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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: September 26, 2017

Subject: **Emamectin (Emamectin Benzoate).** Human Health Draft Risk Assessment in Support of Registration Review.

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As part of Registration Review, the Pesticide Re-Evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the hazard and exposure data and conduct dietary (food and drinking water), residential, aggregate, and occupational exposure assessments to estimate the risk to human health that may result from the currently registered uses of emamectin benzoate (referred to in this assessment as emamectin). This memorandum serves as HED's draft human health risk assessment of the dietary, residential, aggregate, and occupational exposures and risks from the registered uses of emamectin. The most recent quantitative human health aggregate risk assessment was completed in 2013 (N. Dodd, D402151, 04/12/2013).

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1.0 Executive Summary

The active ingredient (ai) emamectin benzoate (referred to in this assessment as emamectin) is a mixture of approximately 90% 4′-epi-methylamino-4′-deoxyavermectin B_{1a} and 10% 4′-epi-methylamino-4′-deoxyavermectin B_{1b}. Emamectin is a natural fermentation product of the soil bacterium *Streptomyces avermitilis* and is an insecticide/miticide developed to control insect species by interfering with the nervous system, causing paralysis. Emamectin and abamectin form the candidate common mechanism group (CMG) of the avermectin macrocyclic lactones. The screening-level cumulative risk assessment of the avermectin macrocyclic lactones has been updated and is addressed in a separate assessment (L. Bacon, D442232, 09/26/2017).

Use Profile

Emamectin is registered for agricultural uses and outdoor ornamental nursery production, as a special local need (SLN) on soybean and corn grown for seed by authorized personnel only for research purposes in Puerto Rico only, as a tree injection use, and as a ready-to-use (RTU) gel bait in commercial and residential settings. With the exception of the bait and some tree injection uses, all registered emamectin end-use products are currently designated as restricted use products (RUPs) (i.e., for use by professional certified operators only). Emamectin products are formulated into emulsifiable or soluble concentrate (EC/SC) liquid, RTU liquid and gel, and water dispersible/soluble granule (WDG) formulations that contain between 0.1% and 5% of the ai. Most of the registered products are applied either via aerial, chemigation, airblast, or groundboom equipment; or with handheld equipment. The clothing or personal protective equipment (PPE) requirements for occupational workers vary by formulation and use site; however, all workers that handle emamectin products (with the exception of the RTU gel bait) are required to wear a long-sleeved shirt, long pants, gloves, and shoes plus socks. Where applicable, the restricted entry interval (REI) for emamectin is 12 hours, with the exception of the activities of poling, pruning, and thinning for tree nuts; and propping, pruning, training, thinning, and tying for pome fruit. The REI for those activities is currently 48 hours.

Exposure Profile

Acute and chronic dietary exposures are expected from the existing uses of emamectin. Residential handler non-dietary exposure is not expected, as the labeled uses are not intended for homeowner application or are expected to result in negligible exposures. Post-application residential exposures are not anticipated based on the registered use patterns. In an occupational setting, workers may be exposed while handling the pesticide prior to application, during application, or when entering previously treated areas. The short- and intermediate-term point of departure (POD) is the same, so results of the short-term risk assessment will be protective of intermediate-term exposures. Non-occupational short-term exposures may occur as a result of spray drift from applications of emamectin.

Hazard Assessment

The toxicology database for emamectin is considered complete with respect to guideline toxicity studies. In general, available toxicity data for emamectin showed that with a single dose or repeated dose administration, the primary target organ was the nervous system and that decreased body weight was also one of the most frequent findings. The toxicity endpoints and PODs for all exposure scenarios have been selected from the subchronic and chronic oral toxicity

studies in dogs, based on species sensitivities and review of relevant literature information. The adverse effects seen in the dog studies included clinical signs and neuropathology findings. The POD selected from the dog studies is based on clear no observed adverse effect levels (NOAELs) of 0.25 mg/kg/day that are protective of all adverse effects seen in human-relevant studies conducted in rats, CD-1 mice, and rabbits. Therefore, the Food Quality Protection Act (FQPA) safety factor has been reduced to 1x. The level of concern (LOC) is a margin of exposure (MOE) of 100 for all exposure scenarios (i.e., MOEs < the LOC of 100 are of concern). Emamectin is classified as "not likely to be carcinogenic to humans" based on the absence of compound-related increases in tumor incidence in two adequate rodent (rats and mice) carcinogenicity studies.

Residue Chemistry and Tolerance Enforcement

The residue chemistry database for emamectin is sufficient to support the current registrations of emamectin. The residues of concern for tolerance enforcement are emamectin (MAB_{1a} + MAB_{1b}), the associated 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}), and metabolites/photodegradates AB_{1a}, MFB_{1a}, and FAB_{1a}. Adequate storage stability, field trial, and rotational crop data are available. U.S. tolerances are established for residues of emamectin on several plant and livestock commodities to support the registered agricultural uses. Tolerance recommendations were based on use of the Organization for Economic Cooperation and Development (OECD) Maximum Residue Limit (MRL) calculation procedures, international harmonization considerations, and data translation where appropriate.

Dietary (Food and Water) Exposure and Risk

Acute and chronic dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID), Version 3.16. The acute dietary exposure assessment was a probabilistic assessment for food and drinking water using anticipated residues based on field trial data. The chronic dietary exposure assessment was a somewhat refined assessment for food and drinking water using single point estimates (averages) of anticipated residues based on field trials. Tolerance-level residues were used for tree nuts, cottonseed oil, and grape, wine. Refinements for both the acute and chronic assessments included percent crop treated (PCT) where available, DEEM default processing factors where appropriate, chemical-specific processing factors where available, and anticipated residues based on field trial data for most crops. For the acute assessment, Pesticide Monitoring Program (PDP) data were used for apples, since apple juice contributed significantly to the exposure. A residue distribution file of estimated drinking water concentrations (EDWCs) was used for the acute assessment. A point estimate of EDWC of 0.366 µg/L (ppb) was used for the chronic assessment.

The acute dietary exposure estimates for food and drinking water are below HED's LOC [<100% of the acute population adjusted dose (aPAD)] at the 99.9th percentile of exposure for all population subgroups (20% of the aPAD for the general U.S. population and 44% of the aPAD for all infants < 1 year old, the most highly exposed population subgroup).

Although the acute and chronic dietary PODs are the same for both durations, a chronic dietary exposure assessment was conducted for emamectin for the purpose of the cumulative risk assessment. The chronic dietary exposure estimates for food and drinking water are below

HED's LOC [<100% of the chronic population adjusted dose (cPAD)] for all population subgroups (3.3% of the cPAD for the general U.S. population and 8.1% of the cPAD for all infants < 1 year old).

Tobacco Inhalation Exposure and Risk
Although the use of a pesticide on tobacco is classified as a non-food use and does not require a tolerance or exemption, the Agency has considered the exposure to humans from emamectin residues in tobacco smoke by assessing the short-term inhalation exposure and risks. For the inhalation route of exposure, there were no risk estimates of concern identified in this assessment (i.e. MOE ≥ 100), with the resulting MOE risk estimate of 18,000 for adult smokers.

Residential Exposure and Risk
While emamectin is registered for use as a crack and crevice ready-to-use (RTU) gel bait in and around residential areas, residential exposure is expected to be negligible and a quantitative assessment was not conducted for the use. There are additionally no post-application residential exposures anticipated for adults or children. Therefore, there are no residential MOEs for consideration in the aggregate risk assessment for emamectin.

Aggregate Exposure and Risk
A residential exposure assessment has not been conducted and there are no residential risk estimates recommended for use in the aggregate risk assessment for emamectin. Therefore, all aggregate risk estimates are expected to be equivalent to dietary (food and drinking water) risk estimates and are not of concern.

Non-Occupational Spray Drift Exposure and Risk
Emamectin can be applied via ground, airblast, or aerial equipment, which could result in off-target movement of emamectin residues. A quantitative non-occupational spray drift assessment was conducted for the registered uses of emamectin. Adult dermal and children's (1 to < 2 years old) dermal and incidental oral risk estimates from indirect exposure related to spray drift were assessed. The results of the spray drift assessment indicate dermal MOEs for adults ranged from 17,000 to 31,000 at the field edge (LOC = 100). The combined dermal and incidental oral MOEs at the edge of the field for children 1 to < 2 years old ranged from 2,900 to 5,100 (LOC = 100). These MOEs are not of concern.

Occupational Exposure and Risk
Occupational handler dermal and inhalation exposure and risk estimates were calculated for the registered uses of emamectin. The results of the occupational handler exposure and risk assessments indicate that short- and intermediate-term combined dermal and inhalation risk estimates resulted in MOEs greater than the LOC with baseline attire and without PPE (i.e., no gloves or respirator). Short- and intermediate-term combined dermal and inhalation MOEs ranged from 110 to 520,000 (LOC = 100). Note that only engineering control (enclosed cockpit) data are available to assess risks to handlers operating aircrafts. These MOEs are not of concern.

Occupational post-application dermal exposure and risk estimates were assessed for all registered uses of emamectin using submitted chemical-specific dislodgeable foliar residue (DFR) data. Based on the current exposure assessment, post-application risk estimates are not of

concern at the day of application. Only the highest crop/transfer coefficient combination for each crop category was presented in the assessment; these MOEs are considered protective of all other registered crops in that category and their associated activities. The worst-case MOEs by crop category ranged from 920 to 33,000 on the day of application (LOC = 100). These MOEs are not of concern. Current product label restricted entry intervals (REIs) are generally 12 hours.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for emamectin at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for emamectin.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix G provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

2.0 HED Risk Assessment Conclusions

Acute and chronic dietary exposure and risk estimates are not of concern to HED for the existing uses of emamectin. Residential exposures are not anticipated. Therefore, aggregate risks are equivalent to dietary risk estimates and are not of concern.

The tobacco inhalation assessment exposure and risk estimate is not of concern to HED.

At the field edge, there were no non-occupational spray drift dermal risk estimates of concern for adults, and no combined dermal and incidental oral risk estimates of concern for children 1 to < 2 years old.

The occupational handler dermal, inhalation and combined (dermal and inhalation) risk estimates are not of concern for the existing uses of emamectin with baseline attire and without PPE. All occupational post-application dermal exposures were not of concern on the day of application.

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate methods (Method 244-92-3 and Method 244-92-3, Revision 1) are available for the enforcement of tolerances on plants. The methods determine residues of emamectin and its regulated isomers and degradates/metabolites using high performance liquid chromatography with fluorescence detection (HPLC/FLD). The methods determine residues of emamectin in the following analyte combinations: MAB_{1a} + 8,9-ZB_{1a}, MAB_{1b} + 8,9-ZB_{1b}, AB_{1a}, and MFB_{1a} + FAB_{1a}, with a limit of quantitation (LOQ) of 0.005 parts per million (ppm) for each analyte or analyte combination, for a combined LOQ of 0.02 ppm.

2.2.2 Recommended Tolerance Revisions

Tolerances have been established for residues of emamectin in 40 CFR §180.505. The current tolerance expression in 40 CFR §180.505 is consistent with the S. Knizner memo, dated 5/27/09. The proposed tolerance changes are a result of crop group revisions and new crop group updates. The recommended revisions to the currently established tolerances in 40 CFR §180.505 are presented in Table 2.2.2.; other than these recommended revisions, the other tolerance entries are not recommended to be updated at this time. These changes are summarized as follows:

Update crop groups and commodity terminology
HED is recommending to update several previously-established crop group or subgroup tolerances resulting from crop group updates. The existing Pome fruit group 11; Tree nut group 14; and Fruiting vegetable tolerances should be updated to Pome fruit group 11-10; Tree nut group 14-12; and Fruiting vegetable group 8-10, respectively. In addition, the existing tolerance

for vegetable *Brassica* leafy group 5 should be updated to *Brassica* head and stem vegetable group 5-16 and *Brassica* leafy greens subgroup 4-16B and the existing tolerance for vegetable leafy except *Brassica* group 4 should be updated to Leafy greens subgroup 4-16A; and Leaf petiole vegetable subgroup 22B. Furthermore, individual tolerances for celtuce, fennel Florence and kohlrabi need to be established.

Revise established tolerances
HED is recommending to revise some established tolerances to express these limits with the appropriate number of significant figures.

Remove established tolerance on pistachio
HED is recommending to remove the existing U.S. tolerance for pistachio since this commodity is included in Tree nut group 14-12.

Table 2.2.2. Tolerance Summary for Emamectin.

Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
40 CFR §180.505(a)(1)			
Fruit, pome, group 11	0.025	0.025	*Fruit, pome, group 11-10*
Nut, tree, group 14	0.02	0.02	*Nut, tree, group 14-12*
Pistachio	0.02	None	Remove. Covered by *Nut, tree, group 14-12 tolerance at 0.02 ppm*
Tomato, paste	0.150	0.15	Significant figure revision.
Turnip, greens	0.050	None	Remove. covered by *Vegetable, Brassica, leafy greens group 4-16B tolerance at 0.05 ppm*
Vegetable, Brassica, leafy, group 5	0.050	0.05	*Vegetable, head and stem Brassica, group 5-16 tolerance*
		0.05	*Vegetable, Brassica, leafy greens group 4-16B tolerance*
	None	0.05	*Kohlrabi*
Vegetable, fruiting, group 8	0.020	0.02	*Vegetable, fruiting, group 8-10*
Vegetable, leafy, except Brassica, group 4	0.100	0.10	*Vegetable, leafy greens group 4-16A tolerance at 0.10 ppm*
			Vegetable, leafy petioles, group 22B tolerance at 0.10 ppm
		0.10	*Celtuce*
		0.10	*Fennel, Florence*

2.2.3 International Harmonization

The U.S. and Codex residue definitions are not harmonized. The U.S. residue definition for emamectin includes the sum of emamectin and its metabolites (8,9-isomer) for plants and livestock. The Codex residue definition includes only emamectin for plants and livestock commodities. There are no Canadian maximum residue limits (MRLs) established for emamectin.

Codex has established MRLs for emamectin on various crop commodities. Most of the available Codex MRL values are not in harmony with the U.S. The Codex MRL for fruiting vegetables is harmonized with the U.S. For numerous additional commodities, there are no Codex MRLs. The Federal Food Drug and Cosmetic Act (FFDCA) requires the Agency to harmonize tolerances with Codex MRLs to the extent possible.

HED is not proposing revisions to the established tolerances for harmonization purposes. The registrant could propose revisions depending on trading priorities. HED also encourages the registrant to include a discussion on harmonization of U.S. tolerances with Codex MRLs when providing input on tolerance revisions.

For a complete summary of U.S. tolerances, international tolerances, and MRLs for plant and livestock commodities, refer to Appendix F.

2.3 Label Recommendations

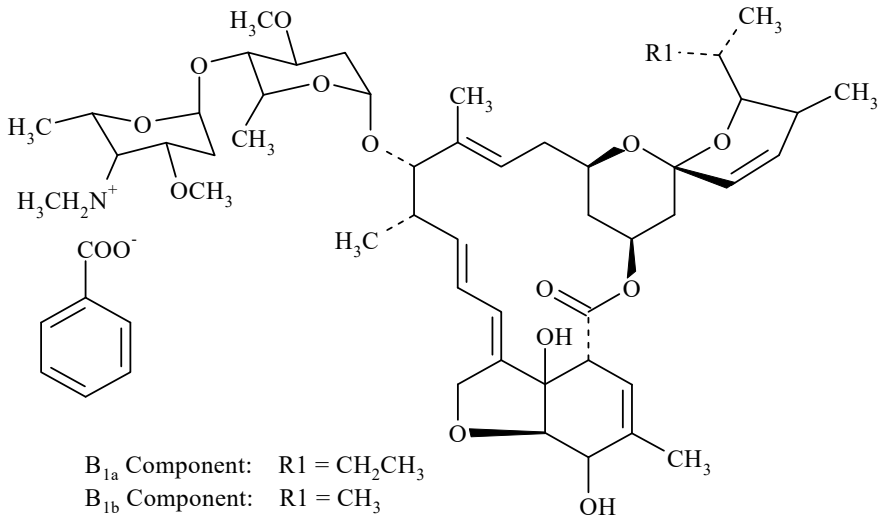
None.

3.0 Introduction

3.1 Chemical Identity

Emamectin is a semi-synthetic avermectin, consisting of two active homologous compounds (a benzoate salt 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}). Emamectin is a natural fermentation product of the soil bacterium *Streptomyces avermitilis* and is an insecticide/miticide developed to control insect species by interfering with the nervous system, causing insect paralysis. Emamectin and abamectin form the candidate CMG of the avermectin macrocyclic lactones.

Tolerances have been established for emamectin in 40 CFR §180.505, including its metabolites and degradates, in or on various crop and livestock commodities at levels ranging from 0.003 ppm to 0.20 ppm. The nomenclature of emamectin is summarized in Table 3.1.

Table 3.1 Test Compound Emamectin Nomenclature	
Chemical Structure	
Empirical Formula	emamectin benzoate B_{1a}: $C_{49}H_{75}NO_{13} \bullet C_7H_6O_2$ emamectin benzoate B_{1b}: $C_{48}H_{73}NO_{13} \bullet C_7H_6O_2$
Common Name	emamectin benzoate; emamectin
Company experimental name	MK244
IUPAC name	Mixture of (10*E*,14*E*,16*E*)-(1*R*,4*S*,5'*S*,6*S*,6'*R*,8*R*,12*S*,13*S*,20*R*,21*R*,24*S*)-6'-[(*S*)-*sec*-butyl]-21,24-dihydroxy-5',11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene)-6-spiro-2'-(5',6'-dihydro-2'*H*-pyran)-12-yl 2,6-dideoxy-3-*O*-methyl-4-*O*-(2,4,6-trideoxy-3-*O*-methyl-4-methylamino-α-L-*lyxo*-hexapyranosyl)-α-L-*arabino*-hexapyranoside benzoate and (10*E*,14*E*,16*E*)-(1*R*,4*S*,5'*S*,6*S*,6'*R*,8*R*,12*S*,13*S*,20*R*,21*R*,24*S*)-21,24-dihydroxy-6'-isopropyl-5',11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene)-6-spiro-2'-(5',6'-dihydro-2'*H*-pyran)-12-yl 2,6-dideoxy-3-*O*-methyl-4-*O*-(2,4,6-trideoxy-3-*O*-methyl-4-methylamino-α-L-*lyxo*-hexapyranosyl)-α-L-*arabino*-hexapyranoside benzoate
CAS Name	(4"R)-4"-deoxy-4"-(methylamino)avermectin B_1 benzoate (salt)
CAS Registry Number	155569-91-8 (formerly 137512-74-4)
Chemical Class	Macrocyclic lactone; Insecticide/Miticide
Known impurities of concern	None

3.2 Physical/Chemical Characteristics

Emamectin is a solid at room temperature with a low vapor pressure; thus, any losses due to volatilization/sublimation are expected to be minimal. Emamectin, the 8,9-Z isomer, AB, MFB, and FAB are expected to be persistent and relatively immobile in the environment due to high degree of sorption to soil particles (K_{OC} from 25,363 to 730,000). Based upon fate data, significant concentrations of parent or formed degradates of toxicological concern are not expected to leach into ground water. Refer to Appendix B for the table of physical/chemical properties.

3.3 Pesticide Use Pattern

Emamectin is registered for use on cotton, pome fruit, tree nuts, leafy vegetables (*Brassica* and non-*Brassica*), fruiting vegetables, turnip greens, and tobacco; on field and container-grown ornamentals and Christmas trees for commercial nursery production; as a tree injection use, as a bait in commercial and residential settings; and as a special local need (SLN) on soybean and corn grown by authorized personnel only for seed for research purposes (Puerto Rico only). There are eight active end-use products for emamectin and two SLN registrations. With the exception of the bait, all registered emamectin end-use products are restricted use products (RUPs) or are limited to non-residential areas. Emamectin products are formulated into EC/SC liquid, RTU liquid or gel, and WDG formulations that contain between 0.1% and 5% of the ai. Appendix C provides the summary of use directions for the registered uses of emamectin. This information was synthesized from the Pesticide Label Use Summary Report, compiled by the Biological and Economic Analysis Division (BEAD) of OPP, with additional review of individual end-use product registrations.

3.4 Anticipated Exposure Pathways

Humans may be exposed to emamectin in food and drinking water, since emamectin may be applied directly to growing crops and in outdoor settings which may result in residues in foods or residues reaching sources of drinking water. Residential handler exposure is not expected based on the use patterns and registered labels.

In occupational settings, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated fields.

There is a potential for spray drift of emamectin residues that may result in exposures in non-occupational settings. Additionally, there is the potential for inhalation of tobacco products that have been previously treated with emamectin. This risk assessment considers all of the aforementioned exposure pathways based on the existing emamectin uses.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are

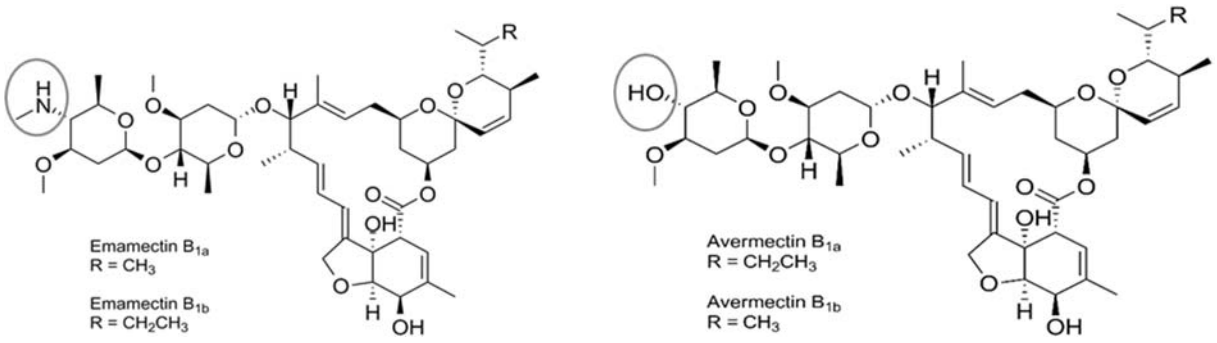
analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures are also evaluated based on home use of pesticide products which includes calculating associated risks for adult applicators and for toddlers, youths, and adults entering or playing in previously treated areas. Spray drift can also potentially result in exposure and it was also considered in this analysis. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

As mentioned in Section 3, emamectin is a derivative of abamectin. Emamectin is a mixture of two components, B_{1a} and B_{1b}, which have similar biological and toxicological properties. The only difference between abamectin and emamectin is that the hydroxyl moiety at the 4" position of the tetrahydropyran ring in abamectin is replaced by a methylamine moiety to become emamectin (circled groups in the following figures).

Figure 4.1. Chemical Structures

Emamectin **Abamectin**



Since the last completed quantitative risk assessment for emamectin (N. Dodd, D402151, 04/12/2013), the Agency has re-evaluated the entire emamectin and abamectin toxicological databases to ensure consistent hazard evaluation for these structurally related pesticides. The updated hazard characterization and dose-response assessment represents a more refined analysis than previous assessments, using the literature data to enhance the characterization of the studies submitted to the Agency. In 2016, the two chemicals were screened for the potential for cumulative risk. While no common mechanism group has been established for the avermectin macrocyclic lactones of abamectin and emamectin (*i.e.,* key events leading from the molecular initiating event to apical neurotoxicity cannot be causally determined), the Agency conducted a screening level cumulative evaluation based on screening guidance, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. The framework was

used to assess the potential for cumulative risk and the extent to which additional toxicity information is needed to determine the key events for a common mechanism grouping. That screening-level cumulative assessment was previously conducted in conjunction with a risk assessment on abamectin (D426599, L. Nollen, 04/18/2016).

For the purposes of Registration Review, and in consideration of an additional new use for abamectin, an updated screening-level cumulative assessment was conducted for the avermectin macrocyclic lactones, and that assessment may be relied upon for the purposes of this assessment (L. Bacon, D442232, 09/26/2017).

Mode of Action

While much of the mechanistic data for abamectin and emamectin were generated by using abamectin, emamectin is thought to act in a similar manner. In nematodes, abamectin blocks signal transmission from the central command interneurons to the peripheral motor neurons, leading to paralysis and death. In the mammalian toxicity studies submitted by the registrant, mydriasis, tremor and paralysis are the common findings prior to moribund sacrifice or death. The *in vitro* data derived from a primary culture of rat cerebellar granular neurons show that, on the cellular level, abamectin acts by binding to gamma-aminobutyric acid (GABA) gated chloride channels at two different sites, a high affinity binding site that activates the channel and a low affinity site that blocks the channel (Pong et al., 1982; Huang and Casida, 1997; and Dawson et. al., 2000). GABA plays a critical role in the nervous system through both non-synaptic (Represa and Ben-Ari, 2005) and synaptic (Nguyen et. al., 2001) mechanisms. The literature data show that, within the mammalian brain, abamectin binding to GABA receptors is widespread, but particularly abundant in the cerebellum (Wang and Pong, 1982). Abamectin also has been suggested to act on GABA receptors in the enteric nervous system and induces longitudinal rhythmic contractions in the isolated ileum (Kerr and Ong, 1986). Abamectin may, therefore, influence GABA-mediated regulation of metabolism, food intake and body weight at multiple sites (Meister, 2007). Although GABA receptor mediated neurotoxicity is a solid hypothesis, as described in detail in the cumulative risk assessment of the avermectin macrocyclic lactones, data in mammalian preparations linking alterations in GABA receptor function to disruptions in neuronal excitability *in vitro* and *in vivo,* and ultimately adverse outcomes, are currently lacking.

4.1 Toxicological Studies Available for Analysis

All of the required toxicity studies on emamectin are available, and the database is sufficient for selecting toxicity endpoints and PODs for risk assessment. The subchronic inhalation study has been waived (HASPOC Report, TXR 0051377, 03/12/2015). The studies available for this evaluation include:

- Subchronic oral toxicity studies in rats, dogs and mice,
- Combined chronic toxicity/carcinogenicity study in rats,
- Chronic toxicity study in dogs,
- Carcinogenicity study in mice,
- Developmental toxicity studies in rats and rabbits,
- Reproduction study in rats;

- Acute and subchronic neurotoxicity studies in rats;
- Developmental neurotoxicity study in rats;
- Mutagenicity studies; metabolism study in rats;
- Dermal absorption study in monkeys;
- 5-day inhalation study in rats,
- Immunotoxicity study- CD-1 mice
- 15-day neurotoxicity studies in CF-1 mice.

The toxicity profile table with a brief summary of all studies submitted may be found in Appendix A. Several literature studies were used for characterization and are cited throughout this document.

4.2 Absorption, Distribution, Metabolism, and Excretion (ADME)

With oral administration, emamectin is absorbed quickly; the absorbed radioactivity was quickly distributed into the tissues and eliminated via bile in feces mostly unchanged. The absorbed emamectin was approximated 20% of the administered dose. The times to maximal blood level were 6 hours and 11 hours for post-dosing low dose (0.5 mg/kg) and high dose (20 mg/kg), respectively. Greater than 83% of the administered dose was eliminated within 48 hours. Major portion of elimination was via feces (62-70% with 24 hours of dosing with lesser amount recovered in subsequent 24 hour). Urinary elimination accounted for <1% of the administered dose. At the termination of the study (7 days after dosing), the combined radioactivity from the tissues and carcass accounted for only 1.6% of the administered dose. The carcass and harderian gland were found to contain the highest residue levels (0.8% & 0.2% of the administered dose, respectively). Based on tissue distribution, biliary cannulation, and elimination data, a marginal amount of emamectin was metabolized by the rat. The predominant metabolite was N-demethylated compound.

4.2.1 Dermal Absorption

The results of a Rhesus monkey study indicated that dermal absorption was minimal and was approximately 1.8% of the administered dose.

4.3 Toxicological Effects

Consistent with the postulated mode of action as described in Section 4.0, the main target organ for emamectin is the nervous system; treatment-related clinical signs (tremors, ptosis, ataxia, mydriasis, and hunched posture) and neuropathology (neuronal degeneration in the brain and in peripheral nerves and muscle fiber degeneration) were found in most of the emamectin studies in rats, dogs, rabbits, and mice. Decreased body weight was also a frequent finding.

Integral to the dose-response assessment in mammals for this class of compounds is the role of P-glycoprotein (P-gp) in target tissues. P-gp is a member of adenosine triphosphate (ATP) binding cassette transporter proteins, which reside in the plasma membrane and function as a transmembrane efflux pump, moving xenobiotics from the intracellular to the extracellular domain. P-gp is found in the canallicular surface of hepatocytes, the apical surface of proximal tubular cells in the kidneys, brush border surface of enterocytes, luminal surface of blood capillaries of the brain (blood brain barrier), placenta, ovaries, and the testes. As an efflux

transporter, P-gp acts as a protective barrier to keep xenobiotics out of the body by excreting them into bile, urine, and intestinal lumen, and prevents accumulation of these compounds in the brain and gonads, as well as in the fetus. Therefore, test animals with genetic polymorphisms that compromise P-gp expression are particularly susceptible to emamectin and abamectin induced neurotoxicity (Lankas et al., 1997).

In this connection, some CF-1 mice have a polymorphism for the gene encoding P-gp and are either devoid (homozygous) or have diminished (heterozygous) levels of P-gp. These mice are found to be uniquely sensitive to the neurotoxic effects of emamectin and abamectin. In addition, the neonatal rat is also particularly sensitive to emamectin and abamectin as P-gp is undetectable in the neonatal rat brain. The first detection of P-gp is on post-natal day (PND) 7 and does not reach adult levels until approximately PND 28 (Matsuoka, 1998). As shown in the reproductive and DNT studies, neonatal rats are sensitive to the effects of abamectin induced pup body weight reductions and death. In contrast, in the developing human fetus, the presence of P-gp was found as early as 22 weeks of gestation (Daood, 2008; van Kalken, et al., 1991). Based on the difference in the ontogeny of P-gp in neonatal rats and human newborns, the Agency does not believe that the early post-natal findings in the rat are relevant to human newborns or young children, at this time.

The human multidrug resistance (*MDR-1*) gene encoding P-gp and polymorphism of *MDR-1* gene are well studied. The literature data are inconclusive with respect to the functional significance of the genetic variance in P-gp in human. Currently, the reported cases of polymorphism of the *MDR-1* gene in human populations have not been shown to result in a loss of P-gp function similar to that found in CF-1 mice (Macdonald & Gledhill, 2007). Given the ontogeny of P-gp and the lack of convincing evidence from the literature on human polymorphism of *MDR-1* gene resulting in diminished P-gp function, the Agency considers the results of the studies with CF-1 mice not relevant for human health risk assessment. Therefore, the Agency is using results from toxicological studies conducted in the species that do not have diminished P-gp function for selecting toxicity endpoints and PODs for risk assessment. Among the test animals with fully functional P-gp, the beagle dog is the most sensitive species. The details regarding the sensitivity of beagle dogs are presented in Appendix A, Section A.3.

Emamectin did not elicit increased sensitivity in developmental toxicity studies in rats and rabbits. In the reproductive toxicity study, emamectin produced neuronal degeneration in the brain and spinal in parental and offspring animals at similar dose level (1.8 mg/kg/day), and no increase in quantitative sensitivity was found in the pup with respect to the neurotoxicity. However, in the developmental neurotoxicity study in rats, there as an increase in both quantitative and qualitative sensitivity in the pups as no adverse effect was seen at the highest dose tested (3.6/2.5 mg/kg/day) in parental animals, while at 0.6 mg/kg/day, the pups showed a dose-related decrease in open field motor activity at post-natal day 17. Body tremors, hind-limb extension, and auditory startle were also observed in the high dose pups (3.6/2.5 mg/kg/day).

The carcinogenicity and mutagenicity studies provide no indication that emamectin is carcinogenic or mutagenic. Emamectin is classified as "not likely to be carcinogenic to humans." A toxicity profile for emamectin is presented in Appendix A.

The acute toxicity studies indicate that emamectin has low to moderate acute toxicity by the oral, dermal and inhalation routes. It is not irritating to the skin, nor is it a dermal sensitizer. However, depending on the technical test substance, emamectin has been shown to be a severe eye irritant. Appendix A provides details as to the acute toxicity profile for emamectin (Appendix A, Section A.2.).

4.4 Safety factor for Infants and Children (FQPA Safety Factor)[2]

The current analysis of the new information on the relevance of P-gp deficiency in neonatal rats and the effects seen in the pups led the Agency to re-assess the FQPA safety factor established in 2008 and used in previous risk assessments. The previous FQPA safety factor was 3x to account for the steepness of dose-response in CF-1 mice (Report of FQPA Safety Factor Committee, 4/23/1998). However, currently, the toxicity endpoint and point of departure for all exposure scenarios are selected from the subchronic and chronic oral toxicity studies in the dogs, which do not have steep dose-response curves. The point of departure was selected from the dog studies that were considered co-critical, and is based on clear a NOAEL and is protective of all the adverse effects seen in the studies conducted in rats, CD-1 mice, and rabbits. Therefore, the FQPA safety factor was reduced to 1x.

4.4.1 Completeness of the Toxicology Database

The toxicology database for emamectin is complete for human health risk assessment. A waiver request was granted for the subchronic inhalation toxicity study (TXR 0051377, J. Leshin, 03/12/2015). No outstanding data requirement exists for emamectin at this time.

4.4.2 Evidence of Neurotoxicity

The proposed MOA is interaction with GABA receptors leading to neurotoxicity. The clinical signs observed in the emamectin database are consistent with the proposed MOA. Following emamectin exposure, neurotoxicity has been seen across multiple studies and species of test animals. Neurotoxic effects seen in various studies are consistent with the MOA of emamectin, and the selected toxicity endpoints and POD is protective of the neurotoxic effects in the data.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

As discussed in Section 4.3, The developmental neurotoxicity study showed an increase in both quantitative and qualitative sensitivity in the pups as indicated by a dose-related decrease in open field motor activity at post-natal day 17 at 0.6 mg/kg/day. Body tremors, hind-limb extension, and auditory startle were also observed in the high dose pups (2.5 mg/kg/day), while no adverse effects were seen in the parental animals at the highest tested dose (3.6 mg/kg/day). However, the toxicity endpoint and POD selected for risk assessment are protective of the effects seen in the pups.

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties for emamectin with respect to the exposure databases. Although the dietary exposure estimates are partially refined, anticipated residue estimates for most commodities were derived from field trials which may still be considered conservative since field trials are conducted under maximum use conditions (maximum allowed application rate and number of applications, minimum pre-harvest interval, etc.). Monitoring data were used for apples in the acute assessment since apple juice had a significant impact on exposure. HED does not believe that the exposure estimates underestimate risk for the established uses of emamectin. EPA made conservative (protective) assumptions in the ground and surface water modeling used to assess exposure to emamectin in drinking water. There are no anticipated exposures to residential handlers, or for post-application exposure of adults and children. These assessments will not underestimate the exposure and risks posed by emamectin.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose Response Assessment

For emamectin, the previous risk assessment employed toxicity endpoints and points of departure derived from the results of CF-1 mice studies. Presently, HED has evaluated the entire toxicity database for emamectin along with that of abamectin and the currently available literature information on the polymorphisms in the human gene encoding P-gp. As mentioned in section 4.0, the toxic effects observed in CF-1 mouse studies are not considered representative of emamectin effects in human, and the CF-1 mouse studies will not be considered for toxicity endpoints and points of departure selections. The toxicity studies in rats, CD-1 mice and beagle dogs, demonstrated that beagle dogs are the next most sensitive species to the effects of abamectin and emamectin (Attachment A). In addition, the beagle dogs contain fully functioning P-gp. The Agency determined it was appropriate to use the results of the dog studies in selecting the toxicity endpoints and points of departure for risk assessment. The summaries of toxicity endpoints and points of departure for human health risk assessment are presented in Tables 4.5.1 and 4.5.2.

Acute Dietary Exposure Endpoint

For acute dietary exposure, whole body tremors, stiffness of the hind legs, axonal degeneration in the pons, medulla, and peripheral nerves (sciatic, sural, and tibial), spinal cord axonal degeneration, and muscle fiber degeneration seen at the LOAEL of 0.5 mg/kg in the subchronic (90-day) and chronic oral toxicity studies in dogs that were selected for this exposure scenario because these effects could be elicited by a single dose. The point of departure (NOAEL) was 0.25 mg/kg. The following support this selection: (1) kinetics data supporting rapid absorption/excretion, (2) acute neurotoxicity observed in rats, and (3) the effects produced by emamectin in beagle dogs did not progress with time.

> *Kinetic data*: Given that emamectin was shown to be readily absorbed (T_{max} at 4-8 hours), rapidly eliminated (≈90% by 48 hours post-dosing), and did not accumulate in the body with repeated dosing; the clinical signs and neuropathological effects seen in the dog

studies were likely resulting from individual dosing or single dose effect.

Acute neurotoxicity study in rats: The conclusion based on the kinetics data was confirmed by results from the acute neurotoxicity studies in rat (range finding and main studies) which showed that, with a single dose, the treated rats developed clinical signs of neurotoxicity such as reduced foot splay reflex, ataxia, tremors, and mydriasis. Most of these effects were consistent with those seen in the subchronic and chronic dog studies; similar effects were observed at higher dose levels as rats were relatively less sensitive to the effects of emamectin compared to the beagle dogs. Therefore, neurotoxicity seen in the emamectin dog studies were likely due to a single dose effect.

Effects seen in the subchronic and chronic dog studies: The effects seen in subchronic and chronic dog studies were similar in lesions and degree of severity, despite longer duration of treatment in the chronic study suggesting the response could be due to each individual exposure rather than to accumulation of emamectin in tissues. Purportedly, as the peak blood level of each administered dose passed, the response diminished or disappeared accordingly.

A total safety factor of 100x (10x for interspecies extrapolation, 10x for intraspecies variations, and 1x for FQPA SF) is appropriate and sufficient in establishing the acute reference dose (aRfD) (0.0025 mg/kg/day) for emamectin.

Chronic Dietary Exposure Endpoint

For chronic dietary exposure, toxicity endpoints are based on the clinical signs and neuropathology found in the subchronic and chronic oral toxicity studies in dogs. The point of departure is 0.25 mg/kg/day (NOAEL).

A total safety factor of 100x (10x for interspecies extrapolations, 10x for intraspecies variations, and 1x for FQPA SF) is appropriate and sufficient in establishing the chronic reference dose (cRfD) of 0.0025 mg/kg/day for emamectin.

Incidental Oral, Dermal, and Inhalation Exposure Endpoints

For short-term incidental oral, and short- and intermediate-term dermal and inhalation exposures, oral subchronic and chronic toxicity studies in dogs were chosen as co-critical studies to establish the toxicity endpoints and points of departure. For dermal exposure assessment a dermal absorption factor (DAF) was 1.8%, and for inhalation exposure assessment toxicity via the inhalation route was assumed to be equivalent to oral route. The adverse effects for establishing the toxicity endpoints are clinical signs and neuropathology findings from the subchronic and chronic toxicity studies in dogs as described before. The POD is 0.25 mg/kg/day. There is a dermal toxicity study in rabbits available, but the rabbits are less sensitive to the effects of emamectin compared to dogs. For inhalation, a subchronic inhalation study has been waived for emamectin (J. Leshin, TXR 0051377, 03/12/2015).

The use of the results from the dog studies in establishing the toxicity endpoint and point of departure (0.25 mg/kg/day) for the inhalation route is appropriate and protective for these exposure scenarios. Although the beagle dogs are more sensitive than rats, an inhalation toxicity

study is seldom conducted in dogs due to technical limitations.

Level of Concern (LOC) for Non-Occupational Risk Assessment: For residential or non-occupational exposure risk assessments, the LOC is 100 based on a total uncertainty factor of 100x (10x for interspecies extrapolation, 10x for intraspecies variations, and 1x for FQPA safety factor).

Level of Concern (LOC) for Occupational Risk Assessment: For occupational exposure risk assessments, the LOC is 100 based on a total uncertainty factor of 100x (10x for interspecies extrapolation and 10x for intraspecies variations).

Table 4.5.4.1 and 4.5.4.2 summarize the toxicity endpoints and points of departure for risk assessment for emamectin.

4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

When common toxicity endpoints are selected for the dermal, oral and inhalation routes of exposure, they may be considered together. Since the toxicity endpoints and PODs for emamectin were chosen from the same co-critical studies, these routes of exposure may be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

Emamectin was classified as "not likely" to be carcinogenic to humans based on the absence of significant increase in tumor incidence in two adequate rodent (i.e., rat and mouse) carcinogenicity studies.

4.5.4 Points of Departure and Toxicity Endpoints Use in Human Health Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Emamectin for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Dietary, all durations (General Population, including Infants and Children)	NOAEL = 0.25 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Acute RfD = 0.0025 mg/kg/day aPAD = 0.0025 mg/kg/day Chronic RfD = 0.0025 mg/kg/day cPAD = 0.0025 mg/kg/day	Subchronic and chronic oral toxicity studies in dogs Subchronic LOAEL = 0.5 mg/kg/day based 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. Chronic LOAEL=0.5 mg/kg/day based on axonal degeneration in the

Incidental Oral Short-Term (1-30 days)	NOAEL = 0.25 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF= 1x	Residential/Non-occupational LOC for MOE = 100	pons, medulla, and peripheral nerves (sciatic, sural, and tibial); whole body tremors; stiffness of the hind legs, spinal cord axonal degeneration, and muscle fiber degeneration
Dermal Short-Term (1-30 days)	NOAEL= 0.25 mg/kg/day *Dermal Absorption Factor = 1.8%*	UF_A = 10x UF_H = 10x FQPA SF= 1x	Residential/Non-occupational LOC for MOE = 100	
Inhalation Short-Term (1-30 Days)	NOAEL = 0.25 mg/kg/day *Toxicity via the inhalation route assumed to be equivalent to oral route.*	UF_A = 10x UF_H = 10x FQPA SF = 1x	Residential/Non-occupational LOC for MOE = 100	
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Emamectin for Use in Occupational Human Health Risk Assessments

Exposure/ Scenarios	Point of Departure	Uncertainty/ Safety Factor	LOC	Study and Toxicological Effects
Dermal (Short-Term and Intermediate-Term)	NOAEL = 0.25 mg/kg/day *Dermal Absorption Factor = 1.8%*	UF_A = 10x UF_H = 10x	Occupational LOC for MOE =100	Subchronic and chronic oral toxicity studies in dogs Subchronic LOAEL = 0.5 mg/kg/day based 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. Chronic LOAEL = 0.5 mg/kg/day based on axonal degeneration in the pons, medulla, and peripheral nerves (sciatic, sural, and tibial); whole

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Emamectin for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenarios	**Point of Departure**	**Uncertainty/ Safety Factor**	**LOC**	**Study and Toxicological Effects**
				body tremors; stiffness of the hind legs, spinal cord axonal degeneration, and muscle fiber degeneration
Inhalation (Short-Term and Intermediate-Term)	NOAEL = 0.25 mg/kg/day *Toxicity via the inhalation route assumed to be equivalent to oral route.*	UF_A = 10x UF_H =10x	Occupational LOC for MOE = 100	Subchronic and chronic oral toxicity studies in dogs Subchronic LOAEL = 0.5 mg/kg/day based 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. Chronic LOAEL = 0.5 mg/kg/day based on axonal degeneration in the pons, medulla, and peripheral nerves (sciatic, sural, and tibial); whole body tremors; stiffness of the hind legs, spinal cord axonal degeneration, and muscle fiber degeneration
Cancer (oral, dermal, inhalation)	Classification: Not likely to be carcinogenic to human based on the absence of significant increase in tumor incidence in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern.

4.6 Endocrine Disruption Screening Program

As required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of Registration Review for emamectin, EPA reviewed these data and selected the most sensitive endpoints for

relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), emamectin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[3] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Emamectin is not on either of these lists.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[4]

5.0 Dietary Exposure and Risk Assessment

Dietary memo: M. Negussie, D440625, 09/25/17

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Plants: The major residue identified in lettuce, cabbage, and sweet corn treated with [^{14}C]emamectin B_{1a} (MAB_{1a}) was the parent MAB_{1a}. The isomer, 8,9-ZB_{1a}, and the metabolites/degradates, AB_{1a}, MFB_{1a}, and FAB_{1a}, were identified at <5% of the TRR. MAB_{1a} initially degrades rapidly to a large number of residues of MAB_{1a}-like structures, nearly all contributing only a small amount to the total residue; these initial degradates undergo further degradation to yield a very complex residue. These degradations are probably a result of

[3] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

[4] https://www.epa.gov/endocrine-disruption

photolysis, and after this photolytic process, these degradates can be fragmented and incorporated into natural plant constituents.

Ruminants: The parent compounds, emamectin (MAB_{1a} + MAB_{1b}), are the only major residue found in goat milk, fat, meat and meat byproducts. However, the analytical method for the determination of residues of emamectin and its metabolites in livestock commodities cannot distinguish between the parent compounds and their metabolites, 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}). In the absence of toxicity data, the metabolites, 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}), are assumed to be of comparable toxicity to the parent.

The residues of concern for the dietary risk assessment and the tolerance expression are summarized in Table 5.1.4.

5.1.2 Summary of Environmental Degradation

Drinking water memo: L. Shanaman, D309157, 3/16/05.

Emamectin, the 8,9-Z isomer, AB, MFB, and FAB are expected to be persistent and relatively immobile in the environment due to a high degree of sorption to soil particles (K_{oc} from 25,363 to 730,000). Based upon fate data, significant concentrations of parent or formed degradates of toxicological concern are not expected to leach into ground water.

5.1.3 Comparison of Metabolite Pathways

The major metabolites identified in plants and livestock treated with [^{14}C]emamectin B_{1a} (MAB_{1a}) was the parent MAB_{1a}. Metabolites 8,9-Z B_{1a}, AB_{1a}, MFB_{1a}, and FAB_{1a} were identified at <5% of the TRR. MAB_{1a} initially degrades rapidly to a large number of residues of MAB_{1a}-like structures, nearly all contributing only a small amount to the total residue; these initial degradates undergo further degradation to yield a very complex residue. These degradations are probably a result of photolysis, and after this photolytic process, these degradates can be fragmented and incorporated into natural plant constituents.

5.1.4 Residues of Concern Summary and Rationale

A summary of the residues of concern for risk assessment and for the tolerance expression may be found in Table 5.1.4.

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression for Emamectin[1]

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crops	emamectin (MAB_{1a} + MAB_{1b}), the associated 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}), and metabolites/degradates AB_{1a}, MFB_{1a} and FAB_{1a}	emamectin (MAB_{1a} + MAB_{1b}), the associated 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}), and metabolites/degradates AB_{1a}, MFB_{1a} and FAB_{1a}

Table 5.1.4. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression for Emamectin[1]			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
	Rotational Crops	Same as for primary crops	Same as for primary crops
Livestock	Ruminant	emamectin (MAB_{1a} + MAB_{1b}) and its 8,9-Z isomers (8,9-ZB_{1a} and 8,9-ZB_{1b})	emamectin (MAB_{1a} + MAB_{1b}) and its 8,9-Z isomers (8,9-ZB_{1a} and 8,9-ZB_{1b})
	Poultry	Not applicable	Not applicable
Drinking Water		emamectin (MAB_{1a} + MAB_{1b}), the associated 8,9-Z isomers (8,9-ZB_{1a} + 8,9-ZB_{1b}), and metabolites/degradates AB_{1a}, MFB_{1a} and FAB_{1a}	Not Applicable

[1] TXR#0050315, Manying Xue, 1/28/02

5.2 Food Residue Profile

Adequate residue data are available to support dietary risk assessment as well as the registered tolerances for the insecticide emamectin. Agricultural uses include cotton, pome fruit, tree nuts, leafy vegetables (*Brassica* and non-*Brassica*), fruiting vegetables, and tobacco. Adequate plant metabolism studies on lettuce, cabbage, and sweet corn are available. Adequate ruminant (goat) and poultry metabolism studies are available. An adequate confined rotational crop study is available. Adequate field trials are available to support registered uses. Adequate processing studies were conducted on apple and tomatoes. Residues of emamectin concentrate in only apple wet pomace and tomato paste. Adequate enforcement methods (high performance liquid chromatography [HPLC] with fluorescence detection) are available to support tolerances for plants and livestock. An adequate cattle feeding study is available. A poultry feeding study is not needed to support registered uses because the calculated dietary burden for poultry is low. Based on the confined rotational crop study, there is no indication that emamectin residues of concern would accumulate (>0.01 ppm) in rotational crops; therefore, no plant-back restrictions are needed on the product labels. Adequate storage stability data are available to support storage conditions for plant and livestock studies.

5.3 Water Residue Profile

Drinking water memo: S. Hafner, DP439720, 5/03/17

The drinking water residues used in the dietary risk assessment were provided by EFED in the following memorandum: “Drinking Water Assessment for Registration Review of Emamectin Benzoate” (S. Hafner, D439720, 5/03/2017), and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.”

The drinking water assessment (DWA) for the Registration Review of emamectin used updated models and guidance. This assessment differs from previous assessments by including revised half-life calculations for aerobic soil metabolism based on new guidance and additional data (MRID 48480102), and thus, also updates the aerobic aquatic metabolism estimation (U.S. EPA, 2015). With these updates, the overall half-life for aerobic soil metabolism has changed from 107.5 days to 299.8 days. The new assessment also uses an updated maximum percent cropped area (PCA) factor of 1.0 for community watersheds (U.S. EPA, 2014).

Due to the lack of toxicity data for these degradates and their structural similarity to the parent chemical, the HED Metabolism Assessment Review Committee's (MARC) conclusion was that these degradates were assumed to be of similar toxicity to that of emamectin and were to be included in a total toxic residues approach for human health risk assessment (U.S. EPA, 2002).

- (8,9-Z)-4"-epimethylamino-4"-deoxy avermectin B1 (8,9 Z isomers);
- 4"-epiamino-4"-deoxyavermectin B1 (AB);
- avermectin B1 monosaccharide (MAB); and
- 4"-epi-(*N*-formyl)-4"-deoxyavermectin B1 (FAB).

The total toxic residues (TTR) approach is used for determining the environmental fate data parameters for modeling using the *Guidance for Selecting Input Parameters in Modeling the Environmental Fate and Transport of Pesticides*, Version 2.1, October 22, 2009, and the draft Guidance for Modeling Pesticides TTR, dated May 20, 2009.

In surface water, the EDWCs for emamectin residues are not expected to exceed 4.67 µg/L for the model-derived 1-in-10 year daily peak, 3.66 µg/L for the 1-in-10 year annual average, and 2.42 µg/L for the 30-year annual average (PRZM5/VVWM). These estimates are highly conservative, given that the sorption properties of emamectin cause accumulation in the modeled reservoir. The highest Tier II EDWCs are the result of the highest use scenario, namely a three-crop rotation of *Brassica* and cole crops (0.24 lb a.i./A annual maximum).

For the acute assessment, HED used a distribution of drinking water numbers from the CA lettuce (ground application) scenario. The EDWC of 3.66 µg/L was used in the chronic assessment.

Table 5.3. Estimated Drinking Water Concentrations for Emamectin Resulting from Maximum Application During a Three-Crop Rotation[1].

Use Scenario	Application Type	1-in-10 Year Peak (µg/L)	1-in-10 Year Annual Average (µg/L)	1-in-30 Year Annual Average (µg/L)
CA lettuceSTD	Aerial	4.55	3.58	2.37
CA ColeCropRLF_V2	Aerial	2.13	1.78	1.21
FL cabbageSTD	Aerial	1.39	0.799	0.619
CA lettuceSTD	**Ground**	**4.67**	**3.66**	**2.42**
CA ColeCropRLF_V2	Ground	2.17	1.80	1.22
FL cabbageSTD	Ground	1.42	0.808	0.625

[1] Highest EDWCs are bolded. Values include parent and degradates.

5.4 Dietary Risk Assessment

Dietary memo: M. Negussie, D440625, 09/25/17

5.4.1 Description of Residue Data Used in Dietary Assessment

Acute Assessment
A probabilistic acute dietary exposure assessment was conducted. For most crops, the anticipated residue estimates were based on field trial data. Tolerance-level residues were used for tree nuts, cottonseed oil, and grape, wine. PDP monitoring data for years 2009, 2010, and 2014 were used for apples since apple juice had a significant impact on exposure. DEEM default processing factors were used except for commodities with chemical-specific processing studies. PCT data provided by the BEAD in 2016 were used. A drinking water residue distribution based on PRZM5 and VVWM in the operating platform of PWC modeling was used.

Chronic Assessment
A partially refined chronic dietary exposure assessment was conducted. For most crops, the anticipated residue estimates were single point estimates (averages) based on field trial data. Tolerance-level residues were used for tree nuts (including pistachios), cottonseed oil, and grape, wine. DEEM default processing factors were used except for commodities with chemical-specific processing studies. PCT data provided by BEAD in 2016 were used. The EDWC of 0.366 µg/L, parts per billion (ppb), for the chronic exposure was based on PRZM5/VVWM in the operating platform of PWC.

5.4.2 Percent Crop Treated Used in Dietary Assessment

A screening level usage analysis (SLUA) dated 08/15/2016 was provided by BEAD based on data years 2005-2015. The estimated maximum PCT was used for the acute dietary risk assessment and the estimated weighted average PCT was used for the chronic dietary risk assessment.

The following maximum PCT estimates (SLUA, 08/15/2016) were used in the acute dietary risk assessment for the following crops that are currently registered for emamectin: almonds: 10%; apples: 20%; broccoli: 20%; Brussels sprouts: 40%; cabbage: 25%; cauliflower: 20%; celery: 40%; cotton: 2.5%; lettuce: 20%; pears: 20%; peppers: 15%; pistachios: 2.5%; spinach: 10%; tomatoes: 20%; and walnuts: 2.5%.

The following average PCT estimates (SLUA, 08/15/2016) were used in the chronic dietary risk assessment for the following crops that are currently registered for emamectin: almonds: 2.5%; apples: 10%; broccoli: 5%; Brussels sprouts: 20%; cabbage: 10%; cauliflower: 5%; celery: 20%; cotton: 1%; lettuce: 10%; pears: 5%; peppers: 5%; pistachios: 2.5%; spinach: 5%; tomatoes: 15%; walnuts: 2.5%.

For livestock commodities, the PCT estimate for apples was used in the residue distribution files (RDFs) for beef and dairy cattle; the PCT for cotton (the only poultry/swine feed item) was used in the RDFs for swine.

5.4.3 Acute Dietary Risk Assessment

As shown in Table 5.4.5, the most highly exposed subgroup was all infants < 1 year old, with exposure of 44% of the aPAD. For the general U.S. population, exposure was 20% of the aPAD. The risk estimates for all populations assessed were below the level of concern.

5.4.4 Chronic Dietary Risk Assessment

As shown in Table 5.4.5, the most highly exposed subgroup was all infants < 1 year old, with exposure of 8.1% of the cPAD. For the general U.S. population, exposure was 3.3% of the cPAD The risk estimates for all populations assessed were below the level of concern.

5.4.5 Summary of Dietary Exposure and Risks Table for Emamectin

The results of the acute and chronic dietary assessments are presented in Table 5.4.5.

Table 5.4.5. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Emamectin.

Population Subgroup	Acute Dietary (99.9 Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD[1]	Dietary Exposure (mg/kg/day)	% cPAD[1]
General U.S. Population	0.000508	20	0.000083	3.3
All Infants (<1 year old)[1]	**0.001098**	**44**	**0.000204**	**8.1**
Children 1-2 years old	0.000854	34	0.000121	4.8
Children 3-5 years old	0.000527	21	0.000101	4.0
Children 6-12 years old	0.000436	17	0.000072	2.9
Youth 13-19 years old	0.000384	15	0.000059	2.3
Adults 20-49 years old	0.000413	17	0.000082	3.3
Adults 50-99 years old	0.000383	15	0.000083	3.3
Females 13-49 years old	0.000420	17	0.000082	3.3

[1] The subpopulations with the highest risk estimates are bolded.

5.4.6 Cancer Dietary Risk Assessment

Emamectin is classified as “not likely to be carcinogenic to humans” based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. Therefore, a cancer dietary exposure assessment is not required.

6.0 Tobacco Inhalation Exposure and Risk Assessment

The non-food use of emamectin on tobacco results in potential exposures to the ai from tobacco products previously treated with emamectin. For non-food uses of pesticides on tobacco, HED assesses the adverse health effects from the use of pesticide-treated tobacco for short-term inhalation exposures. Only short-term inhalation exposures to pesticide residues in tobacco products are assessed since it is well documented that there are adverse health effects from prolonged use of tobacco itself.

A pyrolysis study to assess exposure to humans from pesticide residues in tobacco smoke is not available. However, magnitude of the residue data are available for the use of emamectin on tobacco. HED believes the residue value used to calculate the exposure to humans from emamectin residues in tobacco smoke is conservative. The maximum residue from a field trial conducted at 2x the application rate with a more restrictive PHI of 0-day was used in this assessment.

Field Trial Information
Based on the field trial data provided on tobacco, the maximum residue value was 0.065 ppm for residues of emamectin benzoate in or on green tobacco leaves, following broadcast foliar application (2x label rate). Further information regarding the field trial information may be found in the residue chemistry document (M. Xue, D267346, 02/19/2002).

Tobacco Inhalation Assumptions
In assessing exposure through use of tobacco, HED has assumed that the greatest exposure to emamectin would come from cigarettes (i.e., smoking). Further, HED has assumed that the average U.S. smoker smokes 15 cigarettes per day (J. Pierce, J., 1989). HED has further assumed that 100% of the pesticide residue on the tobacco is inhaled and 100% of inhaled residues are absorbed (i.e., none of the residue is exhaled along with the smoke).

Body Weight
HED assumed an average body weight of 69 kilograms for the adult smoker assessment. This number is the lowest representative bodyweight considered for any adult subpopulation and will result in the highest inhalation dose (mg/kg/day). The selection of 69 kg will be a conservative body weight representation for all adult smokers included in this assessment.

Short-term Inhalation Exposure and Risk Assessment
Based upon the assumptions regarding smoking frequency and absorption, and the maximum residue value of 0.0652 ppm for emamectin benzoate field trial residues in or on green tobacco leaves, HED estimates that exposure to emamectin benzoate will not exceed 0.0000141 mg/kg/day.

[0.0652 μg/g cigarette x 1 g/cigarette x 15 cigarettes/day x 1 mg/1000 μg ÷ 69 kg body weight = 0.0000141 mg/kg/day].

Based on the inhalation NOAEL, the short-term MOE for emamectin exposure from the use of tobacco is estimated to be 18,000 which is higher than the target MOE for inhalation exposures (LOC = 100).

$$MOE = \frac{\text{Inhalation NOAEL}}{\text{Exposure}_{(\text{tobacco})}}$$

MOE = (0.25 mg/kg/day) / (0.0000141 mg/kg/day) = 18,000

The resulting short-term MOE estimate of 18,000 is not of concern to HED (LOC = 100). This is likely an overestimate of actual exposure given the conservative assumptions underlying the assessment. This MOE estimate is representative of short-term adult smoker inhalation exposures from emamectin-treated tobacco products.

7.0 Residential Exposure and Risk Estimates

ORE memo: L. Bacon, D438859, 08/18/2017

Residential exposures are not anticipated from the existing uses of emamectin since they are agricultural uses, restricted use products (i.e., restricted to use by certified applicators only), or are limited to non-residential areas (i.e., commercial and industrial areas) with the exception of a gel bait product. The ready-to-use (RTU) gel bait product is registered for use in multiple locations, including in residential areas. As the RTU product requires no mixing/loading, the only potential for residential handler exposure is via application. When applying this product according to use directions, bait points and bait beads are intended to be placed in cracks and crevices where direct contact by adults is anticipated to be negligible. Post-application exposures for adults and children are also unlikely due to the nature of the application method, and the location of the bait placement. Therefore, a residential exposure assessment has not been conducted and there are no residential risk estimates recommended for use in the aggregate risk assessment for emamectin.

8.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

There are no residential exposures for emamectin; therefore, aggregate exposure and risk estimates are equivalent to the dietary exposure and risk estimates as described in Section 5, and are not of concern.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

ORE memo: L. Bacon, D438859, 08/18/2017

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).

During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis are required for emamectin**.**

10.0 Non-Occupational Spray Drift Exposure and Risk Estimates

ORE memo: L. Bacon, D438859, 08/18/2017

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[5] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of emamectin. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the

[5] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[6] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 10.1 provides the screening level drift related risk estimates.

In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

10.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Emamectin is used on a variety of agricultural crops and can be applied via airblast, groundboom, and aerial equipment. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.
- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.
- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[7]

It should be noted that several registered agricultural uses of emamectin are applied at the same application rate. For the purposes of the spray drift assessment, the representative crops chosen

[6] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift
[7] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture.

for each application scenario are: cotton for aerial applications; fruiting vegetables for groundboom applications; and pome fruit for airblast applications.

Dermal and incidental oral risk estimates were combined for children 1 to < 2 years old because the toxicity endpoint for these routes of exposure is based on the same effect; the applicable LOC for children is an MOE of 100. Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. Results are presented in Table 10.1. There were no dermal risk estimates of concern at the field edge for adults following applications to all registered crops at the maximum registered application rates and assuming screening-level droplet sizes and boom heights as noted above (MOEs > 100). The dermal MOEs for adults range from 17,000 to 31,000 at the field edge. Additionally, there were no combined dermal and incidental oral MOEs of concern at the edge of the field for children 1 to < 2 years old. Combined dermal and incidental oral MOEs ranged from 2,900 to 5,100.

Table 10.1. Summary of Spray Drift Buffers Assuming Screening-Level Droplet Sizes, Canopy Densities, and Boom Heights[1] by Agricultural Crop for Emamectin.

Crop[3]	Application rate (lb ai/A)	Distance From Field Edge	Adult Dermal MOEs[2]			Children 1 < 2 years old Combined Dermal + Incidental Oral MOEs[2]		
			LOC = 100			LOC = 100		
		(Feet)	Aerial	Groundboom	Airblast	Aerial	Groundboom	Airblast
Multiple	0.015	0	17,000	24,000	31,000	2,900	3,900	5,100

[1] Risk estimates presented assuming screening-level droplet sizes (fine to medium for aerial applications; very fine to fine for groundboom applications), sparse canopies for airblast applications; and high booms for groundboom applications. Assuming coarser droplet sizes and lower booms will reduce risks.

[2] Algorithms, assumptions, and calculations for the non-occupational spray drift assessment are provided in Appendix B of the ORE cited in Section 10.0.

[3] It should be noted that several agricultural uses are registered at the same application rate. For the purposes of the spray drift assessment, the representative crops chosen for each application scenario are: Cotton for aerial applications; Groundboom applications to fruiting vegetables; Airblast applications to pome fruit.

11.0 Cumulative Exposure/Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[8] and conducting cumulative risk assessments (CRA)[9]. The Agency has utilized this framework for emamectin and determined that emamectin along with abamectin form a candidate CMG of the avermectin macrocyclic lactones. This group of pesticides is considered a

[8] *Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)

[9] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

candidate CMG because they share characteristics to support a testable hypothesis for a common mechanism of action and there is sufficient toxicological data to suggest a common pathway. However, there are not adequate data to establish those key events in a pathway as described in the mode of action/adverse outcome pathway (MOA/AOP) framework (*e.g.*, lack of dose or temporal concordance of proposed key events).

In 2016, the Agency conducted a screening-level cumulative exposure analysis consistent with the guidance described in the cumulative screening framework. The screening-level cumulative assessment for the avermectin macrocyclic lactones, abamectin and emamectin, indicated that cumulative aggregate dietary and residential exposures for abamectin and emamectin were below the Agency's levels of concern. For the purposes of Registration Review and in conjunction with evaluation of a new use of abamectin, HED determined it was necessary to update the 2016 cumulative risk assessment.

The results of the updated screening level cumulative risk assessment for the avermectin macrocyclic lactones, including emamectin, indicates that cumulative dietary and residential aggregate exposures for emamectin and abamectin are below the Agency's levels of concern.

Additional information regarding cumulative exposure and risk characterization, in general, as well as the screening assessment for the avermectin macrocyclic lactones, in particular, may be found in a separate assessment (L. Bacon, D442232, 09/26/2017).

12.0 Occupational Exposure and Risk Estimates

ORE memo: L. Bacon, D438859, 08/18/2017

The quantitative exposure and risk assessment developed for occupational workers is based on the use patterns and scenarios listed in Appendix C.

12.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the existing uses of emamectin.

Registrations and Application Rates
The quantitative exposure/risk assessment developed for occupational handlers is based on scenarios developed from the Use Summary Table available in Appendix C, which are representative of all registered uses of emamectin.

Occupational Handler Non-Cancer Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed in the occupational and residential exposure memo referenced in Section 12.0.

Additionally, HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Labeled Clothing or PPE Requirements

The emamectin product labels direct mixers, loaders, applicators and other handlers to wear different attire or levels of PPE depending on the exposure scenario. Occupational mixers, loaders, and other handlers (for products other than the gel bait) must wear: long-sleeved shirt and long pants; chemical-resistant gloves made of any waterproof material (such as polyvinyl chloride, nitrile rubber or butyl rubber); and shoes plus socks. In addition to these requirements, several product- and scenario-specific attire/PPE restrictions are listed in Section 8.1 of the ORE assessment referenced in Section 12.0.

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects and points of departure for these exposure routes were the same. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ Combined dermal + inhalation dose (mg/kg/day)

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

The results of the occupational handler exposure and risk assessment indicate that short-term combined inhalation and dermal risk estimates are not of concern (i.e. all MOEs ≥ 100) at baseline (i.e., single layer of clothing) without additional PPE. Since the short- and intermediate-term PODs are the same, the combined short- and intermediate-term MOEs are equivalent, and range from 110 to 520,000.

The requirement of a subchronic inhalation toxicity study has been waived for emamectin based, in part, on information that estimated inhalation MOEs do not fall below 10 times the LOC (LOC = 100) (J. Leshin, TXR 0051377, 03/12/2015). For mixing or loading DF/WDG for aerial broadcast applications to typical field crops, resulting inhalation MOEs are presented for both baseline and baseline plus label-required PPE (i.e., respirator), because the baseline inhalation MOE estimate was below 1,000. HED recommends the continued requirement of a respirator for this use pattern, in order to support the continued waiver for the requirement of the study. The PPE of gloves is also presented for this scenario in order to demonstrate the combined dermal + inhalation MOE with label-required PPE (i.e., gloves and respirator) is 10 times the LOC.

Appendix D, Table D.1, provides details as to the specific scenarios for all occupational exposure and risk estimates.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

12.2 Occupational Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

12.2.1 Occupational Post-Application Dermal Exposure and Risk Estimates

Occupational Post-Application Dermal Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed in the occupational and residential exposure memo cited in Section 12.0.

Guideline 875.2100 - Dislodgeable Foliar Residue (DFR) Data
In accordance with 40 CFR 158, DFR data are required for all occupational (e.g., crop, nursery, greenhouse use sites) or residential (e.g., ornamental and vegetable gardens, pick your own farms, retail tree farms) uses that could result in post-application exposure to foliage. A chemical-specific DFR study is currently available for the use of emamectin on celery (MRID 44007903); a secondary review of the study was conducted in 2001 (T. Swackhammer, HED, 11/23/01, D279209). The predicted Day 0 DFR value of 0.003 ($\mu g/cm^2$) was chosen for risk assessment. This value was not adjusted, because the study application rate is equal to the risk assessment application rate.

Occupational Post-Application Non-Cancer Dermal Risk Estimates
For the occupational post-application assessment of the uses of emamectin, only the highest crop/transfer coefficient combination for each crop category is presented in Appendix E; these

scenarios are considered protective of all other registered crops in that category and all associated activities. All of the dermal post-application exposure scenarios resulted in MOEs greater than the LOC (LOC = 100) on the day of application and are not of concern. Worst-case MOEs by crop category ranged from 920 to 33,000. Refer to Appendix E for further details.

Restricted Entry Interval
Emamectin is classified as Toxicity Category III via the dermal route and Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Short-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. In previous HED assessments, the risks to workers (based on systemic toxic effects of emamectin) who re-entered treated fields on the day of treatment were not of concern for all relevant agricultural activities except thinning (pome fruit) and poling, thinning, pruning and hand-harvesting tree nuts. Those latter activities were previously assigned a 48-hour REI. Based upon the short-term post-application risk estimates which were not a concern on day 0 (12 hours following application) for all post-application activities and the toxicity categories for the active ingredient only, it appears that the 48-hour REI may no longer be necessary. Therefore, upon review of the criteria for the active ingredient only, the [156 subpart K] Worker Protection Statement REI of 12 hours listed on applicable registered emamectin products is adequate to protect agricultural workers from post-application exposures to emamectin.

12.2.2 Occupational Post-Application Inhalation Exposure and Risk Estimates

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies) or further analysis are required for emamectin.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Commercial Indoor Uses
Commercial applicators do not typically return to the treated areas after an indoor commercial pesticide application (sites such as warehouses, food handling establishments, and hotels, etc.)

and thus an occupational post-application inhalation exposure assessment was not performed for commercial applicators.

13.0 Incident and Epidemiological Data Review

Incident report memo: S. Recore, DP# 427020, 06/30/2015.

A Tier I updated review of human incidents and epidemiology was completed in 2015. Emamectin was previously reviewed in 2011 (S. Winfield, 03/1/2011, D386649). At that time, there were no incidents reported involving emamectin in the OPP's IDS database, and two minor severity cases reported involving emamectin in Aggregate IDS from January 1, 2002 to February 1, 2011.

The current IDS analysis from January 1, 2010 through May 27, 2015, shows three incidents reported to Main IDS involving the single chemical, emamectin, and one additional incident reporting involving multiple chemicals. There were three incidents reported to Aggregate IDS. In addition, a query of the Center for Disease Control (CDC)/NIOSH Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides, 1998-2011 identified a total of four cases involving emamectin; all of which involved multiple chemicals.

Information about emamectin is not included in the Agricultural Health Study (AHS).

Based on the low frequency and low severity of incident cases reported for emamectin in both IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time that would warrant further investigation. The Agency will continue to monitor the incident information and if a concern is triggered, additional analyses will be conducted.

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food use for emamectin are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicology Data Requirements for Emamectin

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Nonrodents	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	yes
870.3250	90-Day Dermal Toxicity	CR	
870.3465	90-Day Inhalation Toxicity	CR	waived[a]
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b	Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	no	yes
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	yes
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	CR	yes
870.7800	Immunotoxicity	yes	yes

[a] HASPOC Report: TXR 0051377, 03/12/2015.

A.2. Toxicology Data Requirements

Table A.2.1. Acute Toxicity Profile – Emamectin Benzoate Technical (EPA Reg. No. 100-1270)				
Guideline No.	**Study Type**	**MRID**	**Results**	**Toxicity Category**
870.1100	Acute oral - Rats	47002104	LD_{50} for L-656,748-038 = 53 mg/kg	II
870.1200	Acute dermal - Rabbits (EC)	47002106	LD_{50} > 2.0 g/kg	III
870.1300	Acute inhalation - Rats	47002107	LC_{50} 0.10 mg/L	II
870.2400	Acute eye irritation - Rabbits	47002108	Corneal opacity & iritis were cleared within 7 days.	III
870.2500	Acute dermal irritation - Rabbits	47002109	No dermal irritation	IV
870.2600	Skin sensitization - Guinea pigs	47002110	Not a dermal sensitizer	Negative

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
Acute dermal toxicity study (Not a LD_{50} study)			
	Acute dermal tox.- rabbits MK-0243 0.16 EC formulation	42743611 (1991) Acceptable 0, 0.5, 1.0, & 2.0 mg/kg (2 groups: 4 hr exposure & 24 hr exposure) with collar on the test animals.	4 hr. exposure NOAEL = 2.0 mg/kg/day (HDT) 24 hr. exposure NOAEL = 0.5 mg/kg/day LOAEL = 1.0 mg/kg/day one rabbit had neuron lesion occurred in cerebellar peduncle. Similar effect was not seen in 2.mg/kg group.
	Acute dermal tox. – rabbits (24 hrs exposure with collar on all test animals)	43850111 (1995) Acceptable 0, 10.4, 21.0, or 42.1 mg/kg MK-0244 0.16 EC	NOAEL = 42.1 mg/kg. No treatment-related systemic toxicity was seen in any dosed animals. The acute dermal LD_{50} > 2000 mg/kg for MK-0244
Subchronic toxicity studies			
870.3100	13-Wk oral-CD rats	42794201 (1992) Acceptable 0, 0.5, 2.5, and 12.5 mg/kg/day. 12.5 mg/kg/day was reduced to 8 mg/kg/day at wk 3 then to 5.0 mg/kg/day at wk 9.	Systemic Toxicity NOAEL=2.5 mg/kg/day; Systemic Toxicity LOAEL=5 mg/kg/day based on moribundity, 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.

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
	13-Wk oral-CD-1 mice	42743621 (1992) Acceptable 0, 0.5, 4.5, & 15.0 mg/kg/day. An additional group received a time weighted dose 5.4 mg/kg/day	NOAEL = 5.4 mg/kg/day LOAEL = 15.0 mg/kg/day based on mean body weight decrease and decreased in cumulative body weight gain.
870.3150	90-Day oral – dogs (gavage)	42743623 (1992) Acceptable 0, 1.0, or 1.5 mg/kg/day for the first 2 wks then reduced to 0.25, 0.5, or 1.0 for the rest of the study.	NOAEL = 0.25 mg/kg/day LOAEL = 0.50 mg/kg/day based 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.
	14-Wk oral-dogs (gavage)	43868103 (1994) Acceptable 0.5, 1.0, or 1.5 mg/kg/day for 2 wks for mid and high dose groups and for 3 wks for low dose, then they were reduced to 0.25, 0.5, or 2.0 mg/kg/day. The time weighted doses were 0.29. 0.58, or 0.1.08 mg/kg/day.	NOAEL = 0.29 mg/kg/day LOAEL = 0.58 mg/kg/day based on microscopic lesions in the brain (multifocal white matter degeneration), atrophy of skeletal muscle, and spinal cord lesions.
870.3200	21-Day dermal tox-rabbits MK-0244 0.16 EC formulation	42743625 (1992 Acceptable 0, 50, 100, or 250 mg/kg/day (6 hrs/day)	Systemic tox. NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day based on axonal degeneration of the sciatic nerve. Application site irritation was seen in all treated rabbits.
	22-Day dermal tox. – rabbits MK-0244 0.16 EC formulation	44007902 (1996) Acceptable 0, 250, 500, or 1000 mg/kg/day (6 hrs/day)	NOAEL = 1000 mg/kg/day (highest dose tested [HDT]). No systemic toxicity was seen in any dose groups. *Note: The test animals were collared to prevent oral ingestion of the test material.*
870.3465	5-Day inhalation tox.	49395601(2014) Acceptable/non-guideline 0, 1, 3, 10, or 30 µg/L	Systemic tox: NOAEL =10 µg/L LOAEL = 30 µg/L base on ↓ body weight, tremors, hunched posture, rolling gaits, and abnormal vocalizations. Portal of entry effects: NOAEL= 3 µg/L LOAEL = 10 µg/L based on squamous metaplasia and/or inflammatory cell infliltration in the larynx and nasal cavity, and

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
			olfactory epithelium degeneration in the nasal cavity.
	90-day inhalation	Waived (HASPOC report: TXR 0051377, 03/12/2015)	
Chronic toxicity studies			
870.4100	1-Year oral tox. – dogs (gavage)	42763624 (1992) Acceptable 0, 0.25, 0.5, 0.75, or 1.0 mg/kg/day (4 dogs/sex/dose)	NOAEL= 0.25 mg/kg/day LOAEL=0.5 mg/kg/day based on axonal degeneration in the pons, medulla, and peripheral nerves (sciatic, sural, and tibial); whole body tremors; stiffness of the hind legs, spinal cord axonal degeneration, and muscle fiber degeneration.
	Chronic oral tox. – rats (dietary) (1 year)	42868902 (1992) Acceptable 0, 0.1, 1.0, 2.5 mg/kg (initially females received 5.0 mg/kg then reduced to 2.5 mg/kg at wk 18 due to excessive toxicity)	NOAEL = 1.0 mg/kg/day 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 study-mice (CD-1) (dietary)	4386805 (1994) Acceptable 0, 0.5, 2.5, or 12.5 mg/kg/day (The highest dose was reduced to 7.5 and 5.0 mg/kg/day for males at wk 9 and females at wk 3, respectively)	NOAEL = 2.5 mg/kg/day. LOAEL = 5.0 mg/kg/day for males and 7.5 mg/kg/day for females based on increased mortality, decreased weight gain, tremors, sciatic nerve degeneration, and increased incidence of severity of infections. No treatment-related increase in tumor incidence was seen.
	Combined Chronic/ Carcinogenicity-Rat	43868104 (1994) Acceptable 0, 0.25, 1.0, 2.5/5.0 mg/kg (Initially, high dose level was 5.0 mg/kg; it was reduced to 2.5 mg/kg on wk 6 for males and wk 10 for females due to tremors seen in another study at 5 mg/kg).	NOAEL = 1.0 mg/kg/day LOAEL = 2.5/5.0 mg/kg/day[1] based on marked neural degeneration in the brain and spinal cord of both sexes, brain white matter degeneration in males, and on decreased body weight, body weight gain, and food efficiency in males. No treatment-related increase in tumor incidence was seen.
Developmental and Reproduction Studies			
870.3700	Developmental tox. –rat	42743632 (1992) Acceptable 0, 2, 4, or 8 mg/kg/day 42743631 (range finding study)	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

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
			LOAEL=8 mg/kg/day based on altered growth and an increased incidence of supernumerary rib.
	Developmental tox.- rabbits	42743636 (1992) Acceptable 0, 1.5, 3, or 6 mg/kg/day 42743635 (Range finding study)	Maternal Tox. NOAEL = 3 mg/kg/day, Maternal Tox. 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 Tox. NOAEL =6 mg/kg/day (HDT)
870.3800	2-Gen. reproduction study - rats	42851511 (1993) Acceptable 0, 0.1, 0.6, or 3.8/1.8 mg/kg/day (F_0 & F_{1a} females initially received 3.8 mg/kg, but it was reduced to 1.8 mg/kg/day on GD 0 following the second cohabitation of F_0 females).	Parental NOAEL = 0.6 mg/kg/day. Parental LOAEL = 1.8 mg/kg/day based on neuronal degeneration in the brain and spinal cord in both sexes and generations. Reproductive NOAEL=0.6 mg/kg/day Reproductive LOAEL=1.8 mg/kg/day based on decreased fecundity and fertility indices. Offspring NOAEL = 0.6 mg/kg/day Offspring LOAEL = 1.8 mg/kg/day based on tremors and hind limb extension in the offspring of both generations, neuronal degeneration in the brain and spinal cord.
Mutagenicity Studies			
870.5100	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 0.01 mM or a severely cytotoxic S9-activated dose of 0.04 mM.

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
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.
Neurotoxicity Studies			
870.6200	Acute neurotox. study-rats (gavage)	42743618 (1992) Acceptable 0, 27.4, 54.8 or 82.2 mg/kg (range finding study)	NOAEL was not established. LOAEL= 27.4 mg/kg/day (LDT); clinical signs (tremors, ataxia, loss of righting reflex, and reduced activities) and as histological lesions in the brain, spinal cord and sciatic nerve occurred at all doses tested.
	Acute neurotox. study- rats (gavage)	42743619 (1992) Supplementary 0, 0.5, 2.5, 5.0, 10.0, or 25.0 mg/kg/day	NOAEL = 5.0 LOAEL = 10 mg/kg/day based on tremors irritability. At 25 mg/kg, all rats had tremor and neuronal lesions (white matter degeneration of the brain, degeneration of the spinal cord and sciatic nerve.
	Subchronic neurotox. –SD rats (dietary) (14 day)	42743628 (1992) Acceptable 0, 0.25, 1.0, or 5.0 mg/kg/day	NOAEL=1.0 mg/kg/day LOAEL=5.0 mg/kg/day based on tremors, posture, rearing, excessive salivation, fur appearance, gait, strength, mobility and righting reflex. Neuronal vacuolation in brain and spinal cord; degeneration of nerve fiber in spinal cord and sciatic nerves. Skeletal muscle atrophy. Male rats appeared to be more affected than females.
	Comparative neurotox. – dogs (gavage) (14 days)	42743626 (1992) Acceptable 2 dogs/sex/compound were given 1.5 mg/kg/day of testing compound.	The following effects were seen with different compounds: Tremors Mydriasis MK-0243[a] 2/4 0/4 L-682,901 0/4 0/4 L-653,648 0/4 4/4 L-653,649 2/4 3/4 L-655. 372 3/4 0/4 Histopathology findings were not seen in L-682, 901 and L-653,648 treated dogs. Neuronal degeneration of the brain, spinal cord, and sciatic nerves were seen in dogs treated with MK-0234, L-653, 649, and L-655,372.
	15-Day neurotox. – CD-1 mice (dietary)	42743629 (1992) Acceptable 0, 0.6, 1.2, & 2.0 mg/kg/day	NOAEL=2.0 mg/kg/day (HDT). No characteristic neuronal lesions in the brain, spinal cord or sciatic nerve in mice of high dose group.

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
	15-Day neurotox.- CF-1 mice (dietary) (L-660,599: 4"-epi-(*N*-formyl-*N*-methyl)- amino4"-deoxy-avermectin B1	42851503 (1993) Acceptable 0, 0.05, 0.075, 0.10, or 0.30 mg/kg/day	NOAEL=0.075 mg/kg/day LOAEL=0.10 mg/kg/day based on tremors observed beginning on day 3, ptosis, hunched posture, decreases in body weight and food consumption as well as degeneration of the sciatic nerve. At 0.3 mg/kg, tremors were seen on day 2 and followed by hunched posture and ptosis, ataxia, and labored breathing.
	15-Day neurotox. – CF-1 mice (dietary) (L695-638: 4"-deoxy-4"-epi-methylamino-avermectin B1a-delta-8,9-isomer); photoproduct of MK-0244[b]	42851504 (1993) Acceptable 0, 0.05, 0.075, 0.10, & 0.30 mg/kg/day	NOAEL = 0.30 mg/kg/day (HDT) No treatment-related effects were seen in any dose groups.
	15-Day neurotox. – CF-1 mice (dietary) (L695-638: 4"-deoxy-4"-epi-methylamino-avermectin B1a-delta-8,9-isomer); photoproduct of MK-0244	42851505(1993) Acceptable 0, 0.05, 0.075, 0.10, & 0.30 mg/kg/day	NOAEL = 0.243 (HDT). The targeted dose was 0.30 mg/kg/day. No treatment-related effects were seen in any dose groups. Female mice only to repeat the exposure dose levels of MRID 42851504 because female mice received 15% less than the targeted dose in that study.
	15-Day neurotox.- CF-1 mice (dietary) (L-660,599; formyl methylamino plant metabolite of MK-0244)	42851506 (1993) Acceptable 0, 0.10, 0.30, 0.90 mg/kg/day	LOAEL <0.1 mg/kg/day LDT) based on tremors, hunched posture and piloerection. However no treatment-related findings in histopathology were present.
	15-Day neurotox.- CF-1 mice (gavage) L-930,905; a com-plex mixture of polar MK-244 photodegradates)	42851507 (1993) Acceptable 0, 3, 6, 12, or 18 mg/kg/day	NOAEL = 18 mg/kg/day (HDT) No treatment-related effects were found.
	16-Day neurotox.- CF-1 mice (dietary) MK-0243	42743630 (1992) Acceptable 0, 0.05, 0.10, 0.30, or 0.90 mg/kg/day	NOAEL = 0.1 mg/kg/day LOAEL = 0.30 mg/kg/day based on tremors, decreased activity, and moribund sacrifice starting on day 2. However, no histopathology findings were present.
	15-Day neurotox.- CF-1 mice (dietary) Formyl amino derivative of MK-0244	42868901 (1991) Acceptable 0, 0.050, 0.075, 0.100, & 0.300 mg/kg/day	NOAEL = 0.07 mg/kg/day LOAEL = 0.23 mg/kg/day based on decreased body weight gain.

Table A.2.2. Repeated Dosing and Other Studies on Emamectin			
Guideline No	**Study Type**	**MRID No. (Year)/ Classification/Doses**	**Results**
870.6300	Develop. Neurotox.-rats (SD) (gavage for maternal animals; no direct dosing for neonates) MK-0244	42851508 (1993) Acceptable 0, 0.1, 0.6, 3.6/2.5 mg/kg/day (3.6 mg/kg was reduced to 2.5 mg/kg between GD 17 and 20)	Maternal NOAEL= 3.6/2.5 mg/kg/day (highest dose tested) Develo. Neurotox. NOAEL= 0.10 mg/kg/day Develo. Neurotox. LOAEL = 0.60 mg/kg/day based on the dose-related decrease in open field motor activity in females at postnatal day 17.
870.7485	Metabolism –rats [^{14}C] 4''deoxy-4'-epi-methylamino avermectin B1a benzoate, (MAB1a)	42851523 & 42852524 (1993) Acceptable	Radiolabeled MAB1a 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.
	Bioequivalence - Dog MK-0243 solvate vs. monohy-drate	42743641(1992) Supplemental	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.
	Bioequivalence-Dog MK-0243 benzoate vs. HCL salts	42743640 (1992) Supplemental	The study demonstrated that benzoate and HCl salts are bioequivalent after oral administration in male beagle dogs.
870.7600	Dermal Absorption-Rhesus Monkey	43850113 (1994)	Dermal Absorption was approximated at 1.79% of the administered dose.
870.7800	Immunotoxicity study- CD-1 mice	48980301 (2012) Acceptable/guideline 0, 10, 30, or 60 ppm (0, 1.7, 4.8, or 10.6 mg/kg/day expressed as free base)	Systemic toxicity NOAEL = 10.6 mg/kg/day (HDT). Immunotoxicity: NOAEL = 10.6 mg/kg/day (HDT). No LOAEL was established.

A.3. Data Demonstrating the Sensitivity of Beagle Dogs to the Effects of Abamectin and Emamectin

To illustrate the order of sensitivity to the effects of abamectin and emamectin in test animals that have fully functioning P-gp, the results of the subchronic (90-day) oral toxicity studies on emamectin with rats, CD-1 mice, and dogs were used for comparison. The data indicate that the effects produced in the dogs are qualitatively more severe and have a substantially lower LOAEL relative to those produced in the rats and CD-1 mice, as shown in the table below. Similar data on abamectin also demonstrate this order of sensitivity.

Table A.3. Comparison of the results of subchronic (90-day) oral toxicity studies on emamectin

Test species	NOAEL (mg/kg/day)	LOAEL	Effects seen at LOAEL
Beagle dogs	0.25	0.50	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.
Rats	2.5	5.0	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, and moribundity,
CD-1 mice	5.4	15.0	Mean body weight decrease

Appendix B. Physical/Chemical Properties

Table B. Physicochemical Properties of Emamectin Technical II.		
Parameter	Value	Reference
Molecular Weight	emamectin benzoate B_{1a}: 1008.26 emamectin benzoate B_{1b}: 994.23	DP#335159, Indira Gairola, 8/7/07
Melting point/range	141-146°C	MRID #47002103
pH (at 25°C)	6-7	
Density	1.20 g/cm^3	
Water solubility (21°C) (average of emamectin B_{1a} + emamectin B_{1b})	105 mg/L at pure water 101 mg/L at pH 5.0 93 mg/L at pH 7.0 No peaks were observed at pH 9.0.	
Solvent solubility (25°C)	Toluene 20.8 mg/mL Cyclohexane 0.23 mg/mL NMP 576 mg/mL Acetone 140 g/L Dichloromethane >500 g/L Ethyl acetate 81 g/L Hexane 77 g/L Methanol 270 g/L Octanol 48 g/L Toluene 26 g/L	
Vapor pressure (21°C)	3.0 x 10^{-8} torr or 3.0 x 10^{-8} mmHg	
Dissociation constant, pKa	4.2 (benzoic acid) 7.6 (methyl-amino)	
Octanol/water partition coefficient	Shake Flask Method Log P_{ow} = 5.7 (emamectin B_{1a}) Log P_{ow} = 5.2 (emamectin B_{1b})	
UV/visible absorption (molar absorption coefficients at the absorbance maxima)	Neutral: 37,367 l/mol•cm at 245 nm 22,584 l/mol•cm at 245 nm Acidic: 36,841 l/mol•cm at 245 nm 22,131 l/mol•cm at 245 nm Basic: 28,952 l/mol•cm at 245 nm No further absorption maximum between 280 and 750 nm was observed.	
Aerobic soil metabolism half-life	90th Percentile on the mean: 107.5 days; Mean of all of the values (used in SCI-GROW): 79 days.	

Appendix C. Use Summary for Emamectin

Table 4.1. Summary of Directions for Use of Emamectin.						
Applic. Timing, Type, and Equip.	**Formulation (% ai) [EPA Reg. No.] [1]**	**Applic. Rate (lb ai/A)[2]**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
Brassica (and Non-Brassica) Leafy Vegetables; Brassica Head and Stem Vegetables; Fruiting Vegetables; Tobacco						
Ground, Aerial	WDG [100-904]	4.8 fl. oz P/A; 0.015 lb ai/A	Not specified (NS)	28.8 oz P/A/season (0.09 lb ai/A/season)	7-14	Restricted Use Pesticide (RUP); Do not apply more than 2 sequential applications before rotating to another mode of action (MOA). Restricted entry interval (REI) = 12 hours. Aerial not allowed in NY; greenhouse use prohibited, as is use in nurseries, in plant propagation houses, or on any plants grown for use as transplants; Chemigation prohibited; gallons per acre (GPA) is 5 gal minimum for aerial. 10 GPA for ground (vegetable crops); Re-treatment Interval (RTI) = 7 days
Cavalo Broccolo						
Ground	EC/Liquid (2.15%; 0.16 lb ai/gal product) [100-903]	12.0 fl. oz. P/A; 0.015 lb ai/A; 0.00075 lb ai/gal	NS	72 fl oz P/A/season (0.09 lb ai/A/season)	7	RUP; Aerial, chemigation and greenhouse uses are prohibited; No more than two applications before rotating MOA. 20 GPA minimum. RTI = 7 days. REI = 12 hours
Tobacco						
Ground	EC/Liquid (2.15%; 0.16 lb ai/gal product) [100-903]	12.0 fl. oz./A; 0.015 lb ai/A; 0.00075 lb ai/gal	NS	36 fl oz/A/season 0.045 (lb ai/A/season)	14	RUP; Aerial, chemigation and greenhouse uses are prohibited; No more than two apps before rotating MOA. 20 GPA minimum. REI = 12 hours; RTI = 5 days
Pome Fruit; Tree Nuts						
Ground	WDG (5%) [100-904]	4.8 fl. oz. P/A; 0.015 lb ai/A; 0.00038 lb ai/gal	NS	14.4 lb P/A/season (0.045 lb ai/A/season)	7-14	RUP; Aerial application prohibited; Do not use in greenhouses, nurseries, in plant propagation houses, or on any plants grown for use as transplants; chemigation prohibited; GPA minimum 40 gal.; RTI = 7 days; REI = 12 hours, except for the following tasks: REI = 48 hours for the activities of poling, pruning, and thinning for tree nuts; and propping, pruning, training, thinning, and tying for pome fruit.
Soybean (Grown for Seed) for Research Purposes						
Ground	WDG (5%) [PR170001-SLN, based upon 100-904]	4.8 fl. oz. P/A; 0.015 lb ai/A;	NS	14.4 lb P/A/season 0.045	7	RUP; For use in Puerto Rico only for control of soybean looper infesting soybean grown for seed by authorized research facility personnel for seed research purposes. No food/feed contact. Aerial application prohibited; chemigation prohibited. Label expires in 2022.
Field Corn (Grown for Seed) for Research Purposes						

Table 4.1. Summary of Directions for Use of Emamectin.						
Applic. Timing, Type, and Equip.	**Formulation (% ai) [EPA Reg. No.] [1]**	**Applic. Rate (lb ai/A)[2]**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lb ai/A)**	**PHI (days)**	**Use Directions and Limitations**
Ground	WDG (5%) [PR160002-SLN, based upon 100-904]	4.8 fl. oz. P/A; 0.015 lb ai/A;	NS	14.4 lb P/A/season 0.045	7	RUP; For use in Puerto Rico only for control of fall army worm infesting field corn grown for seed research purposes only. Only for use by authorized research facility personnel on field corn grown for seed. No food/feed contact. Aerial application prohibited; chemigation prohibited. Label expires in 2021.
Cotton						
Aerial, ground	EC/Liquid [100-903] (2.15%; 0.16 lb ai/gal product)	12.0 fl. oz. P/A; 0.015 lb ai/A	NS	48 fl oz P/A/season; 0.06	21	RUP; Chemigation prohibited; No more than 2 sequential applications before rotating MOA. GPA 5 for ground, GPA 2 for aerial; RTI = 5 days. REI = 12 hours. For aerial application, workers must not mix or load more than 194 gallons of product per day and must not mix or load product more than a total of 30 days per year
Trees, Ornamental or Nonbearing (Deciduous, Coniferous, Palm)						
Injection	EC/SC/Liquid [100-1309; 69117-12; 74578-10; 83100-35] (4.0%) (0.36 lb ai/gal product)	1065 ml P/tree (0.10 lb ai/tree)	NS	NS	NS	Some products are RUP, while others are not specified as RUP. Tree injection rates from 0.0382-0.1 lb/tree [specific dosage is based on tree DBH); Some labels specify to not apply product when tree is dormant. Some products for use in conjunction with RTU low-pressure injection technology. Do not apply to trees that may yield food consumed by humans or used in animal feed.
Ornamentals, Herbaceous and Woody (Outdoor, Ground or Container-Grown Nursery); Christmas Tree Nursery						
Groundboom, Airblast, Aerial	WDG (5%) [100-1411]	4.8 fl. oz. P/A; 0.015 lb ai/A;	NS	28.8 fl oz P/A/season (0.09 lb ai/A/season)	NS	RUP; Do not apply more than 3 sequential applications of product before rotating to another MOA. For outdoor-grown plants in commercial nursery production. Greenhouse use prohibited. No aerial applications in New York.
Residential, Instutional and Commerical Sites[3]						
Bait; Crack and Crevice, Spot; Hand Injection Equipment or Bait Station	RTU Gel Bait (0.1%) [100-1290]	0.021; 0.002 (gram ai/yd^2)	NS	NS	NA	For use to control cockroaches. Do not apply to areas accessible to children, pets, or livestock. For heavy infestations, 2 - 4 bait points are recommended per sq. yd. of treatment area. May be used in refillable bait stations; Apply directly into cracks and crevices or voids with syringe applicator or bait injector. Application within food/feed areas of food/feed-handling stablishments is limited to crack-and-crevice treatment only.

[1] Formulations: WDG = water dispersible/soluble granule formulation; EC = emulsifiable concentrate/liquid; SC = soluble concentrate/liquid; RTU = ready-to-use

[2] Application rates are provided in pounds of active ingredient per acre, unless otherwise specified; P = product, not active ingredient fl. oz. P/A = fluid ounces of product per acre; ml P/tree = milliliters of product per tree.

[3] Use sites = residential areas and institutional, warehousing and commercial establishments (including warehouses, food processing plants, animal production and processing facilities, restaurants, supermarkets, hospitals, nursing homes, motels, hotels, schools, apartments, aircraft, buses, boats/ships, and trains).; crack, crevice or void space treatment

Appendix D. Occupational Handler Risk Summary

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Mixer/Loader											
Mixing or Loading DF/WDG for Aerial Broadcast Applications	Nursery Ornamentals, vegetables, trees or Container Stock	100	227	8.96	0.015	60	0.0000459	5400	0.000101	2500	1700
Mixing or Loading DF/WDG for Aerial Broadcast Applications	Field Crop, Typical	100	227; 51.6 (SL/G)	8.96; 1.792 (PF5 R)	0.015	350	0.000268 0.000061 (SL/G)	930; 4100 (SL/G)	0.000588; 0.000118 (PF5 R)	430; 2100 (PF5 R)[1]	290; 640 (SL/No G +PF5 R); 1400 (SL/G + PF5 R)
Mixing or Loading DF/WDG for Airblast Broadcast Applications	Nursery (ornamentals, vegetables, trees, container stock)		227	8.96	0.015	20	0.0000153	16000	0.0000336	7400	5100
Mixing or Loading DF/WDG for Airblast Broadcast Applications	Orchard/Vineyard		227	8.96	0.015	40	0.0000306	8200	0.0000673	3700	2500
Mixing or Loading DF/WDG for Chemigation Broadcast	Nursery (ornamentals, vegetables, trees, container stock)		227	8.96	0.015	60	0.0000459	5400	0.000101	2500	1700

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Applications											
Mixing or Loading DF/WDG for Groundboom Broadcast Applications	Field-grown ornamental crops		227	8.96	0.015	40	0.0000306	8200	0.0000673	3700	2500
Mixing or Loading DF/WDG for Groundboom Broadcast Applications	Nursery (ornamentals, vegetables, trees, container stock)		227	8.96	0.015	60	0.0000459	5400	0.000101	2500	1700
Mixing or Loading DF/WDG for Groundboom Broadcast Applications	Orchard/Vineyard		227	8.96	0.015	40	0.0000306	8200	0.0000673	3700	2500
Mixing or Loading DF/WDG for Groundboom Broadcast Applications	Field crop, typical		227	8.96	0.015	80	0.0000612	4100	0.000135	1900	1300
Mixing or Loading Liquids for Aerial Broadcast Applications	Field crop, typical		220	0.219	0.015	350	0.000261	960	0.0000144	17000	910
Mixing or Loading Liquids for Aerial Applications	Field crop, high-acreage		220	0.219	0.015	1200	0.000891	280	0.0000493	5100	270

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Mixing or Loading Liquids for Tree Injector Applications	Forestry; Nursery (ornamentals, vegetables, trees, container stock)		220	0.219	0.1 ai/tree	160	0.000792	320	0.0000438	5700	300
Mixing or Loading Liquids for Chemigation Broadcast Applications	Field crop, typical		220	0.219	0.015	350	0.000261	960	0.0000144	17000	910
Mixing or Loading Liquids for Chemigation Broadcast Applications	Field crop, high-acreage		220	0.219	0.015	350	0.000261	960	0.0000144	17000	910
Mixing or Loading Liquids for Groundboom Broadcast Applications	Field crop, typical		220	0.219	0.015	80	0.0000594	4200	0.00000329	76000	4000
Mixing or Loading Liquids for Groundboom Broadcast Applications	Field crop, high-acreage		220	0.219	0.015	200	0.000149	1700	0.00000821	30000	1600
Applicator											
Applying Sprays for Aerial Broadcast Applications	Nursery (ornamentals, vegetables, trees,	100	2.08 EC	0.0049 EC	0.015	60	4.21E-07	590000	5.51E-08	4500000	520000

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
	container stock)										
Applying Sprays for Aerial Broadcast Applications	Orchard/Vineyard		2.08 EC	0.0049 EC	0.015	350	2.45E-06	100000	0.000000321	780000	89000
Applying Sprays for Aerial Broadcast Applications	Field crop, typical		2.08 EC	0.0049 EC	0.015	350	2.45E-06	100000	0.000000321	780000	89000
Applying Sprays for Aerial Broadcast Applications	Field crop, high-acreage		2.08 EC	0.0049 EC	0.015	1200	8.42E-06	30000	0.0000011	230000	27000
Applying Sprays for Airblast Broadcast Applications	Nursery (ornamentals, vegetables, trees, container stock)		1770	4.71	0.015	20	0.000119	2100	0.0000176	14000	1800
Applying Sprays for Airblast Broadcast Applications	Orchard/Vineyard		1770	4.71	0.015	40	0.000239	1000	0.0000354	7100	880
Applying Sprays for Groundboom Broadcast Applications	Field-grown ornamental crops		78.6	0.34	0.015	40	0.0000106	24000	0.00000255	98000	19000
Applying Sprays for Groundboom Broadcast Applications	Nursery (ornamentals, vegetables, trees, container stock)		78.6	0.34	0.015	60	0.0000159	16000	0.00000383	65000	13000
Applying Sprays for Groundboom	Orchard/Vineyard		78.6	0.34	0.015	40	0.0000106	24000	0.00000255	98000	19000

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Broadcast Applications											
Applying Sprays for Groundboom Broadcast Applications	Field crop, typical		78.6	0.34	0.015	80	0.0000212	12000	0.0000051	49000	9600
Applying Sprays for Groundboom Broadcast Applications	Field crop, high-acreage		78.6	0.34	0.015	200	0.0000531	4700	0.0000128	20000	3800
Flagger											
Flagging for Aerial Applications	Nursery (ornamentals, vegetables, trees, container stock)	100	11	0.35	0.015	60	0.00000223	110000	0.00000394	63000	40000
Flagging for Aerial Applications	Orchard/Vineyard		11	0.35	0.015	350	0.000013	19000	0.000023	11000	7000
Flagging for Aerial Applications	Field crop, typical		11	0.35	0.015	350	0.000013	19000	0.000023	11000	7000
Flagging for Aerial Applications	Field crop, high-acreage		11	0.35	0.015	350	0.000013	19000	0.000023	11000	7000
Mixer/loader/Applicator											
Mixing, Loading, Applying DF/WDG for Ground/soil-directed Backpack	Orchard/Vineyard	100	8260	2.58	0.00038 lb ai/gal	40 gal	0.0000279	9000	0.000000484	520000	8800

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Mixing, Loading, Applying DF/WDG for Broadcast Foliar Backpack	Christmas Tree farm		58400	69.1	0.0003 lb ai/gal	40 gal	0.000158	1600	0.0000104	24000	1500
Mixing, Loading, Applying DF/WDG for Ground/soil-directed Backpack	Christmas Tree farm		8260	2.58	0.0003 lb ai/gal	40 gal	0.0000223	11000	0.000000388	640000	11000
Mixing, Loading, Applying DF/WDG for Broadcast Foliar Backpack	Nursery (ornamentals, vegetables, trees, container stock)		58400	69.1	0.0003 lb ai/gal	40 gal	0.000158	1600	0.0000104	24000	1500
Mixing, Loading, Applying DF/WDG for Ground/soil-directed Backpack	Nursery (ornamentals, vegetables, trees, container stock)		8260	2.58	0.0003 lb ai/gal	40 gal	0.0000223	11000	0.000000388	640000	11000
Mixing, Loading, Applying DF/WDG for Boradcast Foliar Manually-pressurized Handwand	Christmas Tree farm		100000	30	0.0003 lb ai/gal	40 gal	0.00027	930	0.0000045	56000	910
Mixing, Loading, Applying DF/WDG for Boradcast Foliar Manually-pressurized Handwand	Nursery (ornamentals, vegetables, trees, container stock)		100000	30	0.0003 lb ai/gal	40 gal	0.00027	930	0.0000045	56000	910

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Mixing, Loading, Applying DF/WDG Boradcast Foliar for Mechanically-pressurized Handgun	Orchard/Vineyard		6050	8.68	0.00038 lb ai/gal	1000 gal	0.000511	490	0.0000408	6100	450
Mixing, Loading, Applying DF/WDG for Ground/soil-directed Mechanically-pressurized Handgun	Orchard/Vineyard		6050	8.68	0.00038 lb ai/gal	1000 gal	0.000511	490	0.0000408	6100	450
Mixing, Loading, Applying DF/WDG for Broadcast Foliar Mechanically-pressurized Handgun	Christmas Tree farm		6050	8.68	0.0003 lb ai/gal	1000 gal	0.00041	610	0.0000325	7700	570
Mixing, Loading, Applying DF/WDG for Broadcast Foliar Mechanically-pressurized Handgun	Nursery (ornamentals, vegetables, trees, container stock)		6050	8.68	0.0003 lb ai/gal	1000 gal	0.00041	610	0.0000325	7700	570
Mixing, Loading, Applying DF/WDG for Ground/soil-directed	Nursery (ornamentals, vegetables, trees,		6050	8.68	0.0003 lb ai/gal	1000 gal	0.00041	610	0.0000325	7700	570

Table D.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Emamectin.											
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Dermal Unit Exposure (µg/lb ai)[1]**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Dermal**		**Inhalation**		**Total**
			Level of PPE or Engineering control *(baseline unless otherwise indicated)*		**Unit in lb ai/A *(unless otherwise indicated)***		**Dose (mg/kg/day)[4]**	**MOE[5]**	**Dose (mg/kg/day)[6]**	**MOE[7]**	**MOE[8]**
Mechanically-pressurized Handgun	container stock)										
Mixing, Loading, Applying DF/WDG for Broadcast Ground/Soil or Foliar Mechanically-pressurized Handgun	Field crop, typical		6050	8.68	0.0015 lb ai/gal	1000 gal	0.00204	120	0.000163	1500	110
Mixing, Loading, Applying Liquids for Broadcast Foliar Mechanically-pressurized Handgun	Field crop, typical		6050	8.68	0.00075 lb ai/gal	1000 gal	0.00102	250	0.0000814	3100	230
Mixing, Loading, Applying Liquids for Ground/Soil-directed Mechanically-pressurized Handgun	Field crop, typical		6050	8.68	0.00075 lb ai/gal	1000 gal	0.00102	250	0.0000814	3100	230

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of mitigation: Baseline, unless otherwise indicated. PPE includes EC = Engineering Controls; PF5 R = PF5 Respirator; G =.Gloves. For Mixing or Loading DF/WDG for Aerial Broadcast Applications to typical crops, the respirator currently required on registered labels must remain for those use patterns in order to support the continued waiver of the subchronic inhalation toxicity study.

2 Based on registered labels, as outlined in Table 4.1

3 Exposure Science Advisory Council Policy #9.1. Tree injector scenario assumed 160 trees for mixing/loading
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai)×Conversion Factor (0.001 mg/µg)×Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day)×DAF (1.8%) ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (mg/kg/day) ÷ Dermal Dose + Inhalation Dose

Appendix E. Occupational Post-Application Risk Summary

Table E.1. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Emamectin.							
Crop/Site	**ExpoSAC Policy Crop Group Category**	**Application Rate (lb ai/A)**	**Activities**	**Transfer Coefficient (cm^2/hr)**	**Initial Residue (µg/cm^2)[1]**	**Dermal Dose (mg/kg/day)[2]**	**MOE[3]**
Day 0 After Treatment							
Almond Hazelnut Macadamia nut Pecan Pistachio English walnut	Tree “nut”	0.015	Harvesting, Hand (net)	1400	0.003	0.0000076	33000
Apple Pear	Tree, "fruit", deciduous	0.015	Thinning Fruit	3600	0.003	0.00002	13000
Broccoli Brussels sprouts Cauliflower Cabbage	Vegetable, head and stem Brassica	0.015	Scouting, Harvesting, Hand, Weeding, Hand, Topping, Tying/Training	4200	0.003	0.00002	11000
Cabbage, chinese, Bok choy and Napa Celery, Collards Kale, Leaf Lettuce Mustard Greens Parsley, Spinach Swiss Chard	Vegetable, leafy	0.015	Weeding, Hand	4200	0.003	0.00002	11000
Cotton	Field / row crop, low / medium	0.015	Harvesting, Mechanical, Tramper	5050	0.03	0.00027	920
Eggplant Okra Bell and Chili Pepper Tomato	Vegetable, fruiting	0.015	Irrigation (hand set)	1900	0.003	0.00001	24000
Floriculture Crop	Flowers, cut	0.015	Harvesting, Hand	4800	0.003	0.00003	9600
Forestry; Nursery Crop (Ornamentals, Non-bearing Plants)	Unassigned	0.015	Irrigation (hand set)	1900	0.003	0.00001	24000

Table E.1. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Emamectin.							
Crop/Site	**ExpoSAC Policy Crop Group Category**	**Application Rate (lb ai/A)**	**Activities**	**Transfer Coefficient (cm^2/hr)**	**Initial Residue ($\mu g/cm^2$)[1]**	**Dermal Dose (mg/kg/day)[2]**	**MOE[3]**
Day 0 After Treatment							
Tobacco	Bunch/bundle	0.015	Irrigation (hand set)	1900	0.003	0.00001	24000

1 DFR = Predicted Day 0 residue value derived from celery DFR study, MRID# 44007903 used for all commodities, except for cotton boll harvesting activities for which surrogate boll residue data were used from Policy 3.

2 Daily Dermal Dose = [DFR ($\mu g/cm^2$) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (1.8%)] ÷ BW (80 kg).

3 MOE = POD (0.25 mg/kg/day) / Daily Dermal Dose.

Appendix F. International Tolerance Harmonization

Table F.1 . Summary of US and International Tolerances and Maximum Residue Limits for Emamectin.				
Residue Definition				
US [40 CFR §180.505(a)(1)] US		Canada	Mexico[1]	Codex
emamectin (a mixture of a minimum of 90% 4'-epi-methylamino-4'-deoxyavermectin B_{1a} and maximum of 10% 4'-epi-methylamino-4'-deoxyavermectin B_{1b}) and its metabolites 8,9-isomer of the $B_{1a}$and B_{1b}component of the parent (8,9-ZMA), or 4'-deoxy-4'-epi-amino-avermectin $B_{1a}$and 4'-deoxy-4'-epi-amino-avermectin B_{1b}; 4'-deoxy-4'-epi-amino avermectin B_{1a}(AB_{1a}); 4'-deoxy-4'-epi-(N-formyl-N-methyl)amino-avermectin (MFB_{1a}); and 4'-deoxy-4'-epi-N-formyl)amino-avermectin B_{1a}(FAB_{1a})		None		Emamectin B1a benzoate. The residue is not fat soluble.
Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg)				
Commodity	**US**	**Canada**	**Mexico**	**Codex**
Almond, hulls	0.20			
Apple, wet pomace	0.075			
Cotton, gin byproducts	0.050			
Cotton, undelinted seed	0.025			0.002 Cotton seed
Fruit, pome, group 11	0.025			0.02
Nut, tree, group 14	0.02			0.001
Pistachio	0.02			0.001
Tomato, paste	0.150			
Turnip, greens	0.050			
Vegetable, Brassica, leafy, group 5	0.050			
Vegetable, cucurbit, group 9	0.02			
Vegetable, fruiting, group 8	0.020			0.02
Vegetable, leafy, except Brassica, group 4	0.100			0.7 cos lettuce 0.7 leaf lettuce 1 head lettuce

Residue Definition				
US [40 CFR §180.505(a)(2)] US		Canada	Mexico[1]	Codex
Livestock: emamectin (MAB_{1a}+ MAB_{1b}isomers) and the associated 8,9-Z isomers (8,9-ZB_{1a}+ 8,9-ZB_{1b}) in/on the following commodities when present therein as a result of the application of emamectin to crops listed in the table in paragraph (a)(1)				Emamectin B1a benzoate. The residue is not fat soluble.
Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg)				
Commodity	**US**	**Canada**	**Mexico**	**Codex**
Cattle, fat	0.010			0.02
Cattle, liver	0.050			
Cattle, meat	0.003			0.004
Cattle, meat byproducts, except liver	0.020			

Residue Definition				
US [40 CFR §180.505(a)(2)] US		Canada	Mexico[1]	Codex
Goat, fat	0.010			
Goat, liver	0.050			
Goat, meat	0.003			
Goat, meat byproducts, except liver	0.020			
Hog, fat	0.003			
Hog, liver	0.020			
Hog, meat	0.002			
Hog, meat byproducts, except liver	0.005			
Horse, fat	0.010			
Horse, liver	0.050			
Horse, meat	0.003			
Horse, meat byproducts, except liver	0.020			
Milk	0.003			0.002
Sheep, fat	0.010			
Sheep, liver	0.050			
Sheep, meat	0.003			
Sheep, meat byproducts, except liver	0.020			

[1] Mexico adopts US tolerances and/or Codex MRLs.

Appendix G. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1; the AHETF database; and the ARTF database; are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[10].

[10] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure