



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

Caswell # 063AB

FEB 24 1989

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Avermectin - TAS Analysis of Proposed Section 18  
Exemption for Use on Strawberries (#89-CA-10).

FROM: Susan L. Stanton *Susan L. Stanton* 02/21/89  
Tolerance Assessment Program  
HED/RCB (H7509C)

THRU: R. Bruce Jaeger  
Head, Special Analysis and Outreach Section  
HED/SACB (H7509C) *R. Bruce Jaeger*

TO: D. Stubbs/L. Pemberton, PM Team 41  
Registration Support Branch  
Registration Division (H7505C))

Action Requested

The California Department of Food and Agriculture has requested a Section 18 specific exemption authorizing the use of avermectin to control spider mites on strawberries. SACB has been asked to provide a TAS analysis of dietary exposure to avermectin in conjunction with the proposed new use. The Dietary Exposure Branch has no objections to this Section 18 request (memo J. Smith to L. Pemberton, 02/15/89).

Discussion

I. Analysis of Chronic Dietary Exposure:

1. The reference dose (PADI) used in the analysis was 0.00012 mg/kg body weight/day, based on the NOEL of 0.12 mg/kg body weight/day from a 2-generation rat reproduction study with an uncertainty factor of 1000. This value has been approved by the HED reference dose committee (06/12/87) but not verified at the Agency level. 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.

2. Currently, there are no permanent tolerances established for avermectin. The food uses evaluated in the analysis were the established temporary tolerances (citrus, cottonseed, milk, & cattle) and the proposed use on strawberries. At the request of the Emergency Response and Minor Use Section (L. Pemberton), exposure from recently granted emergency uses on celery, pears, and tomatoes was also included in calculations of the current TMRC. The residue value used for strawberries was 0.02 ppm (memo Smith to L. Pemberton, 02/15/89). A complete listing of residue information is provided in the attached 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 overall U.S. population and the two subgroups with the greatest total exposure to avermectin, non-nursing infants and children, ages 1-6:

|                     | <u>Established<br/>Uses<sup>a</sup></u>       | <u>New Action<br/>(Strawberries)</u> | <u>Total</u>         |
|---------------------|-----------------------------------------------|--------------------------------------|----------------------|
| U.S. Population     | 0.000052 <sup>b</sup><br>(43.3%) <sup>c</sup> | <0.000001<br>(0.6%)                  | 0.000053<br>(43.9%)  |
| Non-Nursing Infants | 0.000151<br>(125.7%)                          | <0.000001<br>(0.5%)                  | 0.000151<br>(126.1%) |
| Children, 1-6 yrs.  | 0.000117<br>(97.8%)                           | 0.000002<br>(1.0%)                   | 0.000119<br>(98.8%)  |

<sup>a</sup>Includes established temporary tolerances and emergency uses on celery, pears, and tomatoes.

<sup>b</sup>Theoretical Maximum Residue Contribution (TMRC) in mg/kg/day.

<sup>c</sup>TMRC 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.

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## 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).

2. 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<br>Daily Exposure<br>(mg/kg body wt) | Average<br>MOS |
|---------------------------------|----------------------------------------------|----------------|
| Established Uses                | 0.000038                                     | 1579           |
| Established Uses + Strawberries | 0.000039                                     | 1538           |

In addition, the distribution of exposure to avermectin indicates that 97% of females 13 years of age and older who consume strawberries have a MOS of at least 500 from all established uses and the proposed use on strawberries and that no members of this subgroup have a MOS less than 250 (See Table 3).

3. 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, DEB (Loranger), Caswell #063AB, RF, Jaeger (SACB), Dykstra (TOX), Engler (SACB).

Table 1

CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

DATE: 02/17/89

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| CHEMICAL           | STUDY TYPE          | EFFECTS                   | REFERENCE DOSES           |    | DATA GAPS/COMMENTS | STATUS                 |
|--------------------|---------------------|---------------------------|---------------------------|----|--------------------|------------------------|
|                    |                     |                           | PADI                      | SF |                    |                        |
| Avelmectin         | 2gen repro- rat     | Decreased pup survival    | Chronic feeding- rat      |    |                    | HED complete 07/11/86  |
| Caswell #063AB     | NOEL= 0.1200 mg/kg  | and body weight; increase | Chronic feeding- dog      |    |                    | HED reassess 06/12/87. |
| CAS No. 65195-55-3 | 0.00 ppm            | in incidence of retinal   | UP of 1000 due to serious |    |                    | EPA not scheduled.     |
| A.I. CODE: 122804  | LEL= 0.4000 mg/kg   | abnormalities. Doses by   | effects in critical study |    |                    |                        |
| CFR No. 180.       | 0.00 ppm            | gavage. No oncogenicity   | and data gaps.            |    |                    |                        |
|                    | ONCO: Undetermined. | data available.           | Mouse teratogen.          |    |                    |                        |

| FOOD CODE | FOOD NAME                         | PETITION NUMBER | TOLERANCE (PPM) |           |
|-----------|-----------------------------------|-----------------|-----------------|-----------|
|           |                                   |                 | NEW             | PUBLISHED |
| 01016AA   | STRAWBERRIES                      | 89-CALD         | 0.020000        | 0.005000  |
| 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  |
| 02004HA   | LEMONS-PEEL                       | 7G3468          |                 | 0.005000  |
| 02004JA   | LEMONS-JUICE                      | 7G3468          |                 | 0.005000  |
| 02005AA   | LIMES-UNSPECIFIED                 | 7G3468          |                 | 0.005000  |
| 02005AB   | LIMES-PULP                        | 7G3468          |                 | 0.005000  |
| 02005HA   | LIMES-PEEL                        | 7G3468          |                 | 0.005000  |
| 02005JA   | LIMES-JUICE                       | 7G3468          |                 | 0.005000  |
| 02006AA   | ORANGES-UNSPECIFIED               | 7G3468          |                 | 0.005000  |
| 02006AB   | ORANGES-PULP                      | 7G3468          |                 | 0.005000  |
| 02006HA   | ORANGES-PEEL                      | 7G3468          |                 | 0.005000  |
| 02006JA   | ORANGES-JUICE                     | 7G3468          |                 | 0.005000  |
| 02007AA   | TANGELOS                          | 7G3468          |                 | 0.005000  |
| 02008AA   | TANGERINES                        | 7G3468          |                 | 0.005000  |
| 02008JA   | TANGERINE-JUICE                   | 7G3468          |                 | 0.005000  |
| 04003AA   | PEARS-FRESH                       | 89-WA06         |                 | 0.025000  |
| 04003DA   | PEARS-DRIED                       | 89-WA06         |                 | 0.005000  |
| 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         |                 | 0.005000  |
| 13016AA   | FENNEL                            | 89-FLO8         |                 | 0.005000  |
| 270030A   | COTTONSEED-OIL                    | 6G3320          |                 | 0.005000  |
| 27003AA   | COTTONSEED-HEAL                   | 6G3320          |                 | 0.001000  |
| 50000DB   | MILK-NON-FAT SOLIDS               | 7G3468          |                 | 0.001000  |
| 50000FA   | MILK-FAT SOLIDS                   | 7G3468          |                 | 0.001000  |
| 50000SA   | MILK SUGAR (LACTOSE)              | 7G3468          |                 | 0.001000  |
| 53001BA   | BEEF-HEAT 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  |

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Table 1 (con't)

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## CHEMICAL INFORMATION FOR CASWELL NUMBER 063AB

| CHEMICAL           | STUDY TYPE          | EFFECTS                   | REFERENCE DOSES   |         | DATA GAPS/COMMENTS        | STATUS                 |
|--------------------|---------------------|---------------------------|-------------------|---------|---------------------------|------------------------|
|                    |                     |                           | IPADI             | SF      |                           |                        |
| Avermectin         | 2gen reprod- rat    | Decreased pup survival    |                   | -->1000 | Chronic feeding- rat      | HED complete 07/11/86  |
| Caswell #063AB     | NOEL= 0.1200 mg/kg  | and body weight; increase | OPP RfD= 0.000120 |         | Chronic feeding- dog      | HED reassess 06/12/87. |
| CAS No. 65195-55-3 | 0.00 ppm            | in incidence of retinal   | EPA RfD= 0.000000 |         | UF of 1000 due to serious | EPA not scheduled.     |
| A.I. CODE: 122804  | LEL= 0.4000 mg/kg   | abnormalities. Doses by   |                   |         | effects in critical study |                        |
| CFR No. 180.       | 0.00 ppm            | gavage. No oncogenicity   |                   |         | and data gaps.            |                        |
|                    | ONCO: Undetermined. | data available.           |                   |         | Mouse teratogen.          |                        |

| FOOD CODE | FOOD NAME                                | PETITION NUMBER | TOLERANCE (PPM) |           |
|-----------|------------------------------------------|-----------------|-----------------|-----------|
|           |                                          |                 | NEW             | PUBLISHED |
| 53001LA   | BEEF (ORGAN MEATS)-LIVER                 | 7G3468          |                 | 0.010000  |
| 53001MA   | BEEF (BONELESS)-LEAN (W/O REMOVABLE FAT) | 7G3468          |                 | 0.010000  |

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## TOLERANCE ASSESSMENT SYSTEM ROUTINE CHRONIC ANALYSIS

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| CHEMICAL INFORMATION                            |                     |                           | STUDY TYPE        | EFFECTS                   | REFERENCE DOSES        | DATA GAPS/COMMENTS | STATUS |
|-------------------------------------------------|---------------------|---------------------------|-------------------|---------------------------|------------------------|--------------------|--------|
| Avermectin                                      | 2gen reprod- rat    | Decreased pup survival    | IPADI SF -->1000  | Chronic feeding- rat      | HED complete 07/11/86  |                    |        |
| Caswell #063AB                                  | NOEL= 0.1200 mg/kg  | and body weight; increase | OPP RFD= 0.000120 | Chronic feeding- dog      | HED reassess 06/12/87. |                    |        |
| CAS No. 65195-55-3                              | 0.00 ppm            | in incidence of retinal   | EPA RFD= 0.000000 | UF of 1000 due to serious | EPA not scheduled.     |                    |        |
| A. I. CODE: 122804                              | LEL= 0.4000 mg/kg   | abnormalities. Doses by   |                   | effects in critical study |                        |                    |        |
|                                                 | 0.00 ppm            | gavage. No oncogenicity   |                   | and data gaps.            |                        |                    |        |
| CFR No. 180.                                    | QNDQ: Undetermined. | data available.           |                   | Mouse teratogen.          |                        |                    |        |
|                                                 |                     |                           |                   |                           |                        |                    |        |
| <u>POPULATION SUBGROUP</u>                      |                     |                           |                   |                           |                        |                    |        |
| U S. POPULATION - 48 STATES                     |                     |                           |                   |                           |                        |                    |        |
| U.S. POPULATION - SPRING SEASON                 |                     |                           |                   |                           |                        |                    |        |
| U.S. POPULATION - SUMMER SEASON                 |                     |                           |                   |                           |                        |                    |        |
| U.S. POPULATION - FALL SEASON                   |                     |                           |                   |                           |                        |                    |        |
| U.S. POPULATION - WINTER SEASON                 |                     |                           |                   |                           |                        |                    |        |
|                                                 |                     |                           |                   |                           |                        |                    |        |
| NORTHEAST REGION                                |                     |                           |                   |                           |                        |                    |        |
| NORTH CENTRAL REGION                            |                     |                           |                   |                           |                        |                    |        |
| SOUTHERN REGION                                 |                     |                           |                   |                           |                        |                    |        |
| WESTERN REGION                                  |                     |                           |                   |                           |                        |                    |        |
|                                                 |                     |                           |                   |                           |                        |                    |        |
| HISPANICS                                       |                     |                           |                   |                           |                        |                    |        |
| NON-HISPANIC WHITES                             |                     |                           |                   |                           |                        |                    |        |
| NON-HISPANIC BLACKS                             |                     |                           |                   |                           |                        |                    |        |
| NON-HISPANIC OTHERS                             |                     |                           |                   |                           |                        |                    |        |
|                                                 |                     |                           |                   |                           |                        |                    |        |
| NURSING INFANTS (< 1 YEAR OLD)                  |                     |                           |                   |                           |                        |                    |        |
| NON-NURSING INFANTS (< 1 YEAR OLD)              |                     |                           |                   |                           |                        |                    |        |
| FEMALES (13+ YEARS, PREGNANT)                   |                     |                           |                   |                           |                        |                    |        |
| FEMALES (13+ YEARS, NURSING)                    |                     |                           |                   |                           |                        |                    |        |
| CHILDREN (1-6 YEARS OLD)                        |                     |                           |                   |                           |                        |                    |        |
| CHILDREN (7-12 YEARS OLD)                       |                     |                           |                   |                           |                        |                    |        |
| MALES (13-19 YEARS OLD)                         |                     |                           |                   |                           |                        |                    |        |
| FEMALES (13-19 YEARS OLD, NOT PREG. OR NURSING) |                     |                           |                   |                           |                        |                    |        |
| FEMALES (20 YEARS AND OLDER)                    |                     |                           |                   |                           |                        |                    |        |
| FEMALES (20 YEARS AND OLDER, NOT PREG. OR NURS) |                     |                           |                   |                           |                        |                    |        |

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

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TABLE 3: ACUTE EXPOSURE ANALYSIS

DETAILED ACUTE ANALYSIS: ALL STATISTICS BASED ON USERS' DAILY CONSUMPTION 10:46 FRIDAY, FEBRUARY 17, 1989 12  
 \* NAME: AVERMECTIN \*  
 \* CASHMELL NO: 063AB \*  
 \* CAS NO: 65195-55-3 SHAUGHNESSY NO: 122804 B \*  
 \* RFD INFO: The NOEL FOR DEVELOPMENTAL TOXICITY IS 0.06 MG/KG BODY WEIGHT. \*  
 \*\*\*\*\*

SUMMARY OF ANALYSIS FOR FEMALES, 13 YEARS OF AGE AND OLDER:

|                           | ESTIMATED % OF POTENTIAL<br>PERSON DAYS THAT ARE USER-DAYS | MEAN DAILY EXPOSURE<br>MG/KG BODY WEIGHT/DAY | AVERAGE |  |
|---------------------------|------------------------------------------------------------|----------------------------------------------|---------|--|
|                           |                                                            |                                              | MOS     |  |
| ESTABLISHED USES:         | 99.73                                                      | 0.000038                                     | 1579    |  |
| ESTABLISHED + NEW ACTION: | 99.73                                                      | 0.000039                                     | 1538    |  |

ESTIMATED % OF POPULATION USER-DAYS WITH EXPOSURE EXCEEDING X UG/KG BODY WEIGHT FOR X =

|                           | 0   | 0.12 | 0.24 | 0.36 | 0.48 | 0.60 | 0.72 | 0.84 | 0.96 | 1.08 | 1.20 | 1.80 | 2.40 | 3.00 | 6.00 | 9.00 | 12.0 |
|---------------------------|-----|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| ESTABLISHED USES:         | 100 | 2    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |
| ESTABLISHED + NEW ACTION: | 100 | 3    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    |

CORRESPONDING MOS: (500) (250) (167)