Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2001-01

Abamectin
Raid Max Roach Bait

The end-use product Raid Max Roach Bait, containing abamectin, for the control of cockroaches in homes, is proposed for registration under Section 13 of the Pest Control Products (PCP) Regulations.

This proposed regulatory decision document (PRDD) provides a summary of data reviewed and the rationale for the proposed full registration of this product. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address listed below.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6602A
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
Information Service:
1-800-267-6315 or (613) 736-3799
Facsimile: (613) 736-3798

Foreword

The submission for the registration of Raid Max Roach Bait (abamectin), manufactured by S.C. Johnson and Son, Ltd., has been reviewed by the PMRA.

Raid Max Roach Bait is an insecticidal bait, containing 0.05% abamectin, for the control of cockroaches in homes. The active ingredient abamectin is currently registered in Canada for the control of insect and mite pests on fruit tree and greenhouse crops. Raid Max Roach Bait represents a new use site category for this registered active ingredient and is a potential replacement for chlorpyrifos based products.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18b, to allow a determination of the safety, merit and value of Raid Max Roach Bait. The Agency has concluded that the use of Raid Max Roach Bait in accordance with the label has merit and value consistent with Section 18c of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18d. Therefore, based on the considerations outlined above, the use of Raid Max Roach Bait is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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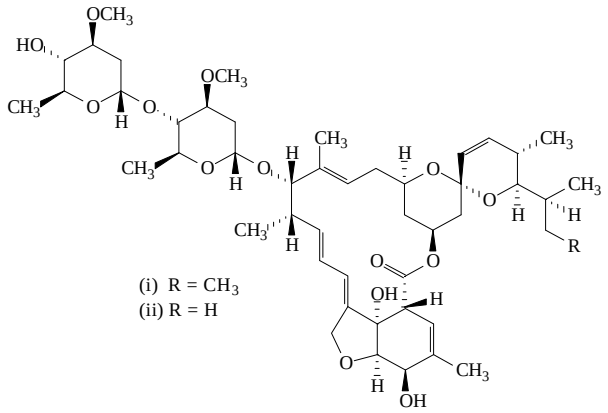
1.0 The active substance, its properties, and uses

1.1 Identity of the active substance

Active substance:	Abamectin
Function:	Insecticide
Chemical name:	
International Union of Pure and Applied Chemistry:	(10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5*N**S*,6*S*,6*N**R*,8*R*.12*S*,13*S*,20*R*,21*R*,24*S*)-6*N*[(*S*)-*sec*-butyl]-21,24-dihydroxy-5*N*,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*N*-(5*N*,6*N*-dihydro-2*N**H*-pyran)-12-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-"-L-*arabino*-hexopyranosyl)-3-*O*-methyl-"-L-*arabino*-hexopyranoside (*i*) mixture with (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5*N**S*,6*S*,6*N**R*,8*R*.12*S*,13*S*,20*R*,21*R*,24*S*)-21,24-dihydroxy-6*N*-isopropyl-5*N*,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*N*-(5*N*,6*N*-dihydro-2*N**H*-pyran)-12-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-"-L-*arabino*-hexopyranosyl)-3-*O*-methyl-"-L-*arabino*-hexopyranoside (*ii*)
Chemical Abstract Services (CAS):	5-*O*-demethylavermectin A_{1a} (*i*) mixture with 5-*O*-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl)avermectin A_{1a} (*ii*)
CAS Number:	65195-55-3 (*i*) B_{1a} 65195-56-4 (*ii*) B_{1b}
Molecular formula:	$C_{48}H_{72}O_{14}$ B_{1a} $C_{47}H_{70}O_{14}$ B_{1b}
Molecular weight:	873.1 B_{1a} 860.1 B_{1b}

Structural formula:



Nominal purity: 74.7% (a mixture containing 80% B_{1a} and 20% B_{1b})

PCP Number: 24484

1.2 Physical and chemical properties of the end-use product

Property	Result
Colour	Light brown
Odour	Sweet peanut type
Physical state	Solid
Formulation type	Solid
Nominal guarantee	Abamectin: 0.05%
Formulants	The product does not contain any United States Environmental Protection Agency (U.S. EPA) List 1 formulants or formulants known to be Toxic Substances Management Policy (TSMP) Track-1 substances as identified in Appendix II of Regulatory Directive, DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*
Container material and description	Plastic or paper 1.5–2.5 g
Specific gravity	1.07
pH	Product is a solid
Oxidizing or reducing action	Product does not contain any oxidizing or reducing agents
Storage stability	Stable when stored for 12 months in commercial packaging
Explodability	Product is not potentially explosive

1.3 Details of uses and further information

Raid Max Roach Bait is proposed as a domestic class product for the control of cockroaches in household dwellings. The proposed formulation is a bait containing 0.05% of the active ingredient abamectin. The product is packaged in plastic, child-resistant bait stations. The bait stations are to be placed in the kitchen, bathroom, utility room or other areas where cockroaches are found.

2.0 Methods of analysis

2.1 Method for formulation analysis

A high performance liquid chromatography method with ultraviolet detection was used to determine the level of the active in the formulation. The method has been assessed to be suitable for use as an enforcement method.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

The submission for abamectin technical included toxicity studies with abamectin, its components, avermectin B_{1a} and avermectin B_{1b}, and the photolytic degradation products. The major photolytic degradation products are in the polar fraction (54%), while 19% are in the nonpolar avermectin B_{1a} fraction, the major component of which was the delta 8,9-*Z* isomer of avermectin B_{1a}.

Metabolism studies on avermectins indicate that avermectin B_{1a} and the delta 8,9-*Z* isomer of avermectin B_{1a} are rapidly excreted, primarily in the feces. The highest tissue levels were in the fat and there was no evidence of bioaccumulation in any tissue or organ examined.

Although absorption data were not available for avermectin, human studies indicate that ivermectin (ivermectin differs in chemical structure from abamectin by the chemical bond between carbons 22 and 23: abamectin has a double bond, while ivermectin has a single bond) is rapidly absorbed and then secreted in the bile for excretion in the feces. The absorption and elimination of avermectin B_{1a} and its delta 8,9-*Z* isomer are expected to be similar.

In acute studies, abamectin technical and its two components were highly toxic to mice and rats when administered orally. The acute toxicity of avermectins was manifested as clinical signs including tremors, ataxia, bradypnea and loss of righting, and death. Avermectin B_{1a} was extremely toxic to infant rats (lethal dose 50% [LD_{50}] = 1.52; infants 24–28 h old). The delta 8,9-*Z* isomer of avermectin B_{1a}, a photolytic metabolite, was less toxic than the parent compound but the clinical signs of toxicity were similar: ataxia and tremors. The polar degradates that result from the photolysis of abamectin technical were

virtually nontoxic to mice when administered orally. The acute dermal toxicity of abamectin technical was not clearly established in rats (LD_{50} > 330 mg/kg bw) and slight in rabbits (limit test) and was manifested as ataxia and tremors. An adequate acute inhalation toxicity study was not available. Abamectin technical was minimally irritating to the eyes and skin of rabbits. An adequate sensitization study was not available.

Acute toxicity data from a surrogate product (formula no. 54-058; 0.05% abamectin) were submitted and accepted for the end-use product, Raid Max Roach Baits (0.05% abamectin). Formula no. 54-058 exhibited low acute toxicity via the oral and dermal routes of exposure, in rats and rabbits, respectively. It was mildly irritating to the eyes of rabbits, was not irritating to the skin of rabbits, and did not produce dermal sensitization in guinea pigs. The registrant submitted a waiver request for the acute inhalation toxicology study on the basis that the vapour pressure of the active ingredient is extremely low and therefore it is very unlikely that the active ingredient in the end-use product will vaporize to pose an inhalation hazard. In addition, it was stated that the end-use product itself is not volatile. This waiver request was considered acceptable.

In repeated-dose studies ranging from short-term to chronic in duration, the primary target site of abamectin and avermectin B_{1a} toxicity was the nervous system, and the main toxicological end points, consistent across all species tested (mice, rats, dogs), were overt clinical signs (tremors, ataxia or lethargy) and death. In long-term rodent studies, abamectin technical was not oncogenic in the rat or the mouse. The hematopoietic system was a target in both species, as evidenced by enlarged spleens (mice), reactive myeloid hyperplasia (mice), extramedullary hematopoiesis in the spleen (rats and mice) and erythroid hyperplasia in bone marrow (rats). The no observable adverse effect level (NOAEL) for chronic systemic toxicity was 4 mg/kg bw/d in mice and 1.5 mg/kg bw/d in rats.

The toxicology database for abamectin does not contain acute or short-term neurotoxicity studies, or a developmental neurotoxicity study to further investigate this end point.

Abamectin was not considered mutagenic, based on the battery of in vitro and in vivo mutagenicity studies submitted. Avermectin B_{1a}, polar photolytic degradates and the delta 8,9-*Z* isomer of avermectin B_{1a} were all negative in in vitro reverse mutation assays.

Rat reproduction studies were submitted for abamectin (a two-generation, two litters per generation study), avermectin B_{1a} (two one-generation, one litter per generation studies) and the delta 8,9-*Z* isomer of avermectin B_{1a} (a one-generation, one litter per generation study). The reproductive toxicity of both abamectin and avermectin B_{1a} was manifested as effects on the pups during lactation. Pups that survived the lactation period recovered following weaning. The NOAEL for reproductive toxicity for abamectin technical was 0.12 mg/kg bw/d, based on increased pup mortality, lower average pup body weights, increased number of pups that were thin, weak and not nursing, and retinal anomalies in weanlings as well as reduced male and female mating indices and female fertility index. The NOAEL for reproductive toxicity for avermectin B_{1a} was 0.1 mg/kg bw/d, based on

dose-related spastic movements in pups during lactation, developmental delay in ear and eye opening, incisor eruption and hair growth. No maternal toxicity was observed in this study, indicating an increased sensitivity of the young to avermectin B_{1a}. No reproductive or maternal toxicity was observed with the delta 8,9-*Z* isomer of avermectin B_{1a} at the highest dose tested of 0.4 mg/kg bw/d. Studies with ivermectin suggest that pups are exposed to higher doses of avermectins than their respective dams through the milk.

Teratology studies were conducted with abamectin technical (rats and rabbits), avermectin B_{1a} and B_{1b} (mice), the delta 8,9-*Z* isomer of avermectin B_{1a} (mice, rats) and the polar degradates of abamectin (mice). Fetotoxicity and teratogenicity was manifested as an increased incidence of cleft palate in mice exposed to avermectin B_{1a} (NOAEL of 0.2 mg/kg bw/d) and the delta 8,9-*Z* isomer of avermectin B_{1a} (NOAEL of 0.03 mg/kg bw/d) and in rabbits exposed to abamectin technical (NOAEL of 1.0 mg/kg bw/d). Other effects observed in fetal rabbits exposed to abamectin included omphaloceles, clubbed feet, skeletal anomalies and incomplete ossification. Fetal effects after exposure to abamectin technical or avermectin B_{1a} occurred at dose levels that were also maternally toxic, whereas fetal effects observed in mice after exposure to the delta 8,9-*Z* isomer of avermectin B_{1a} occurred at a dose level that was less than the maternally toxic dose.

In an antidote study in dogs, ipecac administration within 15 minutes of a single dose of abamectin (8 mg abamectin/kg bw) ensured emesis by 45 minutes and ameliorated clinical signs of abamectin toxicity, and prevented deaths.

In a special study, rhesus monkeys tolerated single oral doses of abamectin, sequentially increased to 24 mg/kg bw/d, without demonstrating tremors or convulsions. Emesis occurred, however, in all monkeys at doses $8.0 mg/kg bw.

3.2 Determination of acceptable daily intake

Consideration of an acceptable daily intake (ADI) is not relevant, due to the non-food use pattern of the current submission.

3.3 Acute reference dose

Consideration of an acute reference dose (ARfD) is not relevant, due to the non-food use pattern of the current submission.

3.4 Toxicology end point selection for occupational and bystander risk assessment

A toxicological end point was not selected for the proposed use, since exposure was considered to be negligible and a quantitative risk assessment was not conducted (see Section 3.5).

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

The product is packaged in a child-proof bait station. Therefore, there is no direct dermal contact with the active by the applicator, and dermal exposure is expected to be negligible. Abamectin is a solid at room temperature and is considered to be nonvolatile, since it has a vapour pressure of less than 2×10^{-10} kPa (Electronic Pesticide Manual, 11th edition, version 1.0, British Crop Protection Council). Inhalation exposure to the active is expected to be negligible therefore while the applicator is handling the bait stations.

3.5.2 Bystanders

Since the product is packaged in a child-proof bait station and is nonvolatile, exposure to bystanders during application is expected to be negligible.

3.5.3 Post-application exposure

Since the product is packaged in a child-proof bait station and is nonvolatile, post-application exposure is expected to be negligible. In addition, the bait stations contain adhesive tape to secure the bait station to surfaces. This would discourage removal of the bait station and accidental ingestion of the bait by children and pets. In addition, the label for each bait station must be visible on the bait station.

4.0 Residues

Not applicable to this product.

5.0 Fate and behaviour in the environment

Not applicable to this product.

6.0 Effects on nontarget species

Not applicable to this product.

7.0 Efficacy

7.1 Effectiveness

Study reports were submitted from 10 laboratory trials to support the efficacy of abamectin baits for the control of cockroaches. The objectives of the laboratory trials included assessments of mortality, effects on reproduction and fecundity, secondary

poisoning (e.g., as a results of cannibalism, coprophagy) and the attractiveness of abamectin baits. All laboratory trials were conducted with the German cockroach or the American cockroach. In addition to the laboratory trials, results were also submitted from two operational field trials conducted in France and Australia that assessed the efficacy of abamectin baits for the control of the German cockroach in dwellings.

In free-choice laboratory trials where test insects were given a choice between the bait and an alternate food source, 0.05% abamectin baits were effective in controlling German cockroaches (adults and nymphs) and American cockroaches (adults) (>90% control after six days of exposure). Results from the trials show that the bait was palatable to German and American cockroaches.

A review of specific label claims is as follows:

Control for three months: The applicant claims that the product is effective for three months. Results from submitted studies showed that bait "aged" for 12 weeks under laboratory conditions remained effective against German cockroach adults. In the two operational trials, trap catches of cockroaches were reduced by >95% compared with pre-treatment levels at three months following the placement of the baits in the homes. These results support the label claim that the bait is effective for three months.

Transfer of bait to other cockroaches: The label claims that "bait continues to kill as it is transferred to other cockroaches." Results from submitted laboratory studies showed that the mortality of cockroaches can result from routes of exposure other than direct ingestion of the bait (e.g., from contact with harbourages from test arenas previously treated with bait). The study authors attribute this "secondary kill" to routes of exposure such as cannibalism, coprophagy or oral secretions; however, the exact routes of lethal exposure were not unequivocally determined. Adequate data have been submitted to support the proposed label claim.

Reproductive effects: The label claims that the product "Kills cockroaches, kills the eggs they carry. Halts eggs production." Results were submitted from laboratory studies that showed that egg viability in gravid females was reduced following the ingestion of the bait. The study authors attributed this effect on egg viability to the death of the female cockroach (and desiccation of the eggs), rather than a direct ovicidal effect that could be attributed to the bait. The activity of abamectin on egg hatch, therefore, would not likely be any different from that of any other insecticidal bait with fairly quick killing action. While the label claims "... kills the eggs they carry. Halts egg production." are indirectly supported, the submitted studies suggest that treatment effects on egg viability and production may be a result of the death of the female cockroach rather than a direct ovicidal effect on the egg.

Effective against resistant strains of cockroaches: The proposed label for Raid Max Roach Bait claims that the bait is effective against strains of cockroaches that are resistant to carbamate, organophosphate and pyrethroid insecticides. Abamectin targets the

nervous system and acts by stimulating the pre-synaptic release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) from nerve terminals and potentiates GABA binding to the post-synaptic receptors. This mode of action differs from that of carbamate, organophosphate and pyrethroid insecticides. In submitted laboratory studies, selected strains of cockroaches that were reported to be resistant to carbamate, organophosphate and pyrethroid chemistries were susceptible to abamectin. No information was provided, however, on the mechanism of resistance in these strains. Although the selected strains tested in these studies appeared to be susceptible to abamectin, it is not possible therefore to conclude that abamectin would be effective against all strains of cockroach that are resistant to carbamate, organophosphate and pyrethroid chemistries. The submitted data are adequate, however, to support the general claim as proposed on the label.

Conclusions: Sufficient efficacy data have been provided to support the use of Raid Max Roach Bait for the control of cockroaches.

8.0 Toxic Substances Management Policy considerations

During the review of Raid Max Roach Bait, the PMRA has considered the implications of the federal TSMP and the PMRA DIR99-03[1] and has concluded the following.

Active ingredient
The *n*-octanol–water partition coefficient of abamectin, 3.99, is below the TSMP Track-1 cut-off criterion. Abamectin, therefore, does not meet the criteria for a TSMP Track-1 substance.

Transformation products
As the principal route of abamectin transformation in baits is expected to be hydrolysis and abamectin hydrolysis is limited, TSMP implications for abamectin transformation products were not considered any further.

Formulants
The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.

9.0 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18*b*, to allow a determination of the safety, merit and value of Raid Max Roach Bait, manufactured by S.C. Johnson and Son, Ltd. The Agency has concluded that the use of Raid Max Roach Bait in accordance with the label has merit and value consistent with

[1] Refer to Regulatory Directive DIR99-03, *The PMRA's Strategy for Implementing the Toxic Substances Management Policy*, March 12, 1999.

Section 18*c* of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18*d*. Based on the considerations outlined above, therefore, the use of Raid Max Roach Bait containing 0.05% abamectin, for the control of cockroaches in homes, is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
bw	body weight
)	delta
DNA	deoxyribonucleic acid
EPA	U.S. Environmental Protection Agency
F_0	parental animals
F_1	1^{st} generation offspring
F_2	2^{nd} generation offspring
GABA	gamma-aminobutyric acid
LD_{50}	lethal dose 50%
LOAEL	lowest observable adverse effect level
MAS	maximum average score (at 24, 48 and 72 h)
MIS	maximum average score (at 24, 48 and 72 h)
mM	millimolar
NZW	New Zealand white
NOAEL	no observable adverse effect level
PCP	Pest Control Products
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
Fg	micrograms

Appendix I Toxicology summary tables

Summary of the toxicity studies with abamectin, its two components (avermectin B_{1a} and avermectin B_{1b}) and the photolytic degradation products (the delta 8,9-*Z* isomer of avermectin B_{1a} and polar degradates)

NOTE: Abamectin (avermectin B_1) is a mixture containing $80% avermectin B_{1a} and #20% avermectin B_{1b}. The B_{1a} component differs structurally from the B_{1b} component in that the former has an ethyl group and the latter a methyl group attached at the 25-carbon position. Photodegradation of abamectin results in the formation of polar (major product) and nonpolar (minor product) degradates. The polar degradates remain unidentified. The main nonpolar degradate is the delta 8,9-*Z* isomer of avermectin B_{1a}.

METABOLISM

Rate and extent of absorption and excretion (avermectin B_{1a}): **Rat**: Tissue residues after oral dosing were dose-dependent and peaked after 24 h. Distribution of the residues was independent of dose and sex. Major route of elimination was the feces (86–100% of administered dose within 7 d), independent of sex and dose.

Urinary excretion accounted for 0.5–1.5% of the administered dose. Metabolism data suggest that % rats metabolize avermectin B_{1a} more rapidly than &.

Metabolism of the) 8,9-*Z* isomer of avermectin B_{1a} in % rats was similar to that of avermectin B_{1a}. The majority of the isomer was eliminated in the feces (94% of administered dose within 7 d) and <1% recovered in the urine after 7 d. Absorption of avermectin B_{1a} and the) 8,9-*Z* isomer was not determined; however, studies in humans with ivermectin (structurally similar to abamectin) indicate rapid absorption, then secretion into the bile for excretion in the feces. Absorption of avermectin B_{1a} and its) 8,9-*Z* isomer are expected to be similar.

Distribution and target organ(s): Residue levels in tissues were greatest in the gastrointestinal tract > fat $ kidney > liver > muscle.

Toxicologically significant compound(s): *After dosing with avermectin B_{1a}*, the majority of the tissue residue was unchanged avermectin B_{1a}. In liver, kidney and muscle tissue, two other metabolites were identified: 30-desmethyl-avermectin B_{1a} (major metabolite) and 24-hydroxymethyl-avermectin B_{1a} (minor metabolite). In fat tissue, metabolites included 30-desmethyl-avermectin B_{1a} and conjugates of both 30-desmethyl-avermectin B_{1a} and 24-hydroxymethyl-avermectin B_{1a}.

After dosing % rats with the) 8,9-*Z* isomer of avermectin B_{1a}, the majority of tissue residue was unchanged) 8,9-*Z* isomer. Other metabolites observed were the 30desmethyl-) 8,9-*Z* isomer and 24-hydroxymethyl-) 8,9-*Z* isomer.

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
ACUTE STUDIES			
Abamectin: technical			
Oral	Mice, CF1 pregnant: 12/dose; and non-pregnant: 10/dose 0, 5, 10, 20, 40, or 80 mg/kg	LD_{50} = 19.0 mg/kg (pregnant) LD_{50} = 41.3 mg/kg (non-pregnant)	**Highly toxic**. Deaths occurred from 73 minutes to 2 d after dosing in pregnant mice and from 83 minutes to 4 d in non-pregnant mice. Death was preceded by loss of righting. Clinical signs of toxicity included tremors and bradypnea seen at all dose levels in the non-pregnant mice and at all but the lowest dose group in pregnant mice.
Oral	Mice, CF1 pregnant and non-pregnant: 20/dose 0, 5, 10, 20, 40, or 80 mg/kg	LD_{50} = 11.8 mg/kg (pregnant) LD_{50} = 15.0 mg/kg (non-pregnant)	**Highly toxic**. This was a repeat of the above study with a larger number of mice. All deaths occurred from about 40 minutes to day 4. Death was preceded by loss of righting. Clinical signs included tremors, bradypnea and loss of righting seen at all dose levels in both pregnant and non-pregnant mice.
Dermal	Rat, CDBR	LD_{50} >330 mg/kg	Ataxia and tremors *(could not find further details of the study)*
Dermal	Rabbit, New Zealand white (NZW)	LD_{50} > 2000 mg/kg	Ataxia and tremors *(could not find further details of the study)*
Inhalation (abamectin in xylene)	Rat, Sprague-Dawley 5/sex nominal concentration of 5.73 mg/L for 1 h	No deaths; however, LD_{50} could not be adequately determined	**Inadequate study**. Many deficiencies including: actual concentration and particle size distribution of abamectin not measured; animals exposed for only 1 h; not clear if nose-only or whole-body exposure
Eye irritation	Rabbit, NZW		Minimally irritating (*could not find further details of the study*)
Skin irritation	Rabbit, NZW		Minimally irritating (*could not find further details of the study*)
Avermectin B_{1a}			
Oral	Mice, CF1, CD-1, ICR 10 **&**/dose 5, 10, 20, 40, 80 mg/kg	LD_{50} = 18.3 mg/kg (CF-1) LD_{50} = 17.4 mg/kg (CD-1) LD_{50} = 18.7 mg/kg (ICR)	**Highly toxic**. Deaths occurred from 40 minutes to 5 d post dosing. Clinical signs were similar in all strains and included tremors, ataxia, decreased activity, and bradypnea (at $10 mg/kg in CF-1 and ICR mice, and at $20 mg/kg in CD-1 mice).

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Oral	Mice, CF1 10 **&**/dose 2.5–80 mg/kg (3 similar studies)	LD_{50} = 13.6–23.8 mg/kg	**Highly toxic**. Deaths occurred from 20 minutes to 4 d post-dosing. Animals exposed to all doses showed clinical signs of ataxia, bradypnea, tremors and loss of righting.
Oral	Rat, CDRCD 10/sex/dose 0, 1, 2, 4, 8, 16, 32 mg/kg	LD_{50} = 11.3 mg/kg (**&**) LD_{50} = 10.6 mg/kg (**%**) LD_{50} = 1.52 (infants: 24–28 h old)	**Highly toxic**. Deaths in adults occurred overnight and up to day 4 post-dosing. Clinical signs in adults appeared (at doses $8mg/kg) on day 2 post-dosing and included tremors, decreased activity, ataxia, chromodacryorrhea and chromorhinorrhea. Deaths in infants occurred from 45 minutes to overnight. The only clinical signs observed in infants were tremors in the 32 mg/kg group.
Avermectin B_{1b}			
Oral	Mice, CF-1 10/sex/dose 0, 5, 10, 20, 40, 80 mg/kg	LD_{50} = 11.4 mg/kg (**%**) LD_{50} = 19.8 mg/kg (**&**)	**Highly toxic**. Deaths occurred between 30 minutes and 6 d post-dosing. Clinical signs included ataxia, tremors, bradypnea, clonic convulsions. Deaths were preceded by loss of righting.
) 8,9-*Z* isomer of avermectin B_{1a}			
Oral	Mice, CF-1 10/sex/dose 0, 5, 10, 20, 40, 80 mg/kg	LD_{50} > 80 mg/kg	Deaths occurred between 2 h and overnight (**%**: 1, 1, 2, 0, 3 deaths and **&**: 0, 1, 1, 0, 1 deaths in the 5, 10, 20, 40, 80 mg/kg dose groups, respectively). Clinical signs of toxicity included decreased activity, bradypnea, ataxia and ptosis observed at all dose levels except **&** at 5 mg/kg.
Polar degradates			
Oral	Mice, CF-1 5/sex/dose 1250, 2500, 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low toxicity**. No treatment related deaths occurred. Clinical signs included decreased activity and bradypnea, which persisted for 4 h.
Acute studies: formulation (raid max roach baits: 0.05% abamectin)			
Oral	Rat, SD 5/sex 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low toxicity**. No mortality occurred. No treatment related clinical signs, necropsy findings, or changes in bw observed

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Dermal	Rabbit, NZW 5/sex 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**. No mortality occurred. No treatment related clinical signs, necropsy findings or changes in bw observed
Eye irritation	Rabbit, NZW 6 animals (sex not specified) 0.1 g	maximum average score (at 24, 48 and 72 h) (MAS) = 5.9 maximum average score (at 24, 48 and 72 h) (MIS) = 15.3 (1 h)	**Mildly irritating**. Conjunctival irritation produced in all treated eyes but disappeared by day 7. Corneal opacity in 1/6 animals disappeared by day 3. Dull cornea in 4/6 animals disappeared by day 3.
Skin irritation	Rabbit, NZW 6 animals (sex not specified) 0.5 g	MAS = 0 MIS = 0	**Non-irritating**. No dermal irritation observed in any of the animals
Skin sensitization (Buehler method)	Guinea pig, Hartley 12 %	Non-sensitizing	**Non-sensitizing**
SHORT-TERM AND SUBCHRONIC TOXICITY: Abamectin			
3-week dietary range-finding study	Mice, CD-1 15/sex/dose 0, 6.0, 9.0 mg/kg bw/d	NOAEL = 6.0 Lowest observable adverse effect level (LOAEL) = 9.0	Decreased bw gain in both sexes
12-week dietary range-finding study	Mice, CD-1 15/sex/dose 0, 0.3, 0.75, 1.5, 4.5 mg/kg bw/d	NOAEL = 4.5	Highest dose tested
8-week dietary range-finding study	Rat, CRCD 10/sex/dose 0, 0.5, 1.0, 1.5, 2.2/2.5, 4.0, 6.0 mg/kg bw/d	NOAEL = 1.0 LOAEL = 2.2	Decreased bw gains and tremors. These occurred at dietary levels of 15 and 20 ppm, which apparently were both approximately equivalent to 2.2 mg/kg bw/d based on food consumption. Doses of 4 and 6 mg/kg bw/d caused tremors and increased mortality (50% by day 5 in 4 mg/kg group; 80% by day 3 in 6 mg/kg group) and these doses were terminated at days 15 and 5, respectively.
12-week dietary range-finding study	Dog, Beagle 2/sex/dose 0, 0.25, 0.5, 1.0, 4.0 mg/kg bw/d	NOAEL = 0.5 LOAEL = 1.0	Mydriasis at $1 mg/kg (reversible), bw loss at highest dose level
53-week dietary study	Dog, Beagle 6/sex/dose 0, 0.25, 0.5, 1.0 mg/kg bw/d	NOAEL = 0.25 LOAEL = 0.5	Mydriasis was observed in all dose groups, but was observed at a low frequency and not considered adverse in the lowest dose group. Decreased bw gain at 1.0 mg/kg

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Avermectin B_{1a}			
14-week oral gavage following in utero exposure	Rat, CD 15/sex/dose 0, 0.1, 0.2, 0.4 mg/kg bw/d	NOAEL = 0.4	Highest dose tested
18-week oral gavage study	Dog, Beagle 3/sex/dose 0, 0.25, 0.5, 2.0, 8.0 mg/kg bw/d	NOAEL = 0.25 LOAEL = 0.5	Mortality occurred at doses $0.5 mg/kg. Clinical signs of toxicity included tremors, ataxia, mydriasis and ptyalism, were observed in all dose groups $0.5 mg/kg. Tonic convulsions and emesis were also observed in the 2 and 8 mg/kg groups. Decreases in bw were observed in 0.5 and 2 mg/kg groups. Histopathological changes were only observed in animals that died or were killed moribund and included hepatocellular vacuolation at doses $0.5 mg/kg and edema of the gallbladder at doses of 2 and 8 mg/kg.
CHRONIC TOXICITY AND ONCOGENICITY: Abamectin			
94-week dietary	Mice, Crl:CD-1 (ICR) 74/sex/dose 0, 2.05, 4.15, 8.25 mg/kg bw/d	NOAEL = 4.15 LOAEL = 8.25	**8.25 mg/kg**: Increased mortality in **%** and decreased bw gain in both sexes. Higher incidence of pale kidneys, pale livers and enlarged spleens in **%**. **%** at this dose also had higher average spleen and adrenal weights (absolute and relative), and a higher incidence of dermatitis, reactive myeloid hyperplasia and extramedullary hematopoiesis in the spleen. A higher incidence of tremors was also reported in high-dose animals; however, it is unclear whether these were treatment-related or associated with disease processes. **Not oncogenic**

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
105-week dietary	Rat, Crl:CD(SD)BR 65/sex/dose 0, 0.75, 1.5, 2.05 mg/kg bw/d	NOAEL = 1.5 LOAEL = 2.05	Tremors in both sexes at 2.05 mg/kg bw/d. Animals with tremors had decreased bw but no histomorphologic changes. Hematologic changes in the high dose group (occurred independently of the tremors) included anemia (**%**, **&**) and increased leukocytes, neutrophils and lymphocytes (**&**). Changes were supported by evidence of increased extramedullary hematopoiesis in the spleen and erythroid hyperplasia in bone marrow. **Not oncogenic**
REPRODUCTIVE TOXICITY: Abamectin			
Range-finding reproduction; in drinking water	Rat, Crl:CD(SC)BR Sprague-Dawley 12 **&**/dose 0, 0.15, 0.5, 1.5, 5.0 mg/mL	NOAEL (maternal) = 5 mg/mL NOAEL (offspring) = 1.5 mg/mL LOAEL (offspring) = 5 mg/mL (approximately equivalent to 0.5–0.7 mg/kg bw/d) NOAEL (reproductive) = 5 mg/mL	**5 mg/mL**: decreased pup bw (days 7–21 postpartum), increased pup mortality (days 7–14 postpartum) No signs of maternal toxicity
Multigeneration reproduction; gavage (2 generations, 2 litters/generation)	Rat, Crl:COBS CD(SD) BR 30/sex/dose 0, 0.05, 0.12, 0.4 mg/kg bw/d	NOAEL (parental) = 0.05 LOAEL (parental) = 0.12 NOAEL (offspring) = 0.12 LOAEL (offspring) = 0.4 NOAEL (reproductive) = 0.12 LOAEL (reproductive) = 0.4	**0.12 mg/kg bw/d and above**: reduced bw gains during first and second lactation periods in F_0 dams (36–86% lower than controls) and during second lactation period in F_1 dams (13–28% lower than controls) **0.4 mg/kg bw/d**: increased pup mortality (day 4–21) in both litters of the F_0 and F_1 generations, lower average pup bw and greater number of pups that were thin, weak and not nursing. Retinal anomalies in both F_1b and F_2b weanlings. In the F_0–F_1b litter, this dose was associated with "increased estrous stages," reduced **%** and **&** mating indices and increased d in cohabitation. **&** fertility index was reduced in both F_2 litters at this dose.

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Avermectin B_{1a}			
One-generation reproduction; gavage	Rat, CD 12 **&**/dose 0, 0.5, 1.0, 2.0/1.5 mg/kg bw/d (after 5 doses the high dosage was reduced to 1.5 mg/kg, due to tremors observed in 3 rats)	NOAEL (maternal) = 1.0 LOAEL (maternal) = 1.5 NOAEL (offspring) not established LOAEL (offspring) = 0.5 NOAEL (reproductive) = 1.5	**0.5 mg/kg bw/d and above**: dose dependent decrease in pup survival (survival rates of 76, 14 and 0% in 0.5, 1.0 and 1.5 mg/kg bw/d groups, respectively, compared with 98% in pooled controls). Death was preceded by rapid wasting and an absence of milk in the stomach. **1.5 mg/kg bw/d**: mortality of 2 dams, one killed moribund pre-mating. Clinical signs prior to death included whole body tremors, ataxia, ptylism, ocular and nasal discharges.
One-generation reproduction; gavage	Rat, CD 15 **&**/dose 0, 0.1, 0.2, 0.4 mg/kg bw/d	NOAEL (maternal) = 0.4 NOAEL (offspring) = 0.1 LOAEL (offspring) = 0.2 NOAEL (reproductive) = 0.4	**0.2 mg/kg bw/d and above**: dose-related spastic movements in pups during lactation, developmental delay in ear and eye opening, incisor eruption and hair growth **0.4 mg/kg bw/d**: mean pup weight significantly lower ($p \# 0.05$) than pooled controls from days 7–21 postpartum
) 8,9-*Z* isomer of avermectin B_{1a}			
One-generation reproduction; gavage	Rat, CD (SD) BR 20 **&**/dose 0, 0.06, 0.12, 0.4 mg/kg bw/d	NOAEL (maternal) = 0.4 NOAEL (offspring) = 0.4 NOAEL (reproductive) = 0.4	Highest dose tested. No treatment-related maternal or reproductive toxicity observed at any dose level
DEVELOPMENTAL TOXICITY: Abamectin			
10 Fg dietary maternotoxicity	Mice, CF1 20 pregnant 0, 0.08, 0.23, 0.47 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.08 LOAEL (maternal) = 0.23	**0.23 mg/kg bw/d and above**: treatment-related tremors observed. Administered by diet to compare maternal toxicity with gavage studies. Fetuses were not examined.
Range-finding developmental toxicity; gavage	Rat, CRCD 10 mated **&**/dose 0, 0.25, 0.5, 1.0, 2.0 mg/kg bw/d on days 6–17 of gestation	NOAEL (maternal) = 1.0 LOAEL (maternal) = 2.0	Weight loss and tremors were observed in one **&** at 2.0 mg/kg bw/d. Fetuses were not examined.

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Developmental gavage	Rat, CRCD 25 mated **&**/dose 0, 0.4, 0.8, 1.6 mg/kg bw/d on days 6–19 of gestation	NOAEL (maternal) = 1.6 NOAEL (developmental) = 1.6	No overt signs of maternal toxicity in highest dose group, therefore the study did not meet Organisation for Economic Co-operation and Development guidelines. Fetal anomalies occurred in all dose groups but at incidence within that of historical controls and without relationship to treatment or dose level. **No evidence of teratogenicity**
Range-finding developmental toxicity; gavage	Rabbit, New Zealand Albino 10 artificially inseminated **&**/dose 0, 0.5, 1.0, 2.0, 3.0 mg/kg bw/d on days 6–18 of gestation	NOAEL (maternal) = 2.0 LOAEL (maternal) = 3.0	3.0 mg/kg bw/d: reduced food and water consumption, reduced bw and clinical signs of toxicity. Fetuses were not examined.
Developmental toxicity; gavage	Rabbit, New Zealand Albino 18 artificially inseminated **&**/dose 0, 0.5, 1.0, 2.0 mg/kg bw/d on days 6–27 of gestation	NOAEL (maternal) = 1.0 LOAEL (maternal) = 2.0 NOAEL (developmental) = 1.0 LOAEL (developmental) = 2.0	2.0 mg/kg bw/d: maternal bw loss; fetal malformations including cleft palate and omphaloceles, clubbed feet, skeletal anomalies and incomplete ossification **Evidence of teratogenicity at maternally toxic dose levels**
Avermectin B_{1a}			
Range-finding developmental toxicity studies (2); gavage	Mice, CF-1 5 mated **&**/dose doses ranging from 0.1 to 8 mg/kg bw/d from days 6–15 of gestation	LOAEL (maternal) = 0.1	Mortality, tremors and coma. Decreased maternal weight gains during the treatment period at doses $1.0 mg/kg bw/d
Developmental toxicity (2 studies); gavage	Mice, CF-1 25 mated **&**/dose 0, 0.1, 0.2, 0.4, 0.8 mg/kg bw/d from days 6–15 of gestation	LOAEL (maternal) = 0.1 NOAEL (developmental) = 0.2 LOAEL (developmental) = 0.4	**0.1 mg/kg bw/d**: maternal mortality preceded by tremors and coma **0.4 mg/kg bw/d and above**: dose-dependent increase in the incidence of cleft palate in fetuses **Evidence of teratogenicity at maternally toxic dose levels**

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Developmental toxicity; oral catheter	Mice, CF-1 20 mated **&**/dose 0, 0.1, 0.2, 0.4, 0.8 mg/kg bw/d for days 6–15 of gestation	LOAEL (maternal) = 0.1 NOAEL (developmental) = 0.2 LOAEL (developmental) = 0.4	**0.1 mg/kg bw/d and above**: Treatment-related maternal deaths in 1, 3 and 2 **&** in the 0.1, 0.4 and 0.8 mg/kg bw/d dose groups, respectively. Tremors preceded death in the 0.1 and 0.4 mg/kg bw/d groups. **0.4 mg/kg bw/d and above**: increased incidence of cleft palate in fetuses **0.8 mg/kg bw/d**: increased incidence of incompletely ossified fetuses **Evidence of teratogenicity at maternally toxic dose levels.**
Maternal toxicity study; oral gavage	Mice, CF-1 20 mated **&**/dose 0, 0.025, 0.05, 0.075, 0.1 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.05 LOAEL (maternal) = 0.075	**0.075 mg/kg bw/d and above**: treatment-related death and sacrifice occurred in one animal from the 0.075 and 0.1 mg/kg bw/d groups, respectively. Tremors and coma preceded death and sacrifice. Number of pregnant mice was low for all groups irrespective of dose (12/20, 12/20, 14/20, 12/20 and 10/20 in the 0, 0.025, 0.05, 0.075 and 0.1 mg/kg bw/d groups, respectively). Fetuses were not examined.
Avermectin B_{1b}			
Developmental toxicity; gavage	Mice CF-1 12 mated **&**/dose 0, 0.025, 0.05, 0.075, 0.1 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.05 LOAEL (maternal) = 0.075 NOAEL (developmental) = 0.1	**0.075 mg/kg bw/d**: tremors preceding mortality in 2 **&** No fetotoxicity or teratogenicity was noted at any dose based on external examination of the pups.
) 8,9-*Z* isomer of avermectin B_{1a}			
Range-finding maternal toxicity; gavage	Mice, CF-1 BR 7–11 mated **&**/dose 0, 1.5, 3.0, 6.25, 12.5, 25, 50 mg/kg bw/d from days 6–15 of gestation	LOAEL (maternal) = 1.5 LOAEL (developmental) = 1.5	Mortality at all dose levels. Increased incidence of cleft palate in fetuses **Evidence of teratogenicity at maternally toxic dose levels**

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL AND LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Range-finding maternal toxicity; gavage	Mice, CF-1 BR 12 mated **&**/dose 0, 0.05, 0.1, 0.5, 1.0 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.1 LOAEL (maternal) = 0.5 NOAEL (developmental) = 0.05 LOAEL (developmental) = 0.1	**0.1 mg/kg bw/d and above**: increased incidence of cleft palate (no clear dose–response) **0.5 mg/kg bw/d and above**: mortality (1 animal/dose)
Developmental toxicity; gavage	Mice, CF-1 BR 25 mated **&**/dose 0, 0.015, 0.03, 0.06 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.06 NOAEL (developmental) = 0.06	No evidence of maternal toxicity or fetotoxicity or teratogenicity at any dose level
Developmental toxicity; gavage	Mice, CF-1 BR 25 mated **&**/dose 0, 0.015, 0.03, 0.1, 0.5 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 0.1 LOAEL (maternal) = 0.5 NOAEL (developmental) = 0.03 LOAEL (developmental) = 0.1	One **&** in the 0.5 mg/kg bw/d group was sacrificed in moribund condition. **0.1 mg/kg bw/d and above**: increased incidence of cleft palate in fetuses **Evidence of teratogenicity**
Developmental toxicity; gavage	Rat, Sprague-Dawley 25 mated **&**/dose 0, 0.25, 0.5, 1.0 mg/kg bw/d from days 6–17 of gestation	NOAEL (maternal) = 1.0 NOAEL (developmental) = 1.0	No evidence of maternal toxicity or fetotoxicity or teratogenicity at any of the dose levels tested
Polar degradates of abamectin			
Developmental toxicity; gavage	Mice, CF-1 BR 25 mated **&**/dose 0, 0.25, 0.5, 1.0 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 1.0 NOAEL (developmental) = 1.0	**&** were gavaged with polar degradates of abamectin generated in vitro. No evidence of maternal toxicity or fetotoxicity or teratogenicity at any of the dose levels tested
Developmental toxicity; gavage	Mice, CF-1 BR 25 mated **&**/dose 0, 0.25, 0.5, 1.0 mg/kg bw/d from days 6–15 of gestation	NOAEL (maternal) = 1.0 NOAEL (developmental) = 1.0	**&** were gavaged with polar degradates removed from citrus fruits sprayed with 4% abamectin. No evidence of maternal toxicity or fetotoxicity or teratogenicity at any of the dose levels tested

STUDY	SPECIES OR STRAIN OR CELL TYPE AND CONCENTRATIONS OR DOSES EMPLOYED	RESULTS
GENOTOXICITY: Abamectin		
Reverse mutation in bacteria (in vitro)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 100, 300, 1000, 3000, 10000 Fg/plate with metabolic activation	Negative
Reverse mutation in bacteria (in vitro)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 100, 300, 1000, 3000, 10000 Fg/plate without metabolic activation	Negative
Reverse mutation in bacteria (in vitro)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 3, 10, 30, 100, 300, 1000 Fg/plate with or without metabolic activation	Negative
Forward mutation assay (in vitro)	Chinese hamster lung cells (HGPRT) 0.03, 0.04, 0.045, 0.05 millimolar (mM) with metabolic activation 0.003, 0.004, 0.005, 0.006 mM without metabolic activation	Negative
Chromosomal aberrations (in vitro)	Chinese hamster ovary cells 0.005, 0.01, 0.015, 0.02, 0.025 mM with metabolic activation 0.01, 0.015, 0.02, 0.025, 0.03, 0.035 mM without metabolic activation	Negative
DNA strand breaks (in vitro) 4 studies	Rat hepatocytes 0.01–0.6 mM	Positive at >0.15 mM
DNA strand breaks (in vivo)	Rat hepatocytes 0, 1.06, 3.5, 10.6 mg/kg bw single oral gavage dose	Negative
Chromosomal aberrations (in vivo)	Mouse bone marrow (CD-1 %) 1.2, 4, 12 mg/kg bw single gavage dose	Negative
Avermectin B_{1a}		
Reverse mutation in bacteria (in vitro)	*S. typhimurium* TA92, TA98, TA100, TA1537 2, 200, 2000 Fg/plate with or without metabolic activation	Negative
) 8,9-*Z* isomer of avermectin B_{1a}		
Reverse mutation in bacteria (in vitro)	*S. typhimurium* TA97a, TA98, TA100, TA1535 *Escherichia coli* WP2, WP2 uvrA, PW2 uvra pKM101 10, 30, 100, 300, 1000, 3000 Fg/plate with or without metabolic activation	Negative

STUDY	SPECIES OR STRAIN OR CELL TYPE AND CONCENTRATIONS OR DOSES EMPLOYED	RESULTS
Polar degradates of abamectin		
Reverse mutation in bacteria (in vitro)	*S. typhimurium* TA97a, TA98, TA100, TA1535 *E. coli* WP2, WP2 uvrA, PW2 uvra pKM101 100, 300, 1000, 3000 Fg/plate with or without metabolic activation	Negative
SPECIAL STUDIES: Abamectin		
Oral toxicity; gavaged with single oral doses that were sequentially increased	Monkeys, Rhesus 2/sex/dose Received single doses that were sequentially increased from 0.2 to 24 mg/kg bw (0.2, 0.5, 1, 2, 4, 6, 8, 12, 24 mg/kg bw) at 2- to 3-week intervals	Doses $2 mg/kg bw resulted in emesis. The incidence of emesis was dose related and the onset tended to decrease with increasing dose. Marked mydriasis was observed only in animals treated with 24 mg/kg bw. Slight to moderate sedation was observed in 3/4 of animals treated with 24 mg/kg bw, but no tremors or convulsions occurred. Plasma levels of abamectin peaked between 8 and 24 h and increased with dose.
Antidote study; single oral gavage in sesame oil	Dogs, Beagle 3–5 dogs/groups 1–7; 21 dogs in groups 8 and 9 combined Received single oral doses of abamectin followed by ipecac or charcoal administration (stomach intubation) after various time intervals ranging from 15 minutes to 2 h	Ipecac given 15 minutes after abamectin administration lessened the clinical signs of abamectin toxicity (mydriasis, ataxia, tremors) and prevented deaths. Ipecac or charcoal given at 30 minutes or later did not prevent coma and death.
Compound-induced mortality: Treatment-related mortality was observed in short-term studies with avermectin B_{1a} (dogs), in chronic studies with abamectin (mice), in reproductive toxicity studies with abamectin (rat pups) and avermectin B_{1a} (rat pups and dams), and in developmental toxicity studies with avermectin B_{1a} and B_{1b} and the) 8,9-*Z* isomer of avermectin B_{1a} (mice, maternal deaths only).		
ARfD: Not relevant, due to the non-food use pattern of the current submission		
ADI: Not relevant, due to the non-food use pattern of the current submission		