 COOKED-FRESH-BROILED	8F3592	N 0.020000	0.020000		100.00	0.020000

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Table 2

TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

DATE: 07/03/89 PAGE: 1

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 UF -->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.

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	0.000000	0.000133	33.154750	33.129000	0.000115	28.83725
U.S. POPULATION - SPRING SEASON	0.000000	0.000129	32.228500	32.202250	0.000115	28.69125
U.S. POPULATION - SUMMER SEASON	0.000000	0.000129	32.194500	32.168750	0.000113	28.22100
U.S. POPULATION - FALL SEASON	0.000000	0.000136	34.047500	34.021750	0.000118	29.38000
U.S. POPULATION - WINTER SEASON	0.000000	0.000137	34.150750	34.125250	0.000116	29.05050
NORTHEAST REGION	0.000000	0.000148	37.115000	37.090750	0.000138	34.59200
NORTH CENTRAL REGION	0.000000	0.000135	33.820250	33.794750	0.000116	29.08575
SOUTHERN REGION	0.000000	0.000114	28.380500	28.355000	0.000097	24.25025
WESTERN REGION	0.000000	0.000140	35.119250	35.091500	0.000115	28.66325
HISPANICS	0.000000	0.000172	42.902000	42.877500	0.000155	38.67725
NON-HISPANIC WHITES	0.000000	0.000131	32.669500	32.643250	0.000112	27.99400
NON-HISPANIC BLACKS	0.000000	0.000123	30.852500	30.829750	0.000114	28.52800
NON-HISPANIC OTHERS	0.000000	0.000162	40.500000	40.476750	0.000154	38.62075
NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.000132	33.003500	33.000750	0.000106	26.45975
NON-NURSING INFANTS (< 1 YEAR OLD)	0.000000	0.000456	114.108250	114.100750	0.000258	64.50400
FEMALES (13+ YEARS, PREGNANT)	0.000000	0.000100	24.979250	24.960750	0.000089	22.26350
FEMALES 13+ YEARS, NURSING	0.000000	0.000110	27.428500	27.404000	0.000087	21.82475
CHILDREN (1-6 YEARS OLD)	0.000000	0.000344	85.892500	85.846250	0.000298	74.57375
CHILDREN (7-12 YEARS OLD)	0.000000	0.000210	52.438500	52.399500	0.000175	43.62650
MALES (13-19 YEARS OLD)	0.000000	0.000133	33.351000	33.323250	0.000109	27.34200
FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING)	0.000000	0.000111	27.673750	27.649250	0.000096	24.07800
MALES (20 YEARS AND OLDER)	0.000000	0.000085	21.368750	21.347000	0.000076	19.00950
FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS)	0.000000	0.000086	21.407500	21.387500	0.000081	20.33525

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

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