US EPA ARCHIVE DOCUMENT

MEMORANDUM

DATE: 06-APRIL-1999

SUBJECT: PP#6F4628. Section 3 Registration for Emamectin Benzoate on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce, and Celery.

DP Barcode: D241907, D233449	PRAT Case: 287173
PC Code: 122806	Caswell#: 999
Trade Name: Proclaim 0.16 EC and 5SG	Class: Insecticide
EPA Reg #: Not registered	40 CFR: 180.505
MRID# : 440306-02	

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Insecticide-Rodenticide Branch
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THRU: Stephen Dapson, Branch Senior Scientist, RAB3

Novartis Crop Protection, Inc. has submitted a petition (PP#6F4628) proposing to establish permanent tolerances for residues of the insecticide emamectin benzoate (mixture of a minimum of 90% 4"-epi-methylamino-4"deoxyavermectin B_{1a} and a maximum of 10% 4"-epi-methylamino-4"-deoxyavermectin B_{1b} benzoate) and its metabolites in/on the raw agricultural commodities broccoli, Brussels sprouts, cabbage, cauliflower, head lettuce and celery expressed as emamectin benzoate, 8,9-ZMA and metabolites/photodegrates AB1a, MFB1a, and FAB1a. The proposed tolerance level for all of these commodities is 0.025 ppm (combined limits of quantitation). The Health Effects Division risk assessment for this petition follows.

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1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a human health risk assessment for emamectin for the purpose of making a tolerance/registration eligibility decision to establish use on broccoli, Brussels sprouts, cabbage, cauliflower, celery and head lettuce as requested by the petitioner, Novartis Crop Protection, Inc (formerly Merck).

This petition for a permanent tolerance/registration for emamectin residues in/on broccoli, Brussels sprouts, cabbage, cauliflower, celery and head lettuce represent the **first food uses**. There are currently no registered (agricultural, residential or other non-food) use sites. However, a time-limited tolerance for emamectin on cabbage was established for a Section 18, which expired on 12/31/98. There are currently no Codex, Canadian, or Mexican maximum residue limits on emamectin or its metabolites.

Emamectin is a mixture of two active homologous compounds. The petitioner's coded names for emamectin are emamectin benzoate, MK-0244, or MAB1. In this memorandum, the ANSI name, emamectin, will be used.

Emamectin (Proclaim™) is an insecticide developed for the control of lepidopteran insects on cole crops and leafy vegetables. Two formulations are proposed: an emulsifiable concentrate (Proclaim 0.16EC) and a soluble granular (Proclaim 5 SG). The registrant proposes multiple foliar applications made at approximately 0.0075-0.015 lb active ingredient per acre per application using ground equipment with 7-day intervals between applications. The proposed maximum seasonal rate is 0.09 lb ai/A/season, i.e., 6 to 12 applications per acre per season and a 7-day pre-harvest interval (PHI).

HED has evaluated the toxicological, product and residue chemistry, and exposure data bases for emamectin. The HED Metabolism Committee concluded that the following residues should be included in the tolerance expression and dietary risk assessment for the proposed use: emamectin (parent), 8,9ZMA, and metabolites/photodegradates AB1a, MFB1a, and FAB1a. Metabolites / photodegradates 8AOXOMA and 8AOHMA are also of toxicological concern, but based upon the relative low levels compared to residues of emamectin and the other four ememectin-like residues (8,9ZMA, AB1a, MFB1a and FAB1a), these are not needed in the tolerance expression or dietary risk assessment. The proposed enforcement method for residues of emamectin on plant commodities has not been subjected to a complete Agency validation. However, the method is tentatively considered suitable for enforcement purposes pending the outcome of the actual method validation. Therefore, as a condition of registration, the Agency will require a successful method validation and the registrant will be required to make any necessary modifications to the method resulting from the BEAD laboratory validation.

HED's Hazard Identification Assessment Review Committee (HIARC) originally met on February 26, 1998 to evaluate the toxicity data base for emamectin. The Committee met again on July 28 and August 3, 1998 to re-evaluate the toxicity data base and assess the previous

Reference Dose (RfD) and toxicological endpoints selected for acute dietary as well as occupational and residential exposure assessments (Attachment 1). Endpoints selected for acute and chronic dietary, short- and intermediate-term dermal and inhalation exposure were all based on a 15-day oral mouse study in which a variety of effects were observed, including tremors on day 3, clinical signs of neurotoxicity and histopathological lesions in the sciatic nerve.

The toxicological database indicates that technical grade emamectin has moderate acute toxicity, and is a severe eye irritant. The subchronic and chronic toxicity studies demonstrated that the primary effects of emamectin are neurotoxic, and studies in mice indicated that ememectin is neurotoxic at low doses. Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility to *in utero* exposure to emamectin. However, **increased susceptibility was demonstrated in a developmental neurotoxicity study in rats.**

All toxicological data requirements for emamectin technical have been satisfied. Acute data requirements for the emulsifiable concentrate formulation (Proclaim™ 0.16 EC) and the soluble granular formulation (Proclaim™ 5SG) have been satisfied.

OPP's FQPA Safety Factor Committee met on April 13, 1998 and determined that the ten-fold FQPA Safety Factor for the protection of infants and children should be reduced to 3X (Attachment 2). The Committee's decision was based on the following:

- No increased susceptibility was demonstrated in rats or rabbits following *in utero* exposure to emamectin, although increased susceptibility was demonstrated in a developmental neurotoxicity study in rats;
- Although increased susceptibility was demonstrated in a developmental neurotoxicity study in rats, the Committee determined that the 10x factor should be reduced to 3x based on the following weight-of-the-evidence considerations in the developmental neurotoxicity study: 1) the LOAEL was based on a single effect/end point (i.e., decrease in open field motor activity); 2) the effect at the LOAEL was seen only on postnatal day 17 and was not seen either on earlier (Day 13) or later (Day 21) evaluations whereas at the high dose (3.6/2.5 mg/kg/day), this effect was seen on postnatal days 13 and 17; 3) the effect at the LOAEL was not accompanied with other toxicity whereas at the high dose tremors and hindlimb splay were also seen; 4) the decreased performance was lower only when compared to the concurrent control; and 5) there was limited (only 2 studies) historical control data available for comparison.
- Exposure assessments do not indicate a concern for potential risk to infants and children because: 1) the dietary exposure estimates are based on field study data assuming 100% percent crop treated resulting in an overestimate of dietary exposure[1]; 2) modeling data

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[1] Although dietary risk was not calculated based on the assumption of 100% crop treated, HED is confident that the estimate of percent of crop treated which was used, 25%, is an over

were used for the ground and surface source drinking water exposure assessments; the resulting estimates are considered to be reasonable upper-bound concentrations; 3) there are no registered residential uses.

In making its determination of safety finding for human health risks, HED considered potential dietary exposure to emamectin residues in food and water. When assessing acute and chronic (non-cancer) dietary risk, HED considered potential dietary exposure to the U.S. population including infants and children.

HED used Dietary Exposure Evaluation Model (DEEM™) software to conduct a Tier 3 acute and chronic dietary Monte Carlo (food-source) analysis (Attachment #4). Tolerances were recommended as a summation of the limits of quantitation (LOQ) for regulable metabolites of emamectin. Twenty-five percent of all commodities were assumed treated. Consumption data were taken from the USDA Continuing Surveys of Food Intake by Individuals (CSFII), conducted in 1989-1992. The resulting anticipated residue contribution (ARC) occupied no more than 65% of the acute and 4% for chronic population-adjusted dose (PAD) or Reference dose (RfD) for any one population subgroup at the 99.9 percentile.

In the environment, emamectin and its primary degradates are expected to be relatively immobile due to the high degree of sorption to soil particles. Ground or surface water monitoring data for emamectin are not available; therefore, characterization of risk from drinking water was based on the EFED models PRZM/EXAMS (surface water) and SCI-GROW (ground water) (Attachment #6, 6a). The EFED modeling estimated environmental concentrations (EECs) of emamectin and its metabolites were lower than the HED back-calculated drinking water levels of comparison (DWLOCs) for both acute and chronic (non-cancer) dietary exposure. There are no registered residential uses of emamectin, so residential exposure was not included in the aggregate risk assessment. Thus, chronic aggregate risk (food plus water) and acute aggregate risk (food plus water) do not exceed HED's level of concern. No cancer risk assessment was necessary.

There is a potential for workers to be exposed to emamectin during mixing/loading and application operations as well as during post-application activities. The proposed use may result in short- and intermediate-term exposure. The HIARC identified endpoints and doses for both short- and intermediate term exposure based on tremors, moribund sacrifices, decreases in body weight and food consumption and histopathological lesions in the sciatic nerve. The HIARC did not identify endpoints for chronic risk assessment since emamectin use patterns (6-12 applications per season, with 7-day intervals) are not expected to involve chronic exposure. Short- and intermediate -term dermal risk and inhalation risk do not exceed HED's level of concern for occupational exposure, including handler and post application exposure.

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estimate, and HED does not expect more than 25% of any crop to be treated with emamectin.

The Restricted Entry Interval (REI) is based on acute toxicity of emamectin, which is classified in Acute Toxicity Category 1 for primary eye irritation. Therefore, a 48-hour REI is required to comply with the Agency's Worker Protection Standard (WPS). The Registration Division should ensure that a 48-hour REI appears on all emamectin labels. Per the WPS, the minimum level of personal protective equipment (PPE) is based on the acute toxicity of the end use product for handlers and is based on the acute toxicity for the active ingredient for early entry PPE. OPP's Registration Division (RD) is responsible for ensuring the PPE listed on the label is in compliance with the Worker Protection Standard.

In conclusion, HED finds that chronic (non-cancer) aggregate risk and short and intermediate occupational worker risk estimates do not exceed HED's level of concern.

There are no registered residential uses of emamectin. HED can conclude that there is a reasonable certainty that no harm will result to infants, children or adults from the proposed use of emamectin on broccoli, Brussels sprouts, cabbage, cauliflower, celery and lettuce. The product and residue chemistry and toxicology data bases for emamectin have no data gaps and are adequate to assess this agricultural food use with a reasonable level of confidence. These data and the best available exposure data were used in calculating the risk.

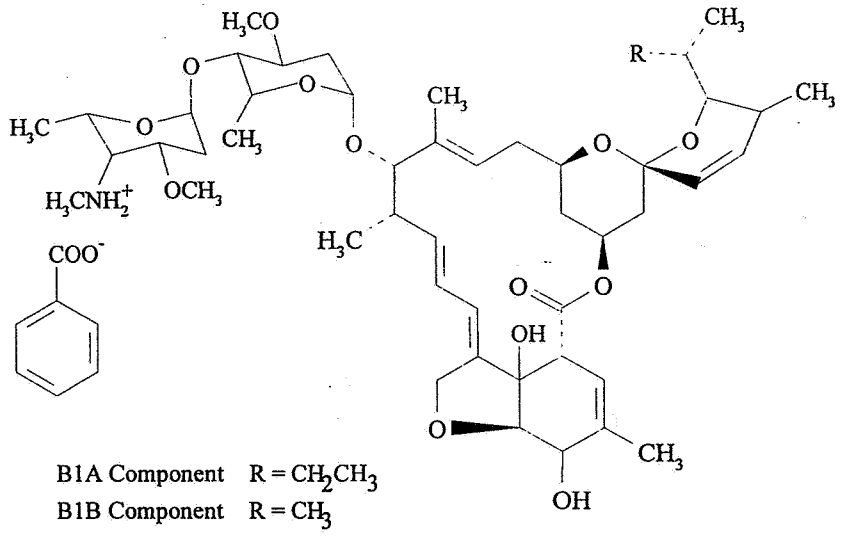
In summary, HED recommends for the establishment of tolerances for residues of emamectin and its metabolites at 0.025 ppm in/on broccoli, Brussels sprouts, cabbage and cauliflower, head lettuce and celery. As a condition of registration, the Agency will require a successful method validation and the registrant will be required to make any necessary modifications to the method resulting form the BEAD laboratory validation. Also, a 48-hour REI is required to comply with the Agency's Worker Protection Standard, since the technical material is in Acute Toxicity Category 1 for primary eye irritation.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Emamectin is a mixture of two active homologous compounds, the benzoate salts of 4"-deoxy-4"-epi- methylamino-avermectin B_{1a} (MAB1A) and 4"-deoxy-4"-epi-methylamino-avermectin B_{1b} (MAB1B). These compounds are derived from the natural fermentation products avermectins B_{1a} and B_{1b} (from Streptomyces avermitilis) in which the 4"-hydroxyl constituent of the avermectin molecule is replaced with an epi-methylamino group.

The product chemistry data base for emamectin is adequate. No further product chemistry information is necessary to support this proposed use.

The chemical structure of emamectin is shown below:



Novartis Crop Protection, Inc. has submitted revised Sections G and F of their petition, in support of their proposal to establish permanent tolerances of 0.025 ppm in/on broccoli, Brussels sprouts, cabbage, cauliflower, head lettuce, and celery. The proposed tolerances are based on a tolerance expression which includes emamectin (mixture of B1a and B1b isomers), 8,9-ZMA, and metabolites / photodegradates AB1a, MFB1a, and FAB1a.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicological database indicates that technical grade emamectin has moderate acute toxicity, and is a severe eye irritant. Emamectin falls into Toxicity Category 2 and 3 for acute oral and dermal toxicity, respectively, and Category 1 for eye irritation. Emamectin did not cause dermal irritation and is not a dermal sensitizer. All toxicological data requirements for emamectin technical have been satisfied. The acute toxicity of emamectin technical is summarized in Table 1 below.

Table 1. Acute Toxicity of Emamectin Technical

Guideline No.	Study Type	MRID#	Results	Toxicity Category
870.1100	Acute Oral- Rats	42851519	LD_{50} for L-656,748-038 = 53 mg/kg	2
870.1200	Acute Dermal- Rabbits	43850111	LD_{50} > 2.0 mg/kg	3
870.1300	Acute Inhalation- Rats	43868101	LC_{50} 0.10 mg/L	4
870.2400	Primary Eye Irritation- Rabbits	42743615	Severe irritation	1
870.2500	Primary Skin Irritation- Rabbits	42743616	No dermal irritation	4
870.2600	Dermal Sensitization- Guinea pigs	42743617	Not a dermal sensitizer	-

The subchronic and chronic toxicity studies demonstrated that the primary effects of emamectin are neurotoxic, and studies in mice indicated that ememectin is neurotoxic at low doses. Prenatal developmental toxicity studies in rats and rabbits provided no indication of increased susceptibility to *in utero* exposure to emamectin. However, **increased susceptibility was demonstrated in a developmental neurotoxicity study in rats.**

Details about the toxicology of emamectin are available in the HED memo, *EPA ID#: 000618-RNI: Application for Establishment of Permanent Tolerance for the Use of Emamectin on Cole Crops and Leafy Vegetables.* G. Reddy. 06/30/98. A summary of the toxicology profile for emamectin is presented in Table 2 below.

Table 2. Toxicity Profile of Emamectin Technical

Guideline No. / Study Type	MRID#(s)	Results
870.3100 Subchronic-Feeding-Rat MK-0243	**42794201, 42743620**	**Systemic Toxicity NOAEL=2.5 mg/kg/day; Systemic Toxicity LOAEL=5 mg/kg/day** based on tremors, hindlimb splaying, urogenital staining, histological changes in brain and spinal cord, sciatic and optic nerves and skeletal muscles in males, emaciation, reduced body weight and reduced food consumption in both sexes.
870.3150 Subchronic-Feeding-Dog MK-0243	**42743623, 42743622**	**Systemic Toxicity NOAEL=0.25 mg/kg; Systemic Toxicity LOAEL=0.50 mg/kg** based on microscopic pathological signs of neurotoxicity consisting of skeletal muscle atrophy and white matter multifocal degeneration in the brains of both sexes and white matter multifocal degeneration in the spinal cords of males.

Guideline No. / Study Type	MRID#(s)	Results
870.3200 **21-Day Dermal Toxicity-Rat**		No Study Available.
870.3700 **Developmental Toxicity-Rat** **MK-0243**	**42743632, 42743631**	**Maternal Toxicity NOAEL=2 mg/kg/day, Maternal Toxicity LOAEL=4 mg/kg/day** based on a significant trend towards decreased body weight gain during the dosing period. **Developmental Toxicity NOAEL=4 mg/kg/day, Developmental Toxicity LOAEL=8 mg/kg/day** based on altered growth and an increased incidence of supernumerary rib.
870.3700 **Developmental Toxicity-Rabbit** **MK-0243**	**42743636, 42743635**	**Maternal Toxicity NOAEL=3 mg/kg/day, Maternal Toxicity LOAEL=6 mg/kg/day** based on a significant trend towards decreased body weight gain during dosing period and increased clinical signs (mydriasis and decreased pupillary reaction). **Developmental Toxicity NOAEL=6 mg/kg/day, Developmental Toxicity LOAEL= Not Determined.**
870.3800 **Reproductive Toxicity-Rat** **MK-0244**	**42851511**	**Systemic Toxicity NOAEL=0.6 mg/kg/day, Systemic Toxicity LOAEL=1.8 mg/kg/day** based on decreased body weight gain and histopathological changes (neuronal degeneration in the brain and spinal cord) in both sexes and generations. **Reproductive Toxicity NOAEL=0.6 mg/kg/day, Reproductive Toxicity LOAEL=1.8 mg/kg/day** based on decreased fecundity and fertility indices and clinical signs (tremors and hind limb extension) in offspring of both generations.
870.4100 **Chronic-Feeding-Dog** **MK-0244**	**42763624**	**Systemic Toxicity NOAEL= 0.25 mg/kg/day, Systemic Toxicity LOAEL=0.5 mg/kg/day** based on axonal degeneration in the pons, medulla and peripheral nerves (sciatic, sural, and tibial) in both sexes, clinical signs of neurotoxicity (whole body tremors, stiffness of the hind legs), spinal cord axonal degeneration, and muscle fiber degeneration in females.
870.4100 **Chronic Feeding-Rat** **MK-0244**	**42868902**	**Systemic Toxicity NOAEL=1.0 mg/kg/day; Systemic Toxicity LOAEL=2.5 mg/kg/day**, based on increased incidence of neuronal degeneration in the brain and spinal cord, decreased rearing, and an increased incidence of animals with low arousal.
870.4200 **Carcinogenicity-Mouse** **(78-week)** **MK-0244**	**43868105**	Systemic Toxicity NOAEL=2.5 mg/kg/day, Systemic Toxicity LOAEL=5.0 mg/kg/day for males and 7.5 mg/kg/day for females based on increased mortality, decreased weight gain, neurological signs, and increased incidence of severity of infections. There were no signs of carcinogenicity in this study.
870.4300 **Chronic Toxicity/** **Carcinogenicity-Rat** **Emamectin**	**43868104**	Systemic Toxicity NOAEL=1.0 mg/kg/day, Systemic Toxicity LOAEL=2.5/5.0 mg/kg/day[1] based on marked neural degeneration in the brain and spinal cord or both sexes, brain white matter degeneration in males, and on decreased body weight, body weight gain, and food efficiency in males. There were no signs of carcinogenicity in this study.

Guideline No. / Study Type	MRID#(s)	Results
870.5100 **Gene Mutation - *Salmonella*** **MK-0243 and L-660,599; L-657,831; L-695,638; L-930,905 (photometabolites of MK-0244)**	**42743637** **42851514** **42851515** **42851516** **42851517**	**Negative** for the induction of reverse gene mutation
870.5300 **Gene Mutation in Cultured V-79 Chinese Hamster Lung Cells** **MK-0243**	**42743638**	**Negative** for the induction of forward gene mutations in Chinese hamster lung fibroblast cells up to a severely cytotoxic nonactivated dose of 0.01mM or a severely cytotoxic S9-activated dose of 0.04mM.
870.5385 **Structural Chromosome Aberration-*in vivo* mouse bone marrow** **MK-0244**	**42851513**	**Negative** for the induction of chromosome aberrations in the bone marrow cells of male CD-1 mice.
870.5500 **DNA Damage-Rat hepatocytes** **MK-0243**	**42743639**	**Negative** for the induction of single strand breaks (SBs) in DNA of rat hepatocytes.
870.6200 **Acute Oral Neurotoxicity -Rat** **MK-0243**	**42743618**	A Neurotoxicity NOAEL was not established, since toxic signs of neurotoxicity as well as histological lesions in the brain, spinal cord and sciatic nerve occurred at all doses tested (27.4, 54.8 or 82.2 mg/kg)
870.6200 **Subchronic Neurotoxicity-Rat** **MK-0243**	**42743628**	Neurotoxicity NOAEL=1.0 mg/kg/day, LOAEL=5.0 mg/kg/day (highest dose tested) based on mild tremors, posture, rearing, excessive salivation, fur appearance, gait, strength, mobility and righting reflex.
870.6200 **Dietary Neurotoxicity-CD-1 Mice** **MK-0243**	**42743629**	Neurotoxicity NOAEL=2.0 mg/kg/day (highest dose tested). No characteristic neuronal lesions in the brain, spinal cord or sciatic nerve in mice of high dose group (2.0 mg/kg/day).
870.6200 **15-day Dietary Neurotoxicity-CF-1 Mice** **MK-244**	**42851503**	Neurotoxicity NOAEL=0.075 mg/kg/day; LOAEL=0.10 mg/kg/day based on tremors observed beginning on day 3, decreases in body weight and food consumption as well as degeneration of the sciatic nerve.
870.6200 **Dietary Neurotoxicity-CF-1 Mice** **L-660,599** **Supplementary Study**	**42851506**	Neurotoxicity NOAEL<0.1 mg/kg/day. One of the low-dose males had tremors, hunched posture and piloerection on day 14.
870.6300 **Developmental Neurotoxicity-Rat** **MK-0244**	**42851508**	Maternal Toxicity NOAEL=3.6/2.5 mg/kg/day (highest dose tested) Developmental Neurotoxicity NOAEL=0.10 mg/kg/day (lowest dose tested). The LOAEL is 0.60 mg/kg/day based on the dose-related decrease in open field motor activity in females at postnatal day 17. This study was the basis of the FQPA Committee's conclusion that emamectin demonstrated increased susceptibility.

Guideline No. / Study Type	MRID#(s)	Results
870.7485 **Metabolism-Rat** **MAB1a**	**42851523**	Radiolabeled MAB1 a benzoate is rapidly absorbed, distributed and excreted following oral and i.v. administration. The feces was the major route of excretion in oral and i.v. groups, while <1% of the administered dose was recovered in the urine 7 days post dosing. Tissue distribution and bioaccumulation appeared minimal. The metabolism of MAB1 a benzoate appears to involve primarily N-demethylation to AB1a. AB1a was the only metabolite detected in the feces while unmetabolized parent compound represented a large amount of the radioactivity.
870.7485 **Bioequivalence -Dog** **MK-0243 solvate/monohydrate**	**42743641**	The study demonstrated that MK-0243 benzoate MTBE solvate and MK-0243 benzoate monohydrate were bioequivalent in male dogs following oral administration as indicated by similar plasma levels for the two compounds.
870.7485 **Bioequivalence-Dog** **MK-0243 benzoate/HCL salts**	**42743640**	The study demonstrated that benzoate and HCl salts are bioequivalent after oral administration in male beagle dogs.
870.7600 **Dermal Absorption-Rhesus Monkey** **MAB1a, MK-244**	**43850113**	Dermal Absorption was approximated at 1.79% of the administered dose.

1. The initial dose of the high dose group was 5.0 mg/kg/day. Due to unacceptable weight loss and/or tremors occurring at this dose in another concurrent study (TT#91-006-0) during week 9 in males and week 11 in females, the dose was lowered to 2.5 mg/kg/day starting at week 6 in males and week 10 in females.

3.2 FQPA Considerations

On April 13, 1998, the FQPA Safety Factor Committee determined the 10x safety factor for the protection of infants and children should be **reduced to 3x**. The Committee's rationale for reducing the FQPA Safety Factor is as follows:

- No increased susceptibility was demonstrated in rats or rabbits following *in utero* and/or postnatal exposure to emamectin. However, increased susceptibility was demonstrated in a developmental neurotoxicity study in rats (MRID 42851508).

- Although increased susceptibility was demonstrated in a developmental neurotoxicity study in rats, the Committee determined that the 10x factor should be reduced to 3x based on the following weight-of-the-evidence considerations in the developmental neurotoxicity study: 1) the LOAEL was based on a single effect/end point (i.e., decrease in open field motor activity); 2) the effect at the LOAEL was seen only on postnatal day 17 and was not seen either on earlier (Day 13) or later (Day 21) evaluations whereas at the high dose (3.6/2.5 mg/kg/day), this effect was seen on postnatal days 13 and 17; 3) the effect at the LOAEL was not accompanied with other toxicity whereas at the high dose

tremors and hindlimb splay were also seen; 4) the decreased performance was lower only when compared to the concurrent control; and 5) there was limited (only 2 studies) historical control data available for comparison.

- Exposure assessments do not indicate a concern for potential risk to infants and children because: 1) the dietary exposure estimates are based on field study data assuming 100% percent crop treated resulting in an overestimate of dietary exposure; 2) modeling data were used for the ground and surface source drinking water exposure assessments; the resulting estimates are considered to be reasonable upper-bound concentrations; 3) there are no registered residential uses.

The FQPA Safety Factor Committee also determined that the FQPA Safety Factor (3x) is applicable for acute dietary risk assessments for the general population including infants and children because the endpoint for this risk assessment is neurotoxicity (tremors), and to chronic dietary because the endpoint for this risk assessment is based on clinical signs of neurotoxicity histopathological lesions in the sciatic nerve following oral exposure.

It should be noted that the rationale stated in the FQPA Safety Factor Committee's report was written in April, 1998, and at that time, 100% crop treated was expected to be assumed for the dietary risk assessment. However, for this action, residues were highly refined: 25% crop treated was assumed, along with residue levels at ½ the limit of quantitation. Since emamectin is a new chemical, it is unlikely that it would be used on 25% of crops. Although dietary risk was not calculated based on the assumption of 100% crop treated (as stated in the FQPA SFC report rationale) HED is confident that the estimate of percent of crop treated which was used, 25%, is an over estimate, and HED does not expect more than 25% of any crop to be treated with emamectin. The DEEM exposure assessment, although refined, confirms the Committee's assertion that the exposure potential for infants and children is low.

3.3 Dose Response Assessment

HED's Hazard Identification Assessment Review Committee (HIARC) originally met on February 26, 1998 to evaluate the toxicity data base for emamectin. The Committee met again on July 28 and August 3, 1998 to re-evaluate the toxicity data base and assess the previous Reference Dose (RfD) and toxicological endpoints selected for acute dietary as well as occupational and residential exposure assessments (Attachment 1). Endpoints selected for acute and chronic dietary, short- and intermediate-term dermal and inhalation exposure were based on the 15-day mouse neurotoxicity study (MRID 42851503) in which a variety effects were observed, including: tremors on day 3, clinical signs of neurotoxicity and histopathological lesions in the sciatic nerve. The results of this study were supported by the results of three other 15-day neurotoxicity studies (MRIDs 42743630, 42868901, 42851504/05). The HIARC stated that it is possible that a longer regimen might result in the enhancement of toxic effects, and therefore the endpoints identified are appropriate for acute as well as chronic risk assessment.

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

Table 3. Doses and Toxicological Endpoints Selected for Risk Assessment for Emamectin

Exposure Scenario	Dose (mg/kg/day)	Endpoint	Study Type, MRID#
Acute Dietary	NOAEL=0.075	Tremors on day 3 of dosing	15-Day-Mouse; 42851503
	UF =100	**Acute RfD = 0.00075 mg/kg/day**	
Chronic Dietary	NOAEL=0.075	Moribund sacrifices, clinical signs of neurotoxicity, decreases in body weight and food consumption and histopathological lesions in the sciatic nerve.	15-Day-Mouse; 42851503
	UF=300	**Chronic RfD = 0.00025 mg/kg/day**	
Carcinogenicity	No evidence of carcinogenicity.		
Short-Term (Dermal) [a]	Oral NOAEL=0.075	Tremors observed on day 3 of dosing.	15-Day-Mouse; 42851503
Intermediate-Term (Dermal) [a]	Oral NOAEL=0.075	Moribund sacrifices, clinical signs of neurotoxicity, decreases in body weight and food consumption and histopathological lesions in the sciatic nerve.	15-Day-Mouse; 42851503
Long-Term (Dermal)	Based on the use pattern, long-term dermal exposure is not a concern; risk assessment is not required		
Inhalation (Any Time Period) [a]	Oral NOAEL=0.075	Moribund sacrifices, clinical signs of neurotoxicity, decreases in body weight and food consumption and histopathological lesions in the sciatic nerve.	15-Day-Mouse; 42851503
Dermal Absorption	Rate: 1.8%		26-Day-Rhesus Monkey; 43850113

a = Appropriate route-to-route extrapolation should be performed for these risk assessments (i.e., the dermal inhalation exposure components using the appropriate absorption rates (1.8% for dermal and 100% for inhalation) should be converted to equivalent oral doses and compared to the oral NOAEL.

An acceptable 21-day dermal toxicity study in rabbits (MRID 44007902) is available with a formulated product (2.5% emamectin). However, the Committee decided to use the oral NOEL from the 15-day mouse study for the short- and intermediate-term exposure scenarios because the toxicology profile for emamectin and its metabolites indicates that mice are the most sensitive species.

As a result of the retention of the FQPA Safety Factor, HED will consider the population-adjusted-doses (PAD) for infants, children and females 13 years and older to be 0.00025 mg/kg/day for acute and and 0.000083 mg/kg/day for chronic dietary exposure. For other

populations (i.e., adult males). exposures will be compared to the acute and chronic RfDs, 0.00075 mg/kg/day and 0.00025 mg/kg/day, respectively.

The registrant submitted additional information in response to the initial HIARC report based on the argument that the animals with compromised P-glycoprotein protection (such as the CF-1 mice used in the 15-day neurotoxicity study) are not relevant to human health risk assessments. The registrant's submission was reviewed, evaluated considered by the Committee, but the HIARC concluded that the doses and endpoints selected in the initial HIARC shall continue to be used for risk assessment. The HIARC went on to state that the endpoints would be reconsidered provided the registrant submits a special study that demonstrates a clear relationship between neurotoxicity and P-glycoprotein deficiency in genotyped CF-1 mice (Attachment 3).

Recommendation for Aggregate Exposure Risk Assessments

There are no registered residential uses for emamectin at the present time. Therefore, aggregate exposure risk assessment will be limited to food exposure plus drinking water exposure.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

There are currently no registered permanent tolerances for ememectin benzoate. A time-limited temporary tolerance was established for head and Napa cabbage which was scheduled to expire on 12/31/98 under an emergency exemption (40 CFR 180.505).

Emamectin is an insecticide for control of lepidopteran insects. Two formulations are proposed: an emulsifiable concentrate (Proclaim 0.16 EC) and a soluble granular (Proclaim 5 SG). The registrant proposes multiple foliar applications made using ground equipment with 7-day application intervals. The use profile proposed for this Section 3 tolerance is summarized in Table 4 below.

Table 4. Use profile for Emamectin on Cole Crops and Leafy Vegetables

Product	Formulation Type	Rate Range for Single Application (lb ai/A)	Maximum Rate per Season (lb ai/A)	Number of Applications per season	REI	PHI	Application Method
Proclaim 5 SG Insecticide	water soluble granules	0.0075 - 0.015	0.09	6-12	48 hours	7 days	ground only
Proclaim 0.16 EC Insecticide	emulsifiable concentrate	0.0075 - 0.015	0.09	6-12	48 hours	7 days	ground only

4.2 Dietary Exposure

4.2.1 Food Source Dietary Exposure

There are no data gaps in the residue chemistry data base for emamectin. The residue chemistry data base for emamectin has been reviewed by HED (Attachment 4a). A very brief summary follows.

Proposed Use. The registrant proposes multiple foliar applications made at approximately 0.0075-0.015 lb active ingredient per acre per application using ground equipment with 7-day intervals between applications. The proposed maximum seasonal rate is 0.09 lb ai/acre/season, i.e., 6 to 12 applications per acre per season and a 7-day pre-harvest interval (PHI).

Rotational Crops. The confined rotational crop data base is adequate. No plantback restrictions need to be listed on labels.

Metabolism in Plants. HED's Metabolism Assessment Review Committee (MARC) concluded that the following residues are required in the tolerance expression and dietary risk assessment for the proposed use: emamectin, 8,9-ZMA, and metabolites/photodegredates AB1a, MFB1a and FAB1a. Metabolites/photodegredates 8AOXOMA and 8AOHMA are also of toxicological concern, but based upon the relative levels to the emamectin and the other four emamectin-like residues (8,9-ZMA, AB1a, MFB1a and FAB1a), these are not needed in the tolerance expression or dietary risk assessment.

Metabolism in Animals. No animal feed items are associated with the commodities for which permanent tolerances are proposed. Therefore, no animal metabolism or feeding studies are required.

Enforcement Method for Plants. The proposed enforcement method for residues of emamectin on plant commodities has not been subjected to a complete Agency method validation at this time. The EPA validation laboratory at Beltsville, MD is currently being relocated, and consequently, the laboratory is not operational at this time. The method trial request has been received by Biological and Economic Analysis Division (BEAD) and a validation is scheduled. In the interim, BEAD has conducted a preliminary review of the method and has indicated that it appears to be suitable for enforcement purposes pending the outcome of the actual method validation. Given that the registrant has provided concurrent fortification data to demonstrate that the method is adequate for data collection purposes and has provided the Agency with a successful Independent Laboratory Validation, coupled with the BEAD laboratory's preliminary review, HED concludes that the method is suitable as an enforcement method to support tolerances associated with a **conditional registration** only. **As a condition of the registration, the Agency will require a successful method validation and the registrant will be required to make any necessary modifications to the method resulting from the BEAD laboratory validation.**

Multiresidue Methods Testing. Data previously submitted by the petitioner show that residues of emamectin are not likely to be recovered by FDA multiresidue methods. The petitioner submitted data pertaining to the multiresidue methods testing of emamectin (B_{1a} and B_{1b} components), AB1a, FAB1a, MFB1a and the 8,9-Z isomer (B_{1a} component). The data have been forwarded to FDA for inclusion in PAM I.

Storage Stability Data. Storage stability data are adequate to support the tolerances requested in this action. Previously submitted storage stability data indicate that emamectin, 8,9-Z-isomer, AB1a, MFB1a, and FAB1a are stable on cabbage for up to 36 months.

Magnitude of Residue. HED has previously concluded that there were sufficient residue field trial data using Proclaim 1.6 EC to support a 0.025 ppm tolerance on broccoli, Brussels sprouts, cabbage, cauliflower, head lettuce and celery. The petitioner has now submitted additional residue trials conducted using Proclaim 5SG on cole crops and on leafy vegetables. The residue data from field trials show that emamectin residues will not exceed the expired time-limited cabbage tolerance or the recommended 0.025 ppm tolerances on broccoli, Brussels sprouts, cauliflower, lettuce, and celery, which are based on data using the EC formulation.

Residues in Meat, Milk, Poultry and Eggs. No animal metabolism or feeding studies were submitted with this petition. However, tolerances in milk, eggs, and animal tissues are not required at this time since no feed items are associated with the subject commodities for which permanent tolerances are being proposed.

4.2.1.1 Acute Dietary Risk from Food Sources

The Dietary Exposure Evaluation Model (DEEM) detailed acute analysis estimates the distribution of single exposures for the overall U.S. population and certain subgroups. The analysis evaluates individual food consumption as reported by respondents inthe USDA 1989-1991 Continuing Survey of Food Intake by Individuals (CSFII) and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of emamectin in the commodity supply.

The percent of the acute PAD ("PAD %") is a measure of how close the high end exposure comes to the PAD and is calculated as the percentage of the exposure to the PAD (exposure/PAD x 100 = % PAD). The percent PAD that would be above HED's level of concern for infants and children would be above 100%. Similarly, the percent RfD that would be above HED's level of concern for adult males would be over 100% RfD. A DEEM acute probabalistic analysis was performed using 1/2 (combined) LOQ level residues and 25% crop treated for all commodities (See Attachment #4). A summary of the dietary risks for the U.S. population and selected sub-groups is presented in Table 5 below.

Table 5 Acute Dietary Exposure and Risk from Food-Source Emamectin

	95th Percentile		99th Percentile		99.9th Percentile	
Population Subgroup	Exposure (ARC[1]) mg/kg/day	Percent PAD/RfD	Exposure (ARC) mg/kg/day	Percent PAD/RfD	Exposure (ARC) mg/kg/day	Percent PAD/RfD
U.S. Population	0.000010	4% PAD	0.000028	11% PAD	0.000078	31% PAD
All Infants (<1 year)	0.000000	<1% PAD	0.000000	<1% PAD	0.000020	8% PAD
Nursing Infants (<1 year)	0.000000	<1% PAD	0.000000	<1% PAD	0.000011	5% PAD
Non-nursing Infants (<1 year)	0.000000	<1% PAD	0.000000	<1% PAD	0.000022	9% PAD
Children (1-6 years)	0.000010	4% PAD	0.000048	19% PAD	0.000163	65% PAD
Children (7-12 years)	0.000010	4% PAD	0.000030	12% PAD	0.000089	36% PAD
Females (13+ years/nursing)	0.000014	6% PAD	0.000035	14% PAD	0.000067	27% PAD
Males (13-19 years)	0.000008	3% Acute RfD	0.000022	9% Acute RfD	0.000049	7% Acute RfD

1. Anticipated residue concentration

The acute analysis for emamectin is a highly refined estimate of dietary exposure with 1/2 LOQ level residues. However, the assumption that 25% of crops are treated is an upper bound market share (verified by BEAD), and should be considered conservative since this is a new chemical with a very small market. The risk from acute dietary exposure to emamectin, as represented by the percent PAD or the percent acute RfD, does not exceed HED's level of concern for any of the DEEM population subgroups.

4.2.1.2 Chronic Dietary Risk from Food Sources

In conducting this chronic dietary risk assessment, HED has made partially conservative assumptions–tolerance level residues and percent of crop treated information were used for selected crops–which result in an over estimate of human dietary exposure. This chronic dietary (food only) exposure assessment should be viewed as a partially refined risk estimate. Further refinement using anticipated residues would result in a lower dietary exposure estimate. Thus, in making a safety determination for these tolerances, EPA takes into account this partially refined exposure assessment. HED is generally concerned with chronic exposures that exceed 100% of the chronic RfD or PAD. The existing emamectin tolerances (published, pending and new) were used to calculate the exposure and risk estimates presented in Table 6 below.

Table 6 Chronic Dietary Exposure and Risk from Food-Source Emamectin

Population Subgroup	Exposure (ARC[1]) mg/kg/day	Percent PAD
U.S. Population	0.000003	4 % PAD
All Infants (<1 year)	0.000000	< 1 % PAD
Nursing Infants (<1 year)	0.000000	< 1 % PAD
Non-nursing Infants (<1 year)	0.000000	< 1 % PAD
Children (1-6 years)	0.000004	5 % PAD
Children (7-12 years)	0.000003	4 % PAD
Females (13+ years/nursing)	0.000004	5 % PAD
Males (20+ years)	0.000003	<1 % Chronic RfD

1. Anticipated residue concentration

The chronic analysis for emamectin is a highly refined estimate of dietary exposure with tolerance-level residues and percent crop treated data for selected crops factored into the calculations. Even without refinements, the risk from chronic dietary exposure to emamectin, as represented by the percent of PAD, does not exceed HED's level of concern for any of the DEEM subgroups.

4.2.1.3 Cancer Dietary Risk from Food Sources

Emamectin was classified as a "not likely" human carcinogen. Therefore, a dietary cancer risk assessment was not conducted.

4.2.2 Drinking Water Exposure and Risk

There are no established Maximum Contaminant Level for residues of emamectin in drinking water. No health advisory levels for emamectin in drinking water have been established.

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for emamectin at this time. The Environmental Fate and Effects Division (EFED) provided ground and surface water exposure estimates for use of emamectin on cabbage (12/2/98). The drinking water values provided by EFED were calculated for the parent compound, emamectin; however, based on an evaluation of available data, these values can be considered to include both emamectin and its metabolites AB1a, MFB1a, and FAB1a. These estimates were compared to back-calculated Drinking Water Levels of Comparison (DWLOCs) for emamectin.

Emamectin (MAB1a) photolytically degrades to 7 individual residues. They are in increasing order of polarity by RP-HPLC, the 8,9 Z isomer of MAB1a (8,9 Z-MAB1a), parent MAB1a, N-demethylated MAB1a (AB1a), the 8α-hydroxy MAB1a (8α OH-MAB1a), 8α oxo-MAB1a, methyl formyl MAB1a (MFB1a), formyl amino MAB1a (FAB1a) and the monosaccharide of MAB1a (MSB1a).

4.2.2.1 Environmental Fate

The Section 3 review in progress for this compound indicates that emamectin and its primary degradates would be expected to be relatively immobile in the environment due to the high degree of sorption to soil particles.

The aerobic metabolism of emamectin in the absence of light was determined in a sandy loam soil. The half-life for emamectin was estimated to be 193.4 days. Emamectin was demonstrated to be hydrolytically stable at pH values of 5.2, 6.2, 7.2 and 8.0. At pH 9, a half-life of 19.5 weeks was estimated.

4.2.2.2 Ground Water

The SCI-GROW (Screening Concentration In Ground Water) model developed in EFED (Barrett, 1997) predicts that emamectin and its metabolites will be found in ground water at extremely small concentrations when the insecticide is applied at the maximum recommended application rate of 0.015 lbs ai/acre with a maximum of six applications. EFED calculated estimated environmental concentrations of emamectin and its metabolites in ground water using the SCI-GROW screening model. The estimate is 6 pptr (parts per trillion). This conservative estimate is a default value generate by EFED's SCI-GROW model.

There may be exceptional circumstances under which ground water concentrations could exceed the SCI-GROW estimate. However, such exceptions should be quite rare since the SCI-GROW model is based exclusively on maximum ground water concentrations from studies conducted at sites and under conditions which are most likely to result in ground water contamination. The ground water concentrations generated by SCI-GROW are based on the largest 90-day average recorded during the sampling period. Since there is relatively little temporal variation on ground water concentrations compared to surface water, the concentrations can be considered as acute and chronic values. It should be noted that the SCI-GROW model defaults to a screening concentration of 6 ppt for immobile compounds (Koc>9995).

4.2.2.3 Surface Water

Refined surface water concentrations were developed for emamectin and its metabolites using PRZM/EXAMS model. The model assumes that emamectin is applied at the maximum label rate (0.015 lb ai/acre; maximum 0.09 lb ai/acre/season). The results indicate that emamectin and its metabolites have a very low potential to reach surface waters as dissolved

species. However, emamectin does have the potential to reach surface water bodies through erosion of soil particles to which the compound is sorbed. The estimated environmental concentrations of emamectin and its metabolites in surface water range from the peak concentration of 107.22 pptr (0.000107 ppm) to the 90-day average of 24.13 pptr (0.000024 ppm). These numbers were used to compare to HED's DWLOCs for emamectin and its metabolites.

4.2.2.4 Drinking Water Levels of Comparison (DWLOCs) for Acute Exposure

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit of a pesticide's concentration in drinking water in light of total aggregate exposure to that pesticide in food and through residential uses. A DWLOC will vary depending on the toxic endpoint, consumption and body weight. Different populations will have different DWLOCs. OPP uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, the DWLOC is used as a point of comparison against conservative model estimates of potential pesticide concentration in water. DWLOC values are not regulatory standards for drinking water.

HED has calculated DWLOCs for chronic (non-cancer) exposure to emamectin and its metabolites for the U.S. population and selected subgroups. Values for acute and chronic DWLOCs are presented in Tables 7 and 8, respectively, below.

Table 7. Summary of Acute DWLOC Calculations.

Population Subgroup[1]	Acute Scenario					
	Acute PAD (mg/kg/day)	Acute Food Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)[2]	SCI-GROW (µg/L)	PRZM/ EXAMS (ppb)	DWLOC (µg/L)
U.S. Population	0.00025	0.000078	0.000172	0.006	0.107	6
Children (1-6 years)	0.00025	0.000163	0.000087	0.006	0.107	1
Females 13+ years/nursing	0.00025	0.000067	0.000183	0.006	0.107	5

[1]Population subgroups chosen were U.S. population (70 kg. body weight assumed), and the two children subgroups with the highest food exposure (10 kg. body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = Acute PAD (mg/kg/day) - ARC from DEEM (mg/kg/day)

4.2.2.5 Drinking Water Levels of Comparison (DWLOCs) for Chronic Exposure

Table 8. Summary of Chronic DWLOC Calculations.

Population Subgroup[1]	Chronic Scenario					
	Chronic PAD (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Maximum Water Exposure (mg/kg/day)[2]	SCI-GROW (µg/L)[3]	PRZM/EXAMS (ppb)	DWLOC (µg/L)
U.S. Population	0.000083	0.000003	0.00008	0.0006	0.0203	3
Children (1-6 years)	0.000083	0.000004	0.00008	0.0006	0.0203	1
Females (13+ years)	0.000083	0.000004	0.00008	0.0006	0.0203	2

[1]Population subgroups chosen were U.S. population (70 kg. body weight assumed), the infant or children subgroup with the highest food exposure (10 kg. body weight assumed), and females 13+ (60 kg body weight assumed).
[2]Maximum Water Exposure (mg/kg/day) = Chronic RfD (mg/kg/day) - ARC from DEEM (mg/kg/day)
[3]The crop producing the highest level was used.

The estimated maximum concentrations of emamectin and its metabolites in surface and ground water are less than HED's DWLOCs as a contribution to acute and chronic aggregate exposure. The estimated concentrations of emamectin and its metabolites in ground and surface water are conservative estimates. Therefore, HED concludes with reasonable certainty that residues of emamectin in food and drinking water would not result in an unacceptable estimate of acute or chronic (non-cancer) aggregate human health at this time.

4.3 Occupational Exposure

An assessment of occupational exposure and risk is included in HED's memo: *Occupational and Residential Risk Assessment to Support Request for Establishment of Tolerance of Emamectin on Cole Crops and Leafy Vegetables* (dated 2/24/99, Attachment #5).

Workers may be exposed to emamectin during mixing, loading, application, and postapplication activities. Based on the proposed application rates, short and intermediate-term exposures may occur. Chronic exposures (≥6 months of continuous exposure) are not expected.

The highest rate for a single application of emamectin on cole crops and leafy vegtables is 0.015 pounds of active ingredient per acre (lb ai/A). This rate was used for assessing risk to workers.

4.3.1 Handler Exposure and Risk

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with HED's Exposure Science Advisory Council (SAC) policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 as presented

in PHED Surrogate Exposure Guide (8/98) was used with other HED default values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. Dermal and inhalation absorption rates used for this assessment were 1.8% and 100%, respectively. Daily dermal and inhalation exposures were summed and then compared to the short- and intermediate- term oral NOAEL of 0.075 mg/kg/day. The MOEs calculated for mixer/loader (soluble granular) and groundboom applicator are 2,300 and 4,400, respectively. For workers, MOEs of 100 or greater do not exceed HED's level of concern. See Table 9 below for specific exposure data.

Table 9. Exposure and Risk Assessment for Occupational Handlers

PHED Scenario Selected from PSEG (8/98)	Personal Protective Equipment	Exposure Route	Application Rate (lb ai/acre)	Acres Treated (acres/day)	PHED Unit Exposure (mg/lb ai)	PHED Data Confidence Level	Absorption Factor	Body Wt (kg)	Daily Dose[1] (mg/kg/day)		Short- and Intermediate-Term Dermal	
											NOAEL (mg/kg/day)	MOE[2]
Mix/load : Dry Flowable, Open Mixing	Long Sleeves, Long Pants, Gloves	Dermal	0.015	80	0.066	High	0.018	70	2.0E-5	Total = 3.3E-5	0.075	2,300
		Inhalation	0.015	80	0.00077	High	1.0	70	1.3E-5			
Groundboom: Open Cab	Long Sleeves, Long Pants, Gloves	Dermal	0.015	80	0.014	Medium	0.018	70	4.3E-06	Total = 1.7E-5		4,400
		Inhalation	0.015	80	0.00074	High	1.0	70	1.3E-5			

[1] Daily Dose =[Application Rate (lb ai/A) x Acres Treated (A/day) x Unit Exposure(mg/lb ai handled) x Absorption Factor]/Body Weight

[2] MOE = NOAEL/Daily Dose

Table 10. Exposure and Risk Assessment for Occupational Postapplication Activities

Work Activity	Application Rate (lb ai/A)	Post-application Day (t)	Fraction of ai Retained on the Foliage	Fraction of Residue That Dissipates Daily	Dislodgeable Foliar Residue (ug/cm^2)	Dermal Transfer Coefficient (cm^2/hr)	Exposure Time (hrs/day)	Dermal Absorption Factor	Body Wt (kg)	Daily Dose[2] (mg/kg/day)	Short- and Intermediate- Term Dermal	
											NOAEL (mg/kg/day)	MOE[3]
Hand Harvest[4]	0.015	0	0.2	0.1	0.034	**2,500**	8	0.018	70	1.7E-4	0.075	440
Scouting and Irrigating	0.015	0	0.2	0.1	0.034	**1,000**	8	0.018	70	7.0E-5		1,100

[1] Dislodgeable Foliar Residue $_{Postapplication\ day}$ (ug/cm^2) = Application rate (lb ai/A) x Fraction of ai Retained on the Foliage x (1- Fraction of Residue That Dissipates Daily) $_{Postapplication\ day}$ x 4.54E+8 ug/lb x 24.7E-9 A/cm^2

[2] Daily Dose = (Dislodgeable Foliar Residue x Absorption Factor x 0.001 mg/ug x Dermal Transfer Coefficient x Exposure Time)/Body weight

[3] MOE = NOAEL/Daily Dose

[4] Hand Harvesting includes other tasks such as thinning leaves (pulling and topping).

4.3.2 Post Application Exposure and Risk

No chemical-specific postapplication exposure data were submitted in support of this Section 3 registration. Therefore, HED default assumptions for dermal transfer coefficient, exposure time, and residue dissipation were selected in accordance with current HED Exposure SAC policy. It was assumed that on the day of application, 20% of the application rate is retained on the foliage. Dermal transfer coefficients of 2,500 cm^2/hr for hand harvest and 1,000 cm^2/hr for scouting/ irrigation were also assumed. Using estimated residue levels for the initial day of application, short- and intermediate-term MOEs are above 100. See Table 10 above for details on the postapplication exposure assessment.

Draft product labels for Proclaim 0.16EC and Proclaim 5 SG have a 12-hour restricted entry interval (REI). The technical material is in Acute Toxicity Category 1 for primary eye irritation. **Therefore, a 48-hour REI is required to comply with the Agency's Worker Protection Standard.**

4.3.3 Occupational Risk-Characterization

HED's exposure and risk estimates (for handlers and workers performing post-application activities) are assumed to be central-tendency to high-end. Furthermore, HED believes that these are reasonable estimates that **do not underestimate** the exposure and risk. See HED's memo: *Occupational and Residential Risk Assessment to Support Request for Establishment of Tolerance of Emamectin on Cole Crops and Leafy Vegetables* (dated 2/24/99) for further information regarding occupational exposure and risk (Attachment #5).

4.4 Residential Exposure

According to HED's REFs, there are no registered residential uses for emamectin. The proposed uses of emamectin in this registration action are not expected to result in residential exposure. Therefore, HED did not calculate residential risk estimates.

4.5 Cumulative Risk Assessment

Emamectin is synthetically derived from avermectin, which is derived from the antibiotic-producing actinomycetes, the source of all of the antibiotic fungicides. Streptomyces avermitilus produces the insecticide abamectin, which is a mixture of two homologs, avermectin B_1a and B_1b, which have equal biological activity. Currently, the only member of this class which is registered for agricultural uses is abamectin. Avermectin and ivermectin are structurally similar to emamectin.

For the purposes of this tolerance action, EPA has not assumed that emamectin has a common mechanism of toxicity with other substances.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

5.1 Acute Aggregate Risk

As discussed earlier in Section 4.2.1.1 above, exposure to emamectin residues in food will occupy no more than 31% of the acute PAD for adult population subgroups and no more than 65% PAD for infant/children subgroups. Residue levels used for food-source dietary risk assessments were partially refined and did incorporate percent of crop treated information. Acute dietary exposure estimates were for the 99.9th percentile. As discussed earlier in 4.2.2.4, estimated concentrations of emamectin residues in surface and ground water are lower than HED's DWLOCs. Estimated drinking water levels were calculated using EFEDs drinking water models, and the values are considered conservative. Therefore, HED does not expect chronic aggregate risk to emamectin residues from food and water sources to exceed HED's level of concern for chronic aggregate risk.

5.2 Short-and Intermediate Term Aggregate Risk

Not applicable.

5.3 Chronic (Non-Cancer) Aggregate Risk

As discussed earlier in Section 4.2.1.2 above, exposure to emamectin residues in food will occupy no more than 4% of the chronic RfD for adult population subgroups and no more than 5% PAD for infant/children subgroups. Residue levels used for food-source dietary risk assessments were partially refined and did incorporate percent of crop treated information. As discussed earlier in 4.2.2.5, estimated concentrations of emamectin residues in surface and ground water are lower than HED's DWLOCs. Estimated drinking water levels were calculated using EFEDs drinking water models, and the values are considered conservative. Therefore, HED does not expect chronic aggregate risk to emamectin residues from food and water sources to exceed HED's level of concern for chronic aggregate risk.

5.4 Cancer Aggregate Risk

Not applicable. There is no evidence of carcinogenicity.

6.0 DATA NEEDS

The Restricted Entry Interval (REI) is based on acute toxicity of emamectin, which is classified in Acute Toxicity Category 1 for primary eye irritation. Therefore, a 48-hour REI is required to comply with the Agency's Worker Protection Standard (WPS). **The Registration Division should ensure that a 48-hour REI appears on all emamectin labels.** Per the WPS, the minimum level of personal protective equipment (PPE) is based on the acute toxicity of the

end use product. OPP's Registration Division (RD) is responsible for ensuring the PPE listed on the label is in compliance with the Worker Protection Standard.

Attachments

1. *Emamectin: Report of the Hazard Identification Assessment Review Committee.* J. Rowland. 03/19/98. HED Doc. No. 012595.
2. *Emamectin: Report of the FQPA Safety Factor Committee.* B. Tarplee and J. Rowland. 04/23/98. HED Doc. No. 012595.
3. *Emamectin: ADDENDUM report of the Hazard Identification Assessment Review Committeee.* J. Rowland. 09/24/98. HED Doc. No. 012882.
4. *Emamectin: Acute and Chronic Dietary Risk Analysis for the Request for Tolerances on Broccoli, Brussels Sprouts, Cabbage, Cauliflower, Lettuce and Celery.* W. Cutchin. 03/11/99.

4a. *PP#6F4628. Emamectin Benzoate on Broccoli, Brussels Sprouts, Cauliflower, Head Lettuce and Celery. Revised Sections G and F. Supplemental Residue Data for the Registration of the Soluble Granular Formulation.* W. Cutchin. 01/26/99.

5. *Occupational and Residential Risk Assessment to Support request for Establishment of Tolerance of Emamectin on Cole Crops and Leafy Vegetables.* S. Weiss. 02/24/99.
6. *Drinking Water Assessment for Emamectin Benzoate*. R. Bloom. 12/02/97. D228127.

6a. *Revised Drinking Water Assessment for Emamectin Benzoate.* R. Bloom. 04/02/98.

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