Health Canada Santé Canada

Evaluation Report for Category B, Subcategory 5.0 Application

Application Number: 2013-4347
Application: New Maximum Residue Limits for Previously Assessed TGAI
Product: Abamectin Technical
Registration Number: 24484
Active ingredients (a.i.): Abamectin
PMRA Document Number : 2566198

Background

Abamectin is an insecticide/miticide which belongs to the avermectin class of chemicals and is a mixture of ≥ 80% avermectin B1a and ≤ 20% avermectin B1b. Members of the avermectin class are natural fermentation products of the soil bacterium *Streptomyces avermitilis*, which act by binding to gamma-aminobutyric acid (GABA)-gated ion channels, resulting in an influx of chloride ions into neurons, with ensuing paralysis and death. A review on abamectin was conducted previously and is summarized in the Proposed Regulatory Decision Document PRDD2001-01 *Abamectin Raid Max Roach Bait*.

Purpose of Application

The purpose of this application was to establish new import maximum residue limits (MRLs) and to amend existing MRLs for abamectin. Specifically to establish MRLs on/in cotton seed, avocado, papaya, celeriac, mint, Stone fruit (crop group (CG) 12), hops, strawberry, grapes, Leafy Vegetables (CG 4), Fruiting Vegetables (CG 8), Cucurbit Vegetables (CG 9), Tree Nuts (CG 14), Citrus (CG 10), Tuberous and Corm Vegetables (crop subgroup (CSG) 1C), and Herbs (CSG 19A (except chives)).

Chemistry Assessment

A chemistry assessment was not required for this application.

Health Assessments

Toxicology Summary

A detailed review of the toxicology database for abamectin was conducted previously and is summarized in the Proposed Regulatory Decision Document PRDD2001-01 *Abamectin Raid Max Roach Bait*. The database for abamectin included toxicity studies with abamectin, its components avermectin B1a and avermectin B1b, and the photolytic degradation products, including the delta 8,9-isomer of avermectin B1a. As summarized in PRDD2001-01, the primary target of abamectin toxicity is the nervous system, and the main toxicological endpoints, consistent across all species tested, were clinical signs of neurotoxicity (tremors, ataxia or lethargy) and death. In dogs, mydriasis was a common finding in all studies.

Malformations were a treatment-related finding in the fetuses of rabbits as well as CF-1 mice. A steep dose-response was demonstrated in many of the studies. At the time of registration, neurotoxicity studies were not available in the supporting toxicology database for abamectin.

As part of this application, acute and 90-day neurotoxicity studies, as well as two developmental neurotoxicity (DNT) studies, and a non-guideline study comparing maternal and pup systemic exposure, were submitted for review. In addition, a mouse local lymph node assay (LLNA), a 14-day oral gavage range-finding study in juvenile rats, and a 10-day/3-day oral gavage range-finding study in adult rats were available. Recent US EPA reviews of several endocrine disruption screening studies were also taken into consideration in the current assessment. A developmental toxicity study in CD-1 mice with the delta 8,9-isomer of avermectin B1a was not reported previously in the abamectin regulatory documentation and was incorporated in this assessment. Finally, a rationale to support a reduction in uncertainty factors in the risk assessment was submitted. A summary of the findings in the above-noted information is presented below.

Abamectin was negative for skin sensitization when tested in the mouse LLNA. It is noteworthy that animals treated with a 1% concentration of test material were found dead or euthanized on day 2 or 3, illustrating abamectin's high acute toxicity.

In the acute oral gavage neurotoxicity study with abamectin in rats, decreased splay reflex was observed in both sexes. In addition, splayed and tip toe gait, as well as decreased total motor activity, were observed in females at higher doses. There were no treatment-related neuropathological findings.

In the subchronic oral gavage neurotoxicity study, rats in the highest dose group were euthanized during week 7 due to pronounced clinical signs of toxicity (e.g. shaking, irregular breathing, reduced righting and splay reflex, decreased fore- and hindlimb grip strength) and body weight loss. There was no evidence of systemic or neurotoxicity at lower dose levels.

In a 14-day oral gavage range-finding study in juvenile (21-day-old) rats, decreases/loss in body weight and clinical signs (including tremors) were noted early post-dosing. The severity of clinical signs resulted in early termination of animals in the high-dose group. In a 10-day (male) or 3-day (female) oral gavage range-finding study in adult rats that employed sequential dosing, clinical signs of toxicity (including tremors, convulsions, hypoactivity) were noted following administration of a dose approaching/sometimes exceeding the acute oral LD_{50} values, and all animals were euthanized in extremis.

The two DNT studies conducted via oral gavage both employed the same dose levels and strain of rat. The second, or follow-up, study was conducted due to procedural deficiencies in the original study that rendered the brain morphometric data uninterpretable. There was no evidence of maternal toxicity in either study. Pup body weights were reduced post-weaning in both studies; in the follow-up study this was observed down to the lowest dose level. Pup mortality was only observed at the high dose in the follow-up study, with deaths occurring after post-natal day (PND) 8. High-dose pups in this study were also small in size and displayed clinical signs of toxicity (e.g. tremors, dehydration). Sensitivity of the young animal compared to the adult animal to abamectin toxicity was demonstrated in both studies on the basis of the above findings. The

dose levels producing clinical signs of toxicity and mortality in pups in the DNT studies were consistent with those producing the same effects in the reproductive toxicity studies, which were previously reported in PRDD2001-01.

As noted above, due to processing errors, the brain morphometric data in the original study were deemed uninterpretable by the study authors. There were some challenges with respect to the interpretation of the brain morphometric data in the follow-up study. In this study, brain morphometric data were not available for high-dose pups due to early mortality. Initially, only tissues from the control and mid-dose groups were processed. At the mid dose, statistically significant reductions in measurements of several regions of the brain were noted in PND 12 and/or PND 63 animals. Consistently lower values for almost all brain region measurements were recorded for the low-dose group. These consistently lower values were thought to result from longer storage time in wax blocks compared to that of the control and the mid-dose group. In an attempt to address this issue, additional tissues were cut and assessed from all groups after an extended storage period and demonstrated that there was some effect of storage time on tissue shrinkage. In addition to the confounding effect of storage time, not all brain regions were examined in the additional morphometric investigations, making it difficult to directly compare the measurements for the controls with those in the treated groups. Consequently, the low dose level findings were of limited utility in assisting in the interpretation of potential adverse effects. In view of this, the morphometric findings noted in PND 12 and/or PND 63 animals are considered equivocal, and endpoints for risk assessment take into account margins to these findings. In determining the overall level of concern, it is important to note that there were no treatment-related effects on neurobehavioural assessments or brain pathology in either DNT study. Decreased pup brain weights were only noted in the initial DNT study and only at the highest dose.

A series of endocrine disruptor screening studies with abamectin included uterotrophic and Hershberger assays as well as pubertal female/male assays, and estrogen/androgen receptor binding assays. All assays were negative with the exception of the steroidogenesis assay using the human cell line, H295R, which demonstrated a decrease in estradiol production.

In a comparative study investigating maternal and pup exposure to avermectin B1a following dosing of the dams during gestation and lactation, pup plasma and brain levels were 2-fold and 6-fold higher, respectively, than corresponding levels in dams. Pup mortality increased with dose, with most deaths occurring between PND 6-8.

There was no evidence of maternal toxicity in a developmental toxicity study in CD-1 mice with the delta 8,9-isomer of avermectin B1a. There was a slightly increased incidence (on a fetal and litter basis) of cleft palate at the highest dose which fell just above the range of historical control values from a limited set of data. Since cleft palate was observed in fetuses of CF-1 mice and rabbits treated with abamectin, a possible relationship to treatment could not be ruled out and it was considered appropriate to ensure an adequate margin to this finding in the selection of toxicological endpoints.

A key feature of the abamectin toxicity database was the observation, in several studies, of pup mortality which typically began within the first week after birth. Studies in rats with ivermectin , (a member of the avermectin class), which included a cross-fostering study, suggested that the

early pup mortality was a result of exposure through the dam's milk. A rationale was submitted to address the issue of sensitivity of the young animal and subsequently support a reduction in uncertainty factors for human risk assessment. The claim was made that use of the rodent model in human health risk assessment was conservative, since the rodent fetus and neonate are susceptible to abamectin toxicity as a result of differences in P-glycoprotein ontogeny between rodents and humans. Members of the avermectin family, including abamectin, are substrates for P-glycoprotein. Other substrates include drugs such as steroids, statins, and antibiotics. P-glycoprotein is an adenosine triphosphate (ATP)-binding cassette (ABC) transporter, a protein that mediates the active transport of molecules across cellular membranes in an ATP-dependent manner. P-glycoprotein is expressed in adrenal, liver, and kidney cells, intestinal epithelium, and on the luminal surface of blood capillaries in the brain, testes, ovaries, and placenta in rodents and humans, as well other animals, and performs an efflux transporter function, limiting gut absorption, mediating excretion, and controlling entry of a wide range of chemicals to sensitive body compartments, such as the brain.

P-glycoprotein is encoded by the gene ABCB1 (also known as MDR1 or multi-drug resistance gene). The protein is encoded by one gene (MDR1) in humans and dogs and 2 genes (mdr1a and mdr1b, sharing common function) in mice. Spontaneous mutations of the mdr1 gene in the CF-1 strain of mice, as well as disruption of the MDR1 gene in dog breeds related to the collie, have been shown to produce a non-functional P-glycoprotein, resulting in susceptibility to toxicity from ivermectin, a member of the avermectin class. This has been demonstrated in the CF-1 mouse strain through differences in lethality and susceptibility to cleft palate, depending upon P-glycoprotein genotype. In addition, the developmental toxicity data from the CF-1 mice studies provided the overall lowest effect levels in the abamectin database. In humans, although gene disruption in the MDR1 gene encoding for P-glycoprotein is known, the scientific literature reports that a definitive, reproducible correlation between gene disruption and alterations in P-glycoprotein function has not been demonstrated. Having said that, there is a low likelihood that humans will have compromised P-glycoprotein functionality similar to that of the sensitive CF-1 mouse.

In rodents, the blood-brain barrier is not completely developed in the fetus/neonate. In addition, P-glycoprotein is not expressed until approximately PND 7, and not fully developed to adult levels until around PND 28. For these reasons, newborn rodent pups have an increased susceptibility to abamectin toxicity compared to adult rodents. Human infants, on the other hand, are born with an intact blood-brain barrier, and P-glycoprotein is fully expressed before birth. Brain P-glycoprotein expression has been detected in fetuses as early as week 8 of pregnancy and expression of P-glycoprotein in placenta is highest during early pregnancy (60 days), decreasing as gestation progresses.

Evidence in the abamectin database consistent with the timing of P-glycoprotein expression in the developing rodent included the pup mortality occurring in the early postnatal period in the reproductive toxicity and DNT studies, and results from the ivermectin cross-fostering study in rats. The fact that pup mortality did not always occur at the same dose level in these studies is not unexpected given normal biological variability in kinetics and in the timing of P-glycoprotein development, as well the steep dose-response curve for abamectin. Pups exposed to avermectin B1a through their mother's milk exhibited higher brain concentrations of test substance during the postnatal period compared to the maternal animal, consistent with the

ontogeny of P-glycoprotein expression in the blood-brain barrier.

The overall information suggests that rodents are more sensitive than humans to abamectin toxicity as a result of differences in the gene(s) encoding P-glycoprotein, and that the rodent neonate is more sensitive than the human neonate on account of differences in the ontogeny of P-glycoprotein expression as well as differences in the timing of blood-brain barrier development. Notwithstanding the above, the possibility that humans may have compromised P-glycoprotein function cannot be ruled out. For this reason, the results of toxicity testing in rodents were considered relevant for hazard characterization and risk assessment. However, the likelihood that humans will have compromised P-glycoprotein functionality similar to that of the sensitive CF-1 mouse strain is low, suggesting that use of toxicity data from studies conducted with the CF-1 mouse is overly conservative. For this reason, data from the CF-1 mouse were used to inform hazard characterization, but not used for toxicology endpoint selection.

As a result of the submission and review of new data, a re-examination of the endpoints previously selected for dietary risk assessment was undertaken. The re-examination of the toxicological database resulted in an amendment to the no observable adverse effect level (NOAEL) for parental toxicity in the 2-generation reproductive toxicity study with abamectin. This NOAEL, which was previously set at 0.05 mg/kg bw/day based on reduced body weight gains during lactation, was amended to 0.4 mg/kg bw/day (the highest dose tested) since the changes in body weight were not considered to be adverse.

Table 1 of Appendix I contains the amended results of the reproductive toxicity study as well as the results of the newly submitted studies discussed above. In addition, data not previously summarized in PRDD2001-01 are also documented in Table 1. Toxicological endpoints selected for the human health risk assessment are found in Table 2 of Appendix I.

PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for abamectin, as outlined in PRDD2001-01 and above. The database included reproductive toxicity, developmental toxicity, and DNT studies, as well as studies assessing the comparative exposure (plasma and brain levels) of the young versus the adult animal, and several published scientific papers discussing effects in the young animal.

With respect to potential prenatal and postnatal toxicity, the findings in the abamectin toxicology database demonstrated evidence of sensitivity of the young in several studies as well as a steep dose-response. Acute oral toxicity data indicated that the neonatal rat LD_{50} was 6 to 7-fold lower than that in the adult rat. In pups in the reproductive toxicity and DNT studies, decreased body weight, as well as clinical signs and mortality beginning shortly after birth, occurred in the absence of any effects in maternal animals. A cross-fostering study with ivermectin demonstrated

that the early pup mortality observed in these studies was a result of post-natal exposure via the milk, rather than exposure in utero. Although a NOAEL for offspring toxicity was not established in the follow-up DNT study, the LOAEL was based on a reduction in pup body weight, which is not considered a serious effect. A comparative study in rat dams and pups demonstrated higher levels of avermectin B1a in pup plasma and brains compared to dams.

In the developmental toxicity studies, treatment resulted in fetal malformations, including cleft palate in rabbits, CF-1 mice, and possibly CD-1 mice. With the exception of the findings in the rabbit, these serious effects were observed in the absence of maternal toxicity. Equivocal brain morphometric findings in the follow-up DNT study were noted in the absence of maternal toxicity. As noted earlier, there were no treatment-related effects on the neurobehavioural assessments in either DNT study and decreased pup brain weights were only noted in the initial DNT study and only at the highest dose.

Although serious endpoints (pup mortality, malformations) were observed in the abamectin database in the absence of maternal toxicity, concern for these findings is tempered by the fact that the rodent neonate is more sensitive than the human neonate with respect to abamectin toxicity due to differences in the ontogeny of P-glycoprotein expression and blood-brain barrier development. As noted above, the possibility of compromised P-glycoprotein function in humans cannot be ruled out, and any subsequent impact early in gestation, and particularly during critical periods of fetal development, is unclear. For these reasons, there remains uncertainty with respect to sensitivity of the young. This uncertainty was reflected through the use of a PCPA factor of 3-fold in the risk assessment. The use of a 3-fold PCPA factor also takes into account the steep dose-response and provides adequate margins to endpoints of concern in the database.

Acute Reference Dose (ARfD)

To estimate acute dietary risk (1 day), the acute neurotoxicity study in rats with a NOAEL of 0.5 mg/kg bw was selected for risk assessment. At the LOAEL of 1.5 mg/kg bw, decreased splay reflex was observed. Selection of this study and NOAEL is supported by the results in the 12-week dog study for which a NOAEL of 0.5 mg/kg bw/day was established. At the LOAEL of 1.0 mg/kg bw/day, mydriasis was observed in the first week of dosing. The specific timing of this observation was not clear; however, examination of the collective results of the dog studies indicated that at higher doses, mydriasis was observed within 24 hours of initial treatment. Therefore, the possibility that mydriasis may have resulted following a single dose at 1.0 mg/kg bw/day could not be ruled out, and for this reason it was considered supportive evidence for the acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the PCPA Hazard Characterization section, a PCPA factor of 3-fold was considered appropriate. The composite assessment factor (CAF) is thus 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.5 \text{ mg/kg bw}}{300} = 0.0017 \text{ mg/kg bw of abamectin}$$

The ARfD provides margins of 118 to the equivocal brain morphometric findings, 588 to the

NOAEL for malformations in the rabbit developmental toxicity study, and 882 to the NOAEL for cleft palate in the CD-1 mouse developmental toxicity study. The ARfD is considered protective of all populations, including females of child-bearing age and nursing infants.

Acceptable Daily Intake (ADI)

To estimate risk of repeated dietary exposure, the results of the DNT studies in rats were considered. The offspring NOAEL of 0.12 mg/kg bw/day from the initial DNT study was selected for risk assessment. At the LOAEL of 0.2 mg/kg bw/day, decreased pup body weight was observed. The selection of this study was supported by the findings of a supplemental 1-generation reproduction toxicity study with avermectin B1a in rat, in which spastic movements in pups were observed at 0.2 mg/kg bw/day, with no adverse findings recorded at 0.1 mg/kg bw/day. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. For the reasons outlined in the PCPA Hazard Characterization section, a PCPA factor of 3-fold was considered appropriate. The composite assessment factor (CAF) is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.12 \text{ mg/kg bw/day}}{300} = 0.0004 \text{ mg/kg bw/day of abamectin}$$

The ADI provides a margin of 500 to the lowest NOAEL for pup mortality in the database, to the NOAEL for reduced fertility in the abamectin 2-generation reproductive toxicity study, and to the equivocal brain morphometric findings in the developmental neurotoxicity study. It also provides a margin of 300 to the offspring LOAEL for reduced pup body weight in the follow-up DNT study. The ADI is considered protective of all populations, including females of child-bearing age and nursing infants.

Cancer Risk Assessment

There was no evidence of carcinogenicity and therefore, a cancer risk assessment was not necessary.

Food Residues Exposure Assessment

Residue data for abamectin in papaya, avocado, celeriac, basil, cotton, mint, stone fruits, leafy vegetables, fruiting vegetables, cucurbit vegetables, and citrus fruits were submitted to support the maximum residue limits on various imported commodities. In addition, previously reviewed residue data from field trials conducted in/on citrus fruits, leafy vegetables, strawberries, fruiting vegetables, tree nuts, potatoes, grapes, and hops were reassessed in the framework of this petition. In addition, processing studies in treated dried prunes; mint oil; cottonseed hulls, meal, and refined oil; tomato paste and puree, and citrus fruit oil were reviewed or reassessed to determine the potential for concentration of residues of abamectin into processed commodities.

Maximum Residue Limits

The recommendation for MRLs for abamectin was based upon the file and submitted field trial data, and the guidance provided in the OECD MRL Calculator. MRLs to cover residues of avermectin B_1 and the 8,9-Z isomer in/on imported crops and processed commodities are proposed as shown in Table 1. Residues in processed commodities not listed in Table 1 are covered under the proposed MRLs for the raw agricultural commodities (RACs).

TABLE 1. Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs)

Commodity	Application Method/ Total Application Rate (g a.i./ha)	PHI (days)	Residues* (ppm)		Experimental Processing Factor	Currently Established MRL (ppm)	Recommended MRL (ppm)
			LAFT	HAFT			
Papayas	Foliar/ 89.2 – 93.0	14	0.0061	0.0083	n/a	None	0.03
Avocado	Foliar/ 52.5 – 54.9	14	<0.004	<0.009	n/a	None	0.02
Spearmint tops and Peppermint tops	Foliar/ 63.9	28	<0.004	<0.009	0.14 (mint oil)	None	0.01
Undelinted cotton seeds	Foliar/ 42.6 – 43.7	19 – 20	<0.006	<0.014	0.6x (refined oil)	None	0.02
Fresh basil leaves	Foliar/ 66.8 – 67.1	13 – 14	<0.005	<0.010	n/a	None	0.03 (CSG 19A, except chives)
Dried basil leaves	Foliar/ 66.8	13	<0.026		n/a	None	
Sweet cherries	Foliar/ 52.4	21	<0.006	<0.019	n/a	None	0.09 (CG 12)
Tart cherries	Foliar/ 52.4	21	<0.008	0.053	n/a		
Peaches	Foliar/ 52.4	21 – 22	<0.004	0.026	n/a		
Plums	Foliar/ 53.8	21	<0.004	<0.006	1.9x (dried prunes)		
Almonds	Foliar/ 81	21	<0.01	<0.01	n/a	0.005	0.01 (CG 14 and pistachios)[1]
Pecans	Foliar/ 81	21	<0.01	<0.01	n/a	None	
Oranges	Foliar/ 51.1 – 54.4	7	<0.004	<0.007	7x (citrus oil)	0.02 (citrus fruits)[2]	0.10 (citrus oil)
Grapefruit	Foliar/ 51.1 – 53.4	6 – 7	<0.004	<0.006			
Lemons	Foliar/ 51.5 – 53.1	7	<0.004	<0.008			

TABLE 1. Summary of Field Trial and Processing Data Used to Support Maximum Residue Limits (MRLs)

Commodity	Application Method/ Total Application Rate (g a.i./ha)	PHI (days)	Residues* (ppm)		Experimental Processing Factor	Currently Established MRL (ppm)	Recommended MRL (ppm)
			LAFT	HAFT			
Head lettuce w/ wrapper leaves	Foliar/ 61.7 – 65.3	5 – 7	<0.004	<0.010	n/a	0.05 (head lettuce)	0.10 (CG 4)[3]
Leaf Lettuce	Foliar/ 61.8 – 64.9	6 – 7	<0.007	<0.034	n/a	n/a	
Celery	Foliar/ 63.6 – 66.0	7	<0.006	<0.018	n/a	0.05 (celery)	
Spinach	Foliar/ 64.1 – 65.8	7	<0.004	0.052	n/a	n/a	
Tomatoes (standard size and cherry tomatoes)	Foliar/ 62.0 – 64.9	7	<0.006	<0.008	1.00x (paste) 0.63x (puree)	0.01 (tomatoes)	0.02 (CG 8)[4]
Bell peppers	Foliar/ 63.3 – 65.6	7	<0.006	<0.012	n/a	0.01 (pepper)	
Nonbell peppers	Foliar/ 61.9 – 64.5	7	<0.006	<0.010	n/a		
Cantaloupe	Foliar/ 63.5 – 110.9	7	<0.006	<0.010	n/a	0.005 (cucumbers)	0.01 (CG 9)[5]
Cucumber	Foliar/ 63.5 – 97.4	6 – 7	<0.006	<0.010	n/a		
Summer Squash	Foliar/ 63.6 – 88.5	6 – 7	<0.006	<0.010	n/a		
Celeriac roots	Foliar/ 66.0 – 66.1	7	<0.004	<0.004	n/a	None	0.05
Celeriac tops	Foliar/ 66.0 – 66.1	7	<0.007	<0.016	n/a	None	0.05
Potatoes	Foliar/ 64 – 672	14 – 15	<0.004	<0.010	No quantifiable residues in the RAC at exaggerated rates.	0.01 (potatoes)	0.01 (CSG 1C, except potatoes)[6]

LAFT = lowest average field trial; HAFT = highest average field trial; n/a = not applicable

* Total residues of avermectin B_1 (avermectin B_{1a} and avermectin B_{1b}) and the 8,9-Z isomer

[1] Replace the currently established MRLs of 0.005 ppm in/on almond nuts, English walnuts, and black walnuts.

[2] Although there is currently a MRL established for residues of abamectin in/on "citrus fruits" and no new MRLs for this crop group are being recommended, the previously established MRL of 0.02 ppm for "citrus fruits" will be replaced by MRLs of 0.02 ppm for each commodity listed under Crop Group 10 –Citrus Fruits (DIR98-02) to reflect the current terminology for these commodities.

[3] Replaces the current established MRLs of 0.05 ppm in/on head lettuce and celery.
[4] Replaces the current established MRLs of 0.01 ppm in/on tomatoes and peppers.
[5] Replaces the current established MRL of 0.005 ppm in/on cucumbers.
[6] Potatoes are excluded as a 0.01 ppm MRL is already established for the commodity in Canada.

Environmental and Value Assessments

Environmental and value assessments were not required for this application to amend MRLs.

Conclusion

Following the review, MRLs as proposed in Table 1 are recommended to cover residues of abamectin. Residues in these crops at the proposed MRLs will not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

List of Abbreviations

♀	female
♂	male
µM	mirco molar
a.i.	active ingredient
ABC	ATP-binding cassette
ADI	acceptable daily intake
ARfD	acute reference dose
ATP	adenosine triphosphate
bw	body weight
bwg	bodyweight gain
CAF	composite assessment factor
CG	crop group
CSG	crop subgroup
DNT	developmental neurotoxicity
F0	initial parental generation
F1	first generation
F2	second generation
fc	food consumption
g	gram
GABA	gamma-aminobutyric acid
GD	gestation day
ha	hectare
HAFT	highest average field trial
hr(s)	hour(s)
kg	kilogram
LAFT	lowest average field trial
LD_{50}	lethal dose to 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
M	molar
mg	milligram(s)

MRL	maximum residue limit
n/a	not applicable
NOAEL	no observed adverse effect level
OECD	Organization for Economic Cooperation and Development
PCPA	*Pest Control Product Act*
PHI	preharvest interval
PMRA	Pest Management Regulatory Agency
PND	postnatal day
ppm	parts per million
PRD	Proposed Registration Decision
RAC	raw agricultural commodity
SI	stimulation index
TSH	thyroid stimulating hormone
wk	week
wt	weight
US EPA	United States Environmental Protection Agency

Appendix I Tables and Figures

Table 1 Newly Submitted/Amended Toxicity Studies with Abamectin Technical (see also PRDD2001-01)

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/ PMRA #	Study Results
Dermal sensitization (Local lymph node assay) CBA/J Rj Mouse PMRA # 2529314	SI < 3.0 for all dose levels Negative During the Preliminary Irritation test (2♀/group, treated with 0.5% or 1%), animals treated with 1 % were found dead or euthanized on either Day 2 or 3.
14-day oral (gavage) (range-finding) Abamectin Juvenile Sprague Dawley rat PMRA #2529326	Effect levels not established as the study was considered supplemental Effects at 2.5 mg/kg bw/day included: tremors (noted as early as 1 hr post-dosing), clear material around nose and/or mouth, bw loss over first 2-3 days of dosing, ↓bw & bwg Effects at 5 mg/kg bw/day included: severe tremors (♀, approx. 4 hrs after first dose) resulting in sacrifice of all ♀ on PND 22 (and subsequent removal of the ♂ at this dose from the study)

Study Type/Animal/ PMRA #	Study Results
10 day (♂) or 3 day (♀) oral (gavage) (range-finding) Abamectin Sprague Dawley rat (conducted to determine dose levels for an endocrine disruptor screening study) PMRA #2529526	Effect levels not established as the study was considered supplemental Effects at ≥7.5 mg/kg bw/day included: clear/red material around mouth, nose and eyes, bw loss Effects at ≥15 mg/kg bw/day included: all animals euthanized in extremis following 1-2 doses, clinical signs of toxicity (tremors, convulsions, hypoactivity, hunched posture, shallow respiration, prostration, clear/coloured material around the mouth, nose, eyes, and urogenital area).
2-generation reproduction (gavage) Abamectin Sprague Dawley rat PMRA #1238577	Parental NOAEL = 0.4 mg/kg bw/day (highest dose tested) Parental LOAEL not established as there were no adverse effects observed Reproductive NOAEL = 0.12 mg/kg bw/day Reproductive LOAEL = 0.4 mg/kg bw/day Effects at the reproductive LOAEL included: ↓male and female mating indices (F0-F1b litter) and ↑days to mating (F0); ↓fertility index (F0-F1b litter), ↑estrous stage (F0-F1b litter) (♀). Offspring NOAEL = 0.12 mg/kg bw/day Offspring LOAEL = 0.4 mg/kg bw/day Effects at the offspring LOAEL included: ↑pup mortality (both litters of the F0 and F1 generations, most deaths between PND 5-15), ↓viability index (PND 4-21), ↓lactation index, ↓pup body weight PND 7-21, ↑number of pups which were thin, weak and not nursing, ↑incidence of retinal anomalies in F1b and F2b weanlings (primarily retinal rosettes). Evidence of increased sensitivity of the young

Study Type/Animal/ PMRA #	Study Results
2-generation reproduction (gavage) Ivermectin Sprague Dawley rat PMRA #2334852	Parental NOAEL = 0.4 mg/kg bw/day Parental LOAEL = 1.2 mg/kg bw/day Effects at the parental LOAEL included: ↓bwg (20%) during lactation (F1b♀) Reproductive NOAEL = 3.6 mg/kg bw/day (highest dose tested) Reproductive LOAEL not established as there were no adverse effects observed Offspring NOAEL not established Offspring LOAEL = 0.4 mg/kg bw/day Effects at the offspring LOAEL included: ↑pup mortality (F1b, F2a), ↓bw (F1b, F2a), ↓auditory startle reflex (F1b) Effects in offspring at higher dose levels included: ↓ time to incisor eruption (F1b, F2a, secondary to ↓bw), delayed vaginal opening and testes descent (F1b), delayed righting reflex and auditory startle reflex (F2a). At the highest dose level (3.6 mg/kg bw/day; F1a litter only), ↑pup mortality, ↓bw, clinical signs (absence of milk in the stomach, lethargy, hypothermia) were additionally observed. Evidence of increased sensitivity of the young
3-generation reproduction (gavage) (supplement to the above study in order to establish a NOAEL for offspring toxicity) Ivermectin Sprague Dawley rat PMRA #2334852	Parental NOAEL = 0.4 mg/kg bw/day (highest dose tested) Parental LOAEL not established as there were no adverse effects observed Reproductive NOAEL = 0.4 mg/kg bw/day (highest dose tested) Reproductive LOAEL not established as there were no adverse effects observed Offspring NOAEL = 0.4 mg/kg bw/day (highest dose tested) Offspring LOAEL not established as there were no adverse effects observed No evidence of increased sensitivity of the young

Study Type/Animal/ PMRA #	Study Results
1-generation cross-fostering study (gavage) Ivermectin Sprague Dawley rat On PND 1 all litters were cross-fostered to dams within or between the treated and control groups (4 groups in total). The study was conducted to determine whether neonatal toxicity was the result of prenatal, postnatal or a combination of pre- and post-natal exposure to ivermectin. A sub-study investigated levels of ivermectin in the plasma and milk of dams, and in pup blood, brain and carcass. Dams were either administered ivermectin for 61 days, then through mating, gestation and until PND 9 (chronic group), or from PND 1-9 only (subacute group). PMRA #2334852	Effect levels not established as the study was considered supplemental ↑pup mortality PND 7-14 was observed in the groups that contained treated dams, regardless of whether the fostered pups had been exposed to ivermectin in utero. ↓bw was also noted in pups from treated dams that were cross-fostered to other treated dams. Survival, growth and development of pups from treated dams that were cross-fostered to control dams were comparable with those of pups that were fostered within the control group. These results indicate that the neonatal toxicity of ivermectin in rats is a function of postnatal exposure only, since the toxicity and increased mortality were restricted to pups from treated and control dams that were cross-fostered to dams continuously administered ivermectin. <u>Levels of ivermectin in maternal plasma and milk:</u> Levels of radioactivity in maternal milk were 3-4-fold higher than those in the plasma, which resulted in significantly higher levels of ivermectin in the brain and plasma of nursing offspring. Plasma radioactivity levels in offspring from the chronic group were very low on PND 1, but increased rapidly until PND 6-10 when the concentration was 2-3 times greater than that found in the lactating dams. Plasma levels in the subacute group reached similar levels to those from the chronic group by PND 10. Residues of ivermectin in the liver, brain and carcass of offspring from both groups were 2-3 times higher than those found in the same tissues of the dams. The plasma-brain ratio of radiolabelled ivermectin in offspring was approx. 1.0 on PND 1 & 4, but increased to 2-3 on PND 6 & 10.

Study Type/Animal/ PMRA #	Study Results
Developmental toxicity study Delta 8,9-isomer of avermectin B1a CF-1 mice (special genotype susceptibility study in which females that were heterozygous (+/-) and homozygous (-/-) or (+/+) for p-glycoprotein were mated to heterozygous and homozygous males) PMRA #2554310	Effect levels not established as the study was considered supplemental No maternal toxicity observed in any of the treated groups that received 1.5 mg/kg bw/day. Cleft palate was observed in 97% of (-/-) fetuses, 40% of (+/-) fetuses, and 0% of (+/+) fetuses.
Developmental toxicity study Delta 8,9-isomer of avermectin B1a CD-1 mouse [(+/+) for the p-glycoprotein gene] PMRA #2542644	Maternal NOAEL = 3.0 mg/kg bw/day (highest dose tested) Maternal LOAEL not established as there were no adverse effects observed Developmental NOAEL = 1.5 mg/kg bw/day Developmental LOAEL = 3.0 mg/kg bw/day Effects at the developmental LOAEL: increased incidence (fetal/litter) of cleft palate [0(0), 2(2), 1(1), 4(3)]. Malformations at a non-maternally toxic dose
Acute neurotoxicity (oral gavage) Sprague Dawley rat PMRA #2334853	NOAEL = 0.5 mg/kg bw LOAEL = 1.5 mg/kg bw Effects at the LOAEL included: ↓splay reflex (day 1, persisting until day 3 in some high dose animals)

Study Type/Animal/ PMRA #	Study Results
90-day neurotoxicity (oral gavage) Sprague Dawley rat PMRA #2334849	NOAEL = 1.6 mg/kg bw/day LOAEL = 4.0 mg/kg bw/day Effects at the LOAEL included: ↓ bw, ↓bwg, clinical signs of toxicity (♂-piloerection, staining around mouth and nose, subdued behaviour, upward curvature of the spine; ♀- shaking, irregular breathing, sides pinched in, tip-toe gait, upward curvature of the spine, stains around mouth and nose, piloerection, reduced righting and splay reflexes); bw loss (wk 7), ↓forelimb & hindlimb grip strength (♀) Clinical signs of toxicity resulted in the early termination of the high dose group in wk 7.
Developmental neurotoxicity (dietary) Range-finding Abamectin Sprague Dawley rat PMRA #2335008	Effect levels not established as the study was considered supplemental. No maternal toxicity was observed up to the highest dose tested (~1.5 mg/kg bw/day). Effects in offspring at 0.876 mg/kg bw/day included: ↓pup survival PND 12 until termination, ↓total litter wt.
Developmental neurotoxicity (oral gavage) Abamectin Sprague Dawley rat PMRA #2334856	Maternal NOAEL = 0.4 mg/kg bw/day (highest dose tested) Maternal LOAEL not established as there were no adverse effects observed Offspring NOAEL = 0.12 mg/kg bw/day Offspring LOAEL = 0.2 mg/kg bw/day Effects at the offspring LOAEL included: ↓ pup bw post-weaning (PND 36 and PND 63(♀) Offspring effects at the next highest dose of 0.4 mg/kg bw/day included: ↓ pup bw on the day of weaning and throughout PND 36-63; delayed vaginal opening (2.8 days), ↓brain wt (PND 63) (♀) **Note**- Due to procedural deficiencies that rendered the brain morphometry data uninterpretable (accidental non-random processing of tissue samples, the use of 2 tissue processing machines and different storage/fixation times between treatment groups), these results should be considered together with those of a follow-up study (reported below; PMRA #2334858). Evidence of increased sensitivity of the young

Study Type/Animal/ PMRA #	Study Results
Developmental neurotoxicity (oral gavage) Abamectin Sprague Dawley rat PMRA #2334858	Maternal NOAEL = 0.4 mg/kg bw/day (highest dose tested) LOAEL not established as there were no adverse effects observed Offspring NOAEL not established Offspring LOAEL = 0.12 mg/kg bw/day Effects at the offspring LOAEL included: ↓pup bw PND 36-63 Offspring effects at the next highest dose of 0.2 mg/kg bw/day included:↓pup bw PND 36-63, ↓in brain morphometric measurements [dorsal cortex thickness (PND 12♂, PND 63♀), cerebellum-preculminate fissure, inner granular layer thickness (PND 12♂, PND 12 ♀, PND 63♂), cerebellum-preculminate fissure, outer granular layer thickness (PND 12♀), thalamus/cortex width (PND 63♂), piriform cortex (PND 63♀)]. Offspring effects at the highest dose of 0.4 mg/kg bw/day included: ↑pup mortality after PND 8, clinical signs of toxicity (including tremors, dehydration, cold, pinched-in sides), pups small in size, ↓pup bw (PND 8-36). <u>Note:</u> due to increased mortality of pups at the high dose level (no surviving pups after PND 38) there were an insufficient number of pups to complete all of the study objectives, and all dams and pups at this dose were removed from the study during PND 15-38. Evidence of increased sensitivity of the young

Study Type/Animal/ PMRA #	Study Results
Comparative maternal and pup exposure following dietary and gavage dosing Avermectin B1a Sprague Dawley rat Pregnant ♀ dosed from GD7-PND 11 or 18. The concentration of radioactivity in dam plasma, milk and brain, and pup plasma, brain and carcass were determined on PND 4, 8, 11, 18. PMRA #2334867	Effect levels not established as the study was considered supplemental. The concentration of radioactivity in all samples increased with dose for both the dam and pup samples. Concentrations were similar between gavage and dietary groups that received doses of a similar magnitude, indicating that exposure in both dams and pups was similar following either gavage or dietary administration. Pup mortality increased with dose (most deaths between PND 6-8). A dose-dependent ↓ in bw was also observed (↓44-58% in high dose animals at PND 11). In dams, the concentration of radioactivity in milk was 3-6 times higher than that in the plasma, and levels in plasma were 6-7 times higher than those in the brain. In pups, plasma levels were 1-2 times higher than levels in the brain. The data showed that the pups were exposed to higher concentrations of radioactivity than the dams. The concentration of radioactivity in plasma was higher in pups than dams at all dose levels and all time points, regardless of route of exposure (average ratio of approximately 2:1). Radioactivity was present in the brains of both pups and dams, however levels were much higher in pup brains [ratio of approximately 6:1 in pups:dams at PND 18 (PND 11 for high dose)]
Estrogen receptor (ER) binding assay Abamectin Sprague Dawley rat uterine cytosol PMRA #2557845	Precipitation occurred at 10^{-3} M in Runs 1 and 2 and at 10^{-4} M in Run 3, and therefore, these data were excluded from evaluation. Abamectin had no significant effect on specific radioligand binding (>75% binding; not interactive) at concentrations of $\leq 10^{-4}$ M in Runs 1 and 2 and $\leq 10^{-5}$ M in Run 3. Classified as Not Interactive in this assay
ERα transcriptional activation assay (ERTA) Abamectin Human cell line HeLa 9903 PMRA #2557845	Considered negative for estrogen receptor transcriptional activation in this test system.

Study Type/Animal/ PMRA #	Study Results
Androgen receptor binding assay Abamectin Sprague Dawley rat prostate cytosol PMRA #2557845	Abamectin had no effect on specific binding of the [3H]-ligand (>75% binding) over the concentration range 10^{-11} to 10^{-4} M. Classified as a Non-Binder in this assay
Steroidogenesis assay Abamectin Human cell line H295R PMRA #2557845	Excessive cytotoxicity was observed at concentrations ≥10 µM. No significant changes in testosterone production were observed after incubation with abamectin, although the mean fold-change decreased at the highest testable concentration. Significant decreases in estradiol production were observed in Run 1 at 0.1 µM (decreased 0.9-fold) and in all 3 runs at 1 µM (0.7-fold at 1 µM).
Aromatase assay Abamectin Human recombinant microsomes PMRA #2557845	Based on the data from the average response curve, abamectin is classified as a non-inhibitor of aromatase activity.
Uterotrophic assay (gavage) Abamectin Ovariectomized Sprague Dawley rats PMRA #2557845	No treatment-related effects at 2.5 mg/kg bw/day. Effects at 7.5 mg/kg bw/day included: tremors (all animals, Day 1 or 2, persisting until Day 4 in 3 animals), pale body, red material around nose, mouth and forelimbs, ↓bw, bw loss, ↓fc No effect at either dose on wet and blotted uterine wts.

Study Type/Animal/ PMRA #	Study Results
Hershberger assay (gavage) Abamectin Castrated Sprague Dawley rats PMRA #2557845	<u>Androgen agonist assay:</u> Effects at 5 mg/kg bw/day included ↓bwg. No treatment-related effects in any of the accessory sex organs of abamectin-dosed animals. <u>Anti-androgen assay:</u> Effects at 5 mg/kg bw/day included: One animal euthanized in extremis on Day 6. Animals at the high dose exhibited bw loss, ↓fc, tremors and red material on the face, mouth and/or forelimbs. Statistically significant changes were not seen in two or more of the five androgen sensitive tissues. Abamectin was considered negative for androgenicity and anti-androgenicity in this assay.
Female Pubertal assay (gavage) Abamectin Sprague Dawley rat PMRA #2557845	No effects were observed on mortality, clinical signs, initial or final bw, bwg, fc, organ wt, clinical chemistry parameters or gross pathology. There were no effects on serum T4 or TSH levels, or thyroid follicular cell height or colloid area. ↓ percentage of ♀ with regular cycles at ≥0.75 mg/kg bw/day. At necropsy, fewer females in diestrus and more in estrus (toxicological implications were considered to be unclear).
Male Pubertal assay (gavage) Abamectin Sprague Dawley rat PMRA #2557845	No effects were observed on mortality, bw, bwg, organ wt, or gross pathology. Changes observed in thyroid, testis and seminal vesicle wts were either not s.s. or did not occur in a dose-dependent manner, and were not supported by microscopic changes in the same organs. No effect observed on age and bw at preputial separation. No effects on serum thyroid hormone or testosterone levels, or thyroid follicular cell height or colloid area.

Table 2 Toxicology Endpoints for Use in Health Risk Assessment for Abamectin

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1]
Acute dietary	Acute neurotoxicity study in rats, supported by the 12-week study in dogs.	NOAEL = 0.5 mg/kg bw Based on decreased splay reflex at 1.5 mg/kg bw in rats, and mydriasis observed in dogs at 1.0 mg/kg bw/day.	300
	ARfD = 0.0017 mg/kg bw		

Repeated dietary	Developmental neurotoxicity study	NOAEL = 0.12 mg/kg bw/day Based on decreased pup body weight in the developmental neurotoxicity study at 0.2 mg/kg bw/day	300
	ADI = 0.0004 mg/kg bw/day		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments

References

A. List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1238577	1984, Reproductive effects of MK-0936 administered orally by gavage to Crl:COBS CD (SD)BR rats for two generations, DACO: 4.5.1
1451507	1996, Trimethyltin Chloride: Investigation of Neurotoxicity in Rat Pups Using Morphometrics and Startle Response, DACO: 4.8
1863282	2003, Dizocilphine and Mecamylamine: Positive Control Water Maze Study in Rats, DACO: 4.5.13
1863284	2003, Motor Activity: Positive Control Study in Rat Pups, DACO: 4.5.14
2334849	2006, Abamectin Technical (MK936) - 90 Day Combined Oral Toxicity and Neurotoxicity Study in Rats, DACO: 4.3.1,4.5.13
2334852	1989, Effects of ivermectin on reproduction and neonatal toxicity in rats, DACO: 4.5.1,4.5.2
2334853	2006, Abamectin Technical (MK936) - Acute Neurotoxicity Study in Rats, DACO: 4.5.12
2334855	Lankas, G.R. et al., 1997, P-glycoprotein deficiency in a subpopulation of CG-1 mice enhances avermectin-induced neurotoxicity, Toxicology and Applied Pharmacology 143:357-365. DACO: 4.5.14
2334856	2005, Abamectin: Developmental neurotoxicity study in rats final report, DACO: 4.5.14
2334857	2006, Abamectin: Developmental Neurotoxicity Study In Rats (MRID 467274-03) Final Report Amendment (Supplement - 001), DACO: 4.5.14
2334858	2007, Abamectin Assessment of Developmental Neurotoxicity in Rats Final Report, DACO: 4.5.14
2334859	2011, Abamectin DNT Study Dates, DACO: 4.5.14
2334860	2004, Abamectin: Developmental Neurotoxicity Study In Rats - Protocol, DACO: 4.5.14
2334861	2004, Abamectin: Developmental Neurotoxicity in Rats - Protocol Amendment Number 002, DACO: 4.5.14

2334862 2006, Abamectin: Assessment of Developmental Neurotoxicity in Rats - Protocol, DACO: 4.5.14

2334867 2005, Avermectin B1A: Comparative Maternal and Pup Exposure Following Dietary and Gavage Dosing in the Rat, DACO: 4.8

2334873 N Macdonald, 2007, Potential impact of ABCB1 (p-glycoprotein) polymorphisms on avermectin toxicity in humans, Arch Toxicol 81:553-563. DACO: 4.8

2334879 GD Leschziner, T Andrew, M Pirmohamed and Mr Johnson, 2007, ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research, The Parma. J. 7:154-179. DACO: 4.8

2334897 S Choudhuri and C D. Klaassen, 2006, Structure, Function, Expression, Genomic Organization, and Single Nucleotide Polymorphism of Human ABCB1 (MDR1), ABBCC(MRP), and ABCG2 (BCRP) Efflux Transporters, Int. J. Tox. 25:231-259. DACO: 4.8

2529314 2013, Abamectin technical -Local Lymph Node Assay in the Mouse, DACO 4.2.6

2529326 2012, Abamectin - A 14-Day Dose Range-Finding Oral (Gavage) Toxicity Study in Juvenile Rats, DACO 4.3

2529526 2012, Abamectin A Dose Range-Finding Oral (Gavage) Toxicity Study in Young Adult Rats, DACO 4.3

2542644 1996, Revised Report L-652,280: Oral Developmental Toxicity Study in CD-1 Mice, DACO: 4.5.2

2334848 2011, Abamectin - DACO 4: Summary of Neurotoxicity Studies and a Rationale in Support of Reduced Uncertainty Factors, DACO: 4.1

2334854 2007, Response to US EPA's Questions About 2005 (EPA MRID 46727403) & 2007 (EPA MRID 47116201) Developmental Neurotoxicity Studies with Abamectin Technical in the Rat, EPA Reg. No. 100-895, DACO: 4.5.12

657890 1994, Determination of the Magnitude of the Residues of Avermecin B1 and 8,9-Z Avermectin B1 in/on Curcurbits from Abamectin 0.15 EC Applications Made with Ground Equipment, DACO: 7.4.1

2334944 2000, Abamectin - Magnitude of the Residue on Avocado, DACO: 7.2.1,7.4.1

2334948 2003, Residue Study with Abamectin (MK 936) in or on Papaya in Brazil, DACO: 7.2.1,7.4.1,7.4.2

2334949 2003, Residue Study with Abamectin(MK 936)in or on Papaya in Brazil, DACO: 7.2.1,7.4.1,7.4.2

2334950 2003, Residue Study with Abamectin(MK 936)in or on Papaya in Brazil, DACO: 7.2.1,7.4.1,7.4.2

2334951 2003, Residue Study with Abamectin(MK 936)in or on Papaya in Brazil, DACO: 7.2.1,7.4.1,7.4.2

2334952 2000, Abamectin - Magnitude of the Residue on Celeriac (Roots and Tops), DACO: 7.4.1

2334953	2006, Abamectin - Magnitude of the Residue In or On Mint (Addendum to MRID 45096706), DACO: 7.4.1
2334955	1999, Abamectin - Magnitudes of the Residue In or On Representative Commodities of Crop Group 12: Stone Fruits, DACO: 7.4.1
2334956	1999, Abamectin - Magnitude of the Residue In or On Mint, DACO: 7.4.1
2334957	1998, Determination of the Magnitude of Residues of Avermectin B1 and 8,9-Z Avermectin B1 In/On the Raw Agricultural Commodity, Plums (including fresh and dried prunes) from Abamectin 0.15 EC Applied with Horticultural Spray Oil by Ground Equipment, DACO: 7.4.1
2334969	2000, Abamectin- Magnitude of the residues in or on representative commodities of Crop Group 4: Leafy vegetables, DACO: 7.4.1
2334970	1998, Determination of the magnitude of residues of avermectin B1 and 8,9-Z avermectin B1 in or on the raw agricultural commodities leaf lettuce and spinach Abamectin 0.15 EC applied with a non-ionic surfactant by ground equipment, DACO: 7.4.1
2334971	1999, Abamectin- Magnitude of the residues in or on representative commodities of Crop Group 8: Fruiting vegetables, DACO: 7.4.1
2334972	1999, Abamectin- Magnitude of the residues in or on representative commodities of Crop Group 9: Cucurbit vegetables, DACO: 7.4.1
2334973	2010, Abamectin SC (A15368D)- Magnitude of the residues in or on cotton final report, DACO: 7.4.1
2334974	2011, Abamectin SC (A15368D)- Magnitude of the residues in or on cotton final report, DACO: 7.4.1
2352135	2008, Abamectin - Magnitude of the Residues in or on Oranges, Grapefruit and Lemon as Representative Commodities of Citrus, Group 10, DACO: 7.4.1,7.4.2
2352139	2009, Abamectin - Magnitude of the Residues in or on Cantaloupe, Cucumber and Summer Squash as Representative Commodities of Cucurbits, Group 9, DACO: 7.4.1,7.4.2
2352140	2009, Abamectin - Magnitude of the Residues in or on Tomatoes and Peppers, including Processing as Representative Commodities of Vegetables, Fruiting, Group 8, DACO: 7.4.1,7.4.2,7.4.5
2352143	2009, Magnitude of the Residues in or on Vegetables, Leafy, Group 4, DACO: 7.4.1,7.4.2
2429153	2007, Abamectin - Storage Stability in Crops Stored Deep Frozen for up to Two Years - Final Report, DACO: 7.3
2429155	2003, Abamectin: Magnitude of the Residue on Basil, DACO: 7.4.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

2554310 Lankas, G.R., et al, 1998, Placental P-Glycoprotein Deficiency Enhances Susceptibility To Chemically Induced Birth Defects In Mice, Reproductive Toxicology, Vol. 12, No. 4, pp. 457-463., DACO: 4.5.2

2557845 2015, US EPA EDSP Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen or Thyroid Pathways – Abamectin., DACO 12.5.4

ISSN: 1911-8082