



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

1-10-97
CB-TS
PP#5E456

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: 1/10/97

SUBJECT: PP#7F3500, #8F3592, and #5E4566. USE OF AVERMECTIN B1 ON
COTTON, CITRUS and HOPS. EXTENSION OF TIME-LIMITED
TOLERANCES.

DP Barcodes: D230333, D230352, D230880

Caswell: 063AB

Trade Names: AGRI-MEK 0.15EC for citrus and hops (Reg# 618-98)
and ZEPHYR 0.15EC for cotton (Reg# 618-97)

Chem#: 122804

Case#: 240762

Class: insecticide/miticide

40 CFR: 180.449, 185.300, 186.300

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122804

INTRODUCTION

In a submission dated 10/1/96, the registrant, Merck and Co., Inc. requested the establishment of permanent tolerances for residues of avermectin B₁ (also known as abamectin) and its delta-8,9-isomer in/on the following commodities: cottonseed, citrus, meat and meat byproducts, milk, dried hops, and processed food/feed commodities. Merck states the submission also addresses the new FQPA criteria.

HED has been requested by RD to perform a reassessment, under FQPA, related to extension of the following time-limited tolerances (expired 4/30/96 and 12/31/96) for avermectin B₁ as outlined below:

40CFR 180.449(a):

citrus, whole fruit	0.02 ppm (expired 4/30/96)
cottonseed	0.005 ppm (expired 4/30/96)
cattle, fat	0.015 ppm (expired 4/30/96)
cattle, meat	0.02 ppm (expired 4/30/96)
cattle, mbyp	0.02 ppm (expired 4/30/96)
milk	0.005 ppm (expired 4/30/96)
hops	0.5 ppm (expired 12/31/96)

40 CFR 185.300

citrus oil	0.10 ppm (expired 4/30/96)
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40 CFR 186.300(a)

dried citrus pulp	0.10 ppm (expired 4/30/96)
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Permanent tolerances have been established for residues of avermectin B₁ and its delta-8,9-isomer on various other commodities under 40 CFR 180.449(b) and 40 CFR 186.300(b).

The time-limited (rather than permanent) tolerances noted above were established due to EFED, not HED; concerns (lack of fish and aquatic organism data). PIRAT notes that although the tolerances listed above have expired, the registrations are still current or have been extended.

RECOMMENDATION

Aggregate risk estimates do not exceed HED's level of concern. Extension of these expired avermectin tolerances should not pose an unacceptable aggregate risk to infants and children. Therefore, HED has no objection to an extension of the expired time-limited tolerances for residues of avermectin B₁ and its regulable metabolites in/on the following commodities:

RACs (plant)	
citrus, whole fruit	0.02 ppm
cottonseed	0.005 ppm
hops, dried	0.2 ppm ¹
RACs (animal)	
cattle, fat	0.015 ppm
cattle, meat	0.02 ppm
cattle, mbyp	0.02 ppm
milk	0.005 ppm
Processed Commodities	
citrus oil	0.10 ppm
dried citrus pulp	0.10 ppm

RISK CHARACTERIZATION

Acute Risk Assessment

The acute dietary (food only) risk assessment used Monte Carlo modeling incorporating anticipated residue and percent of crop treated refinement. While adequate time was not available to do a complete review of the Monte Carlo analysis, HED has examined the assumptions made in conducting the analysis. The resulting high-end exposure estimate of 0.000078 mg/kg/day, which results in a dietary (food only) MOE of 769 for females 13+ years old, should be viewed as a highly refined risk estimate. Prior to the establishment of permanent tolerances, a full review of the acute dietary risk assessment will be required.

As per the recent OPP Risk Cup Decision Logic (as explained at the Food Safety Advisory Committee meeting on 12/5/96), exposure to avermectin residues in water was considered to account for a total of 10% of the acute risk. This estimate is considered conservative.

In the best scientific judgement of HED, the aggregate acute risk (food and water) from the currently registered uses of avermectin is below our level of concern.

Chronic Risk Assessment

The chronic dietary (food only) risk assessment used anticipated residue refinement for commodities with tolerances, but did not incorporate any refinement for percent of crop treated (default of 100% was assumed). Therefore, the resulting exposure estimates should be viewed as partially refined; further refinement for percent of crop treated would result in lower dietary

¹ PIRAT notes that CBTS recommended in favor of a tolerance of 0.2 ppm on hops (not 0.5 ppm) - see memo of W.D. Wassell 6/17/96 concerning PP#5E04566. The corrected tolerance (0.2 ppm) should be published in the CFR.

exposure estimates. For chronic dietary (food only) risk estimates, the population subgroup with the largest percentage of the RfD occupied is non-nursing infants less than 1 year old at 11% of the RfD.

The terrestrial field dissipation data for avermectin indicate a potential mobility in surface water, but probably not in ground water. An assumption of 10% of the chronic aggregate risk was allocated to drinking water, as per Risk Cup Decision Logic, 12/5/96. For avermectin, this estimate is considered conservative and protective of public health.

Based on the nature of the indoor and outdoor residential uses, HED has concluded that a chronic residential exposure scenario does not exist.

Using these conservative estimates, the sum total of the aggregate chronic risk estimates (food and water) for avermectin for the population subgroup with the largest percentage of the RfD occupied (non-nursing infants less than 1 year old) is 21%. In the best scientific judgement of HED, the avermectin aggregate chronic risk is below our level of concern.

Short and Intermediate-Term Risk Assessment

The chronic food and water exposure estimates for the aggregate short and intermediate-term risk assessments are considered conservative for the reasons mentioned above. The indoor residential exposure estimate was based on a California EPA review of an avermectin residential exposure study. Therefore, the default Risk Cup Decision Logic assumptions were not used to estimate indoor residential exposure. Based on the nature of the outdoor residential uses (spot treatment), HED has concluded that residential exposure resulting from outdoor uses will not be significant. For the most highly exposed population subgroup (non-nursing infants less than 1 year old), an aggregate short- and intermediate-term (food, water, and residential indoor exposures) MOE of 733 was calculated. HED views this estimate of total aggregate short and intermediate-term exposure as somewhat conservative.

For avermectin, HED does not have concerns for short and intermediate-term risk because the MOE is greater than 333 (as per Risk Cup Decision Logic, 12/5/96). In the best scientific judgement of HED, the short and intermediate-term aggregate risk from the currently registered uses of avermectin is below our level of concern.

CONCLUSIONS

Hazard Assessment

1) Non-Dietary Endpoint Selection

- a) Short- and Intermediate Term Occupational or Residential Dermal or Inhalation Risk. For short- and intermediate-term MOE calculations, the TES Committee (5/24/96) recommended use of the developmental NOEL of 0.2 mg/kg/day from

the oral developmental toxicity study in CF1 mice (MRID No.00164014). At the LEL of 0.4 mg/kg/day, there was an increased incidence of cleft palate.

- b) **Chronic Occupational or Residential Risk.** For chronic MOE calculations, the TES Committee (5/24/96) recommended use of the developmental NOEL of 0.12 mg/kg/day from a 2-generation rat reproduction study (MRID No. 00265576). At the LEL of 0.4 mg/kg/day, there were increased pup deaths during lactation, decreased pup body weight, and an increased incidence of retinal rosettes.
- c) **Dermal Absorption.** Based on a monkey dermal absorption study (MRID No. 00265590), the TES Committee (5/24/96) recommended use of a value of 1%.

2) Dietary Endpoint Selection

- a) **Acute Risk.** For acute dietary risk assessment, the TES Committee (5/24/96) recommended use of the developmental (pup) NOEL of **0.06 mg/kg/day**, based on cleft palate (MRID No. 00164011) at the LEL of 0.10 mg/kg/day, from the developmental toxicity study in the CF1 mouse with the delta-8,9-photoisomer of avermectin. This risk assessment will evaluate acute dietary risk to females 13+ years. For the purpose of these time-limited tolerances, an MOE of 300 is considered necessary to be adequately protective for dietary (food only) exposure. After applying the new Risk Cup Decision Logic, for aggregate exposure (food, water, and residential), an MOE of greater than 333 is required to be adequately protective.
- b) **Chronic Risk.** The RfD Committee (6/27/96) established the RfD at **0.0004 mg/kg/day** based on a 2-generation rat reproduction study (MRID No. 00265576) with a NOEL of 0.12 mg/kg/day and an **uncertainty factor of 300**. In addition to the Uncertainty Factor of 100 for inter- and intra- species variations, a Modifying Factor (MF) of 3 was used for a total uncertainty factor of 300. The MF was used because of the severity of the effects (pup deaths) and the steep dose-response curve. At the LEL of 0.40 mg/kg/day, there was decreased pup body weight and viability during lactation as well as an increased incidence of retinal rosettes in F_{2b} weanlings.
- c) **Cancer Risk.** Avermectin has been classified as a Group E "evidence of non-carcinogenicity for humans" chemical by the RfD/Peer Review Committee (6/27/96).
- d) **Infants and Children -** The HED Developmental and Reproductive Toxicity Peer Review Committee has discussed avermectin (7/8/93). This Peer Review Committee concluded that avermectin and related compounds induced developmental toxicity in several species.

i) Developmental Toxicity Studies

Rat - From the rat developmental study (MRID# 00249152), the maternal (systemic) NOEL was ≥ 1.6 mg/kg/day (HDT). The developmental (pup) NOEL was 1.6 mg/kg/day (HDT).

Rabbit - From the rabbit developmental study (MRID# 00249152), the maternal (systemic) NOEL was 1.0 mg/kg/day, based on decreased body weight and decreased food and water consumption at the LOEL of 2.0 mg/kg/day. The developmental (pup) NOEL was 1.0 mg/kg/day, based on clubbed foot, and delayed ossification of sternebrae, metacarpals, and phalanges at the LEL of 2.0 mg/kg/day.

ii) Reproductive Toxicity Studies

Rat - From the rat reproduction study (MRID #0026557), the maternal (systemic) NOEL was 0.4 mg/kg/day (HDT). The developmental (pup) NOEL was 1.2 mg/kg/day, based on decreased viability indices, decreased pup body weight and retinal fold in weanlings at the LEL of 0.4 mg/kg/day. The reproductive (parental) NOEL was 0.4 mg/kg/day (HDT).

Occupational Exposure

HED policy is not to conduct occupational exposure assessments for extensions of time-limited tolerances. Since this action only involves expired tolerances (the registrations are still current or have been extended), occupational exposure has not been addressed.

Exposure Scenarios

Dietary Exposure

1. The nature of the residue in plants and animals is adequately understood. The residues of concern are avermectin B₁ and its delta-8,9-isomer, as stated in 40 CFR 180.449.
2. Adequate analytical methodology are available as follows to enforce the tolerance expression:

Citrus: Merck Method# 1009, Rev. 3 has been submitted to FDA for inclusion in PAM II as Method I (submitted in support of PP#8F3592).

Cottonseed: Merck Method# 6004 has been submitted to FDA for inclusion in PAM II as Method IA (submitted in support of PP#7F3500).

Hops: Merck Method# M-036.2 (MRID# 440076-01) has undergone successful EPA method validation and has been submitted to FDA for inclusion in PAM II as a roman numeral method (submitted in support of PP#5E4566).

Animal Commodities: Merck Method# 32A has been submitted to FDA for

inclusion in PAM II as Method II (submitted in support of PP#7F3500).

All these methods are based on HPLC-fluorescence and should be adequate to enforce the current tolerance expression.

3. Residues of avermectin B₁ and its delta-8,9-isomer are not expected to exceed the following levels as a result of the current Section 3 registrations:

RACs (plant)

citrus, whole fruit	0.02 ppm
cottonseed	0.005 ppm
hops, dried	0.2 ppm ²

RACs (animal)

cattle, fat	0.015 ppm
cattle, meat	0.02 ppm
cattle, mby	0.02 ppm
milk	0.005 ppm

Processed Commodities

citrus oil	0.10 ppm
dried citrus pulp	0.10 ppm

Cotton gin byproducts have recently been added to Table 1 of the Pesticide Assessment Guidelines, Subdivision O. No residue data for this commodity have been provided to the Agency by Merck. Due to the recent nature of this residue data requirement, no data will be needed for the purposes of the time-limited tolerance extension for cotton, and no time-limited tolerance will be established for cotton gin byproducts. In order to establish a permanent tolerance for cotton, data for cotton gin byproducts will be required.

4. Initial review of the results of the confined rotational crop study (165-1) by EFGWB indicated that avermectin residues accumulated in some rotational crops at levels up to 10 - 12 ppb. However, following further review and in consultation with TOX, EFGWB concluded that the majority of the radioactivity was due to polar degradates that were of little of toxicological concern as compared to the parent compound avermectin B₁ and/or the delta-8,9-isomer (see memo of P. Mastradone dated 4/24/88). Therefore, the requirements for field rotational crop studies (GRN 165-2) are waived.
5. No CODEX MRLs have been established for avermectin residues on citrus, cotton, and hop commodities.

² PIRAT notes that CBTS recommended in favor of a tolerance of 0.2 ppm on hops (not 0.5 ppm) - see memo of W.D. Wassell 6/17/96 concerning PP#5E04566. The corrected (0.2 ppm) should be published in the CFR.

6. **Acute Dietary Risk.** The endpoint of concern for avermectin is developmental toxicity. The Agency conducted an acute dietary risk assessment in conjunction with the Section 18 request on grapes (see Attachment II - run dated 6/4/96 and performed in conjunction with 96CA0030). For all commodities with tolerances, 100% crop treated was assumed. Anticipated residues were provided for commodities with tolerances. For the population subgroup of concern, females 13+ years, a Margin Of Exposure (MOE) value of 60 was calculated using high end exposure values. At the 98th percentile, an MOE of 120 was calculated.

The registrant has submitted an acute dietary risk assessment dated 10/17/96 using Monte Carlo modeling and Tier 3 exposure assessments (*Final Office Policy for Performing Acute Dietary Exposure Assessment*, D. Edwards, 6/13/96). The Agency has considered the results reported to the extent possible to support extension of the time limited tolerances which are the subject of this memorandum. While adequate time is not available to do a complete review of the analysis, HED has considered the assumptions made in conducting the analysis. Some minor discrepancies were noted, however, it is our best scientific judgement that those minor changes would not significantly alter the Monte Carlo acute risk assessment. PIRAT notes that the registrant has used a NOEL of 0.05 mg/kg/day in their assessment. HED currently considers the appropriate NOEL to be 0.06 mg/kg/day; therefore the registrant's MOE values have been corrected to reflect this higher NOEL. At the calculated high end exposure of 0.000078 mg/kg/day, the acute dietary (food only) MOE for females 13+ years is 769. The registrant is advised that prior to the establishment of a permanent tolerance, a full review of the acute dietary risk assessment will be required.

7. **Chronic Dietary Risk.** The chronic dietary exposure estimates (DRES) for avermectin are summarized in Attachment I (run dated 6/4/96 and performed in conjunction with 96CA0030, Section 18 registration for avermectin on grapes). For all commodities with tolerances, 100% crop treated was assumed. Anticipated residues were provided for commodities with tolerances. The existing avermectin tolerances plus the proposed tolerances in this memo result in an Anticipated Residue Contribution (ARC) that is equivalent to the following percentages of the RfD:

	ARC _{food} (mg/kg/day)	%RfD
U.S Population	0.000020	5%
Nursing Infants (<1 year old)	0.000025	6%
Non-Nursing Infants (<1 year old)	0.000043	11%
Children (1-6 years old)	0.000038	10%
Children (7-12 years old)	0.000025	6%
Northeast Region	0.000023	6%
Western Region	0.000024	6%
Hispanics	0.000022	6%

The subgroups listed above are: (1) the U.S. population (48 states); (2) those for infants

and children; and, (3) the other subgroups for which the percentage of the RfD occupied is greater than that occupied by the subgroup U.S. population (48 states).

8. **Cancer Risk.** Avermectin B1 has been classified as a Group E chemical by the RfD/Peer Review Committee (6/27/96). Therefore, a dietary cancer risk assessment is not required.

Exposure from Water

EFED studies indicate that avermectin is moderately persistent and not very mobile. Based on the data available, avermectin would not be found extensively in ground water, but could be found in surface water, if it were bound to soil and the soil moved in water. EFED studies indicate that, under anaerobic conditions in the absence of light, avermectin does not degrade.

There is no established Maximum Concentration Level for residues of avermectin in drinking water. No Health Advisory Levels for avermectin in drinking water have been established.

HED does not have available data to perform a quantitative drinking water risk assessment for avermectin at this time. Although avermectin data indicate little potential for soil mobility or leaching, avermectin is moderately persistent in the environment. Therefore, risk from residues potentially present in water will be assumed to account for 10% of the total allowable chronic and acute risk at this time (as per the Risk Cup Decision Logic, 12/5/96). Based on analysis of water monitoring data for a large number of pesticides with varying toxicities, soil mobility characteristics, environmental stabilities, physical/chemical properties, and toxicities, the assumption of 10% of the total acute and chronic risk allocated to residues in drinking water is considered conservative and protective of the public health.

Non-occupational Exposure

Avermectin is registered for various uses, including use on ornamentals (herbaceous and woody), household dwellings (indoor and outdoor), and non-food areas of food handling establishments.

Indoor Residential Use Risk Assessment

The Medical Toxicology and Worker Health and Safety Branches of the Department of Pesticide Regulation of California EPA produced a risk characterization document for avermectin in conjunction with the Section 3 registration of AVERT® Prescription Treatment 310 Abamectin Dust (T.A. Formoli, document dated 10/2/91; updated 3/11/92). These data have not been reviewed by HED. **The registrant is advised that prior to the establishment of a permanent tolerance, a full review of the indoor residential risk assessment will be required.** For the purposes of these time-limited tolerance extensions, the HED Risk Cup Committee (1/6/97)

concluded that the California EPA risk characterization document should be used to estimate residential indoor risk from registered uses of avermectin. The conclusions pertaining to residential exposure that were drawn in the document are outlined below.

Estimate of Infant Exposure

Indoor residue monitoring has shown 42 ng and 3 ng abamectin per 100 cm² on horizontal surfaces immediately and 24 hours respectively after application of Avert Prescription Treatment 310³.

Children spend much of their time on the floor and their tendencies of hand to mouth contact and pica are a recognized potential route of exposure⁴. A model that has been used to estimate dermal exposure from indoor surface pesticides in the absence of any data is the equilibrium model⁵. It assumes pesticide residues on a surface come to equilibrium with residues on the body, so that dermal exposure is equal to the human body surface area exposed. Based on this scenario, the estimate of unclothed infant's dermal exposure to abamectin will be 1.64 ug/infant/day. Considering infants' (9-10 months old) movement and pica behaviors, it is conceivable that 50% of the dermal exposure would occur on hands and eventually be swallowed. The remaining 0.82 ug abamectin residues on the skin could be absorbed at a dermal absorption rate of 1%⁶.

Indoor ambient air monitoring immediately and 24 hours after application of a 0.05% abamectin dust have demonstrated 0.9 ug/m³ and 0.3 ug/m³ residues in the

³ Whitmire Research Laboratories, Inc. 1991. Abamectin movement study at Ft. Bragg. Whitmire Research Laboratories, Inc., Saint Louis, Missouri. CDFA Registration Doc. No. 50406-167. In a letter dated 11/14/96, Whitmire Micro-Gen gave authorization for Merck to cite and reference this study to support all EPA registration activities relating to avermectin B1.

⁴ Van Wijen, J.H., P. Clausing and B. Brunekreef. 1990. Estimated soil ingestion by children. Environmental Research 51:147-162.

⁵ Fong, H.R., R.K. Brodberg, T.A. Formoli, J.R. Sanborn, T. Thongsinthusak and J. Ross. 1990. Estimation of exposure of persons in California to pesticide products that contain malathion. Worker Health and Safety Branch, California Department of Food and Agriculture, Sacramento, CA. HS-1569

⁶ Thongsinthusak, T. et. al. 1990. Estimation of exposure of a person in California to pesticide products that contain abamectin. Worker Health and Safety Branch, California Department of Food and Agriculture, Sacramento, CA. HS-1567.

air, respectively⁷. Infant respiratory exposure was calculated based on an average 24-hour residues of 0.6 ug/m³ in the air and breathing rates of 4.2 and 1.5 liters/minute during light activity and rest periods, respectively⁸.

Estimated oral, dermal, and respiratory exposure of infants to abamectin as a result of residential use of Avert Prescription Treatment 310 is summarized in Table 1.

Table 1

route of exposure	potential exposure (µg/infant/day)	absorbed daily dosage (µg/kg/day)
oral	0.82	0.09
dermal	0.82	0.001
respiratory	2.50	0.14
TOTAL	4.14	0.23

Based on: Infant body surface area of about 3900 cm², body weight of 9 kg, 100% surface residue transfer to skin, 1% dermal absorption, oral absorption of 100%, respiratory uptake of 50%, 12 hours of light activity and 12 hours of rest.

The most refined estimate of human exposure to surface residues comes from work done with adult humans who's exposures were measured after defined contact with a pesticide treated carpet⁹. From this work it was possible to estimate transfer factors for pesticide residues from treated carpets to individual's bodies. The estimated transfer factor for infants is approximately 800 cm²/hour based on 3500 cm²/hour transfer factor for adults multiplied by the ratio of-infant to adult body surface area (3900/17,700 cm²). Assuming six hours of continual moving contact with the treated surface yields a potential dermal exposure for an infant of 2000 ng. In the human experiment with dermal absorption, the hands

⁷ Whitmire Research Laboratories, Inc. 1991. Abamectin movement study at Ft. Bragg. Whitmire Research Laboratories, Inc., Saint Louis, Missouri. CDFA Registration Doc. No. 50406-167. In a letter dated 11/14/96, Whitmire Micro-Gen gave authorization for Merck to cite and reference this study to support all EPA registration activities relating to avermectin B1.

⁸ Snyder, S. et. al. 1974. Report of the task group on reference man. The International Commission on Radiological Protection, Pergamon Press, New York.

⁹ Ross, J., et al. 1990. Measuring potential dermal transfer of surface pesticide residues generated from fogger use: An interim report. Chemosphere 20(3/4):349-360. HS-.1581.

contributed 14% of the total dermal exposure (Ross et al., 1990). If all hand residues were solvated in the mouth, the oral exposure would be 280 ng. Estimates of exposure by all routes using this model are shown in Table 2.

Table 2

route of exposure	potential exposure ($\mu\text{g}/\text{infant}/\text{day}$)	absorbed daily dosage ($\mu\text{g}/\text{kg}/\text{day}$)
oral	0.28	0.03
dermal	1.70	0.002
respiratory	1.88	0.1
TOTAL	3.86	0.13

Based on: Body weight of 9 kg, 1% dermal absorption, 6 hours of light activity and 18 hours of rest.

HED Comments

The residential indoor exposure scenarios outlined above for infants are much higher than a similar scenario for adults would be (including females 13+ years). The data in Table 1 provides a more conservative ("worst-case") scenario than that in Table 2. From the exposure numbers presented in Table 1 and the NOEL of 0.2 mg/kg/day recommended by the TES Committee for estimating short- and intermediate-term residential dermal and inhalation risk, PIRAT calculated a total indoor residential MOE of 870.

Outdoor Residential Use Risk Assessment

Based on the nature of the outdoor residential uses (spot treatment), HED has concluded that residential exposure resulting from outdoor uses will not be significant.

Summary of Residential Risk Assessment

These calculations indicate that non-occupational exposure to avermectin should pose no unacceptable risks to infants, children, and adults.

Aggregate Risk Assessments

Acute Risk Assessment

The acute aggregate risk assessment takes into account exposure from dietary food and water only. Based on the TES Committee meeting of 5/24/96 and reserving 10% of the acute MOE for water (risk cup), an acute dietary (food only) MOE of greater than 333 would not be of concern to HED. As noted earlier in this memo, the MOE for females 13+ years was calculated to be 769. Therefore, HED has no aggregate acute concern.

Short- and Intermediate-Term Risk Assessment

Short- and intermediate-term aggregate risk takes into account exposure from chronic dietary food and water (considered to be a background exposure level) plus indoor and outdoor residential exposure. Based on the nature of the outdoor residential uses (spot treatment), HED has concluded that the contribution of the outdoor portion of the residential exposure will not be significant. Using the Risk Cup Decision Logic, an acceptable short- and intermediate-term MOE was calculated to be 333, similar to the acute aggregate risk. Using the following equation, PIRAT calculated the following MOEs.

$$\text{MOE} = \text{NOEL} / (\text{ARC}_{\text{food}} + \text{Residential exposure})$$

where NOEL = 0.2 mg/kg/day

ARC_{food} is obtained from the Chronic DRES Analysis (Attachment I)

Residential exposure = 0.00023 mg/kg/day (from Table 1)

<u>DRES Subgroup</u>	<u>ARC_{food}</u>	<u>Res. Exp.</u>	<u>MOE</u>
U.S Population	0.000020	0.00023	800
Nursing Infants (<1 year old)	0.000025	0.00023	784
Non-Nursing Infants (<1 year old)	0.000043	0.00023	733
Children (1-6 years old)	0.000038	0.00023	746
Children (7-12 years old)	0.000025	0.00023	784
Northeast Region	0.000023	0.00023	790
Western Region	0.000024	0.00023	787
Hispanics	0.000022	0.00023	794

Since these MOEs exceed 333, HED has no short- and intermediate-term aggregate risk concerns.

Chronic Risk Assessment

The aggregate chronic risk is equal to the sum of the chronic risk from food + water + indoor residential + outdoor residential. HED has determined that the residential uses of avermectin do not constitute a chronic scenario. Therefore, the aggregate chronic risk for avermectin is equivalent to the following percentages of the RfD:

	<u>food</u>	<u>water</u>	<u>TOTAL</u>
U.S Population	5%	10%	15%
Nursing Infants (<1 year old)	6%	10%	16%
Non-Nursing Infants (<1 year old)	11%	10%	21%
Children (1-6 years old)	10%	10%	20%
Children (7-12 years old)	6%	10%	16%
Northeast Region	6%	10%	16%
Western Region	6%	10%	16%
Hispanics	6%	10%	16%

Cancer Risk Assessment

Avermectin has been classified as a Group E "evidence of non-carcinogenicity for humans" chemical by the RfD/Peer Review Committee (6/27/96). Therefore, an aggregate cancer risk calculation is not warranted.

Cumulative Effects

The Agency has not made a determination that avermectin and other pesticide chemicals which may have a common mode of toxicity would have cumulative effects. For purposes of these time-limited tolerance extension, PIRAT has considered only effects from avermectin. If required, cumulative risks will be assessed as part of Reregistration and tolerance reassessment, and when methodologies for determining common mode of toxicity and for performing cumulative risk assessment are finalized.

Determination of Safety for Infants and Children

The toxicological database for evaluating pre- and post-natal toxicity for avermectin is complete.

Pre-Natal Effects

The developmental and maternal NOELs for avermectin in rats are both ≥ 1.6 mg/kg/day (highest dose tested). For rabbits, the developmental and maternal NOELs and LOELs are both 1.0 and 2.0 mg/kg/day, respectively. Although the developmental study in rats was only tested up to 1.6 mg/kg/day, a pilot study with avermectin in rats produced maternal toxicity at 2.0 mg/kg/day (highest dose tested - MRID No. 00249152). These studies suggest that avermectin does not exhibit any special pre-natal sensitivity.

However, both the delta-8,9-isomer of avermectin (which is included in the tolerance expression) and avermectin per se exhibit cleft palate in CF1 mouse developmental studies. The NOEL for cleft palate for the delta-8,9-isomer is 0.06 mg/kg/day with the LOEL at 0.10 mg/kg/day (MRID# 00164011). For avermectin per se, the NOEL for cleft palate is 0.2 mg/kg/day with the LOEL at 0.4 mg/kg/day (MRID# 00164014). Therefore, pre-natal

sensitivity to the regulated residue for avermectin is demonstrated when considering these in the CF1 mouse.

To evaluate the pre-natal risks, the acute dietary MOE calculations for women 13+ has been conducted using the lowest NOEL for all developmental studies for cleft palate (0.06 mg/kg/day). The MOE of 769 for women 13+ is considered adequate to protect pre-natal exposure.

Post-Natal Effects

With respect to post-natal sensitivity for avermectin per se, the NOEL in the 2-generation rat reproduction study [MRID No. 00265576] is 0.12 mg/kg/day. At the LOEL of 0.4 mg/kg/day [highest dose tested], the effects in the pups included death, decreased body weight and retinal folds. In contrast, the NOEL for parental toxicity is 0.4 mg/kg/day [highest dose tested]. This suggests post-natal sensitivity for infants and children. However, with respect to post-natal sensitivity for the delta-8,9-isomer, a 1-generation rat reproduction study at doses up to 0.4 mg/kg/day did not produce any parental or pup toxicity [MRID No. 40713404].

The RfD Committee (6/27/96) established the RfD at 0.0004 mg/kg/day based on the 2-generation rat reproduction study (MRID No. 00265576) with a NOEL of 0.12 mg/kg/day and an uncertainty factor of 300. In addition to the Uncertainty Factor of 100 for inter- and intra-species variations, a Modifying Factor (MF) of 3 was used for a total uncertainty factor of 300. The MF was used because of the severity of the effects (pup deaths) and the steep dose-response. Therefore, the post-natal sensitivity for infants and children has been considered by employing a 300-fold uncertainty factor in the calculation of the RfD. The highest calculated aggregate percentage of the RfD is 21% for non-nursing infants. This risk estimate with a low percent of the RfD is considered adequate to protect post-natal exposure of infants and children.

SUPPLEMENTAL INFORMATION

Dietary Exposure

Table 3. Residue Consideration Summary Table

CURRENTLY REGISTERED USE			
PARAMETER	CITRUS	COTTON	HOPS
CHEMICAL	avermectin B1	avermectin B1	avermectin B1
FORMULATION	AGRI-MEK 0.15EC	ZEPHYR 0.15EC	AGRI-MEK 0.15EC
PEST	various mites, citrus leafminers, and citrus thrips	various mites	spider mites
TYPE APPLICATION	ground only	ground or air	ground only
# APPLICATIONS	up to 3	up to 2	up to 2
TIMING	during active growth	postemergence	postemergence
RATE/APPLICATION	up to 0.023 lbs ai/A	0.019 lbs ai/A	0.019 lbs ai/A
RATE/YEAR or SEASON	0.046 lbs ai/A/season	0.038 lbs ai/A/season	0.038 lbs ai/A/season
RESTRICTIONS	must be applied with paraffinic oil minimum 7-day PHI minimum of 30 days between applications do not graze treated orchards	minimum of 5 gallons of finished spray per acre minimum 20 day PHI minimum of 21 days between applications do not graze or feed cotton foliage do not apply east of the Mississippi River	minimum of 40 gallons of finished spray per acre minimum 28-day PHI minimum of 21 days between applications do not graze hop yards

Additional Information

The citrus data used for the conclusions drawn in this memo were taken from that submitted for PP#8F3592 (memo of M. Kovacs dated 4/25/88). The data were reexamined and evaluated in acute and chronic dietary risk assessments performed in conjunction with PP#9F3787 (memo of G.J. Herndon dated 12/21/94 - see Attachment III).

The cotton data used for the conclusions drawn in this memo were taken from that submitted in support of PP#6G3320 and PP#7F3500. The data were reexamined and evaluated in acute and chronic dietary risk assessments performed in conjunction with PP#9F3787 (memo of G.J. Herndon dated 12/21/94 - see Attachment III).

The hop data used for the conclusions drawn in this memo were taken from that submitted for PP#5E4566 (memo of W. Wassell dated 3/5/96 - see Attachment IV).

The animal commodity data used in this memo were taken from the acute and chronic dietary risk assessments performed in conjunction with PP#9F3787 (memo of G.J. Herndon dated 12/21/94 - see Attachment III).

Attachment I - Chronic DRES Analysis Table (dated 6/4/96)

Attachment II - Acute DRES Analysis Table (dated 6/4/96)

Attachment III - Acute and Chronic Dietary Risk Assessments for
Avermectin B1, G.J. Herndon, 12/21/94

Attachment IV - Abamectin Residues on Hops, W.D. Wassell, 3/5/96

cc (with Attachments): Herndon (PIRAT), Davis (PIRAT).

cc (without Attachments): Dykstra (PIRAT), PIRAT, OREB (File #122804), Caswell File (#063AB), TOX, CBTS (PP#7F3500, PP#8F3592, and PP#5E4566).

RDI:PIRAT: 1/9/97