Environmental Assessment

to Support an Import Tolerance Request for the

Use of Emamectin Benzoate in Salmonids

DATE:	**March 5, 2019**
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ACRONYMS AND ABBREVIATIONS

API	active pharmaceutical ingredient
BCF	bioconcentration factor
DT_{50}	time to dissipation of 50% of original concentration of the test substance
DT_{90}	time to dissipation of 90% of original concentration of the test substance
EA	environmental assessment
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practices
JECFA	Joint (FAO/WHO) Expert Committee on Food Additives
K_{oc}	adsorption/desorption partition co-efficient normalized to the organic carbon content
MAB_{1a}	4"-epimethylamino-4"-deoxyavermectin B_{1a} benzoate
MAB_{1b}	4"-epimethylamino-4"-deoxyavermectin B_{1b} benzoate
MRL	Maximum Residue Limit
OECD	Organisation for Economic Co-operation and Development
USDA	U.S. Department of Agriculture
WHO	World Health Organization
WWTP	Wastewater treatment plant

1. DESCRIPTION OF PROPOSED ACTION(S) AND NEED

Emamectin benzoate is the subject of this Environmental Assessment (EA), which has been prepared in support of an import tolerance request. Emamectin benzoate is indicated for the control and prevention of crustacean parasites of salmonid species of finfish. It is administered in fish feed to provide a dose of 50 µg of emamectin benzoate/kg body weight/day for seven consecutive days and is approved for use in the following countries: the United Kingdom, Ireland, Norway, the Faroe Islands, Denmark, Finland, Canada, and Chile. The major approved use is in Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). There is occasional use in Chile on a species of Pacific salmon, coho salmon (*Oncorhynchus kisutch*). Both Atlantic salmon and coho salmon are anadromous fish, meaning they migrate from the sea to fresh water to spawn. Rainbow trout are generally freshwater fish, although there are anadromous forms of the coastal rainbow trout (known as steelhead). These three species (*S. salar*, *O. mykiss,* and *O. kisutch*) are included in this EA, as they are salmonid species that can be reared in either saltwater or freshwater aquaculture. Emamectin benzoate is also used in Greece for the treatment of gilthead sea bream (*Sparus aurata*) and European sea bass (*Dicentrarchus labrax*).

Merck Animal Health is requesting the establishment of an import tolerance for residues of emamectin benzoate in edible tissues of salmonids so that imported food derived from salmonids treated with, and containing residues of, emamectin benzoate may be legally marketed in the United States (U.S.) for human consumption.

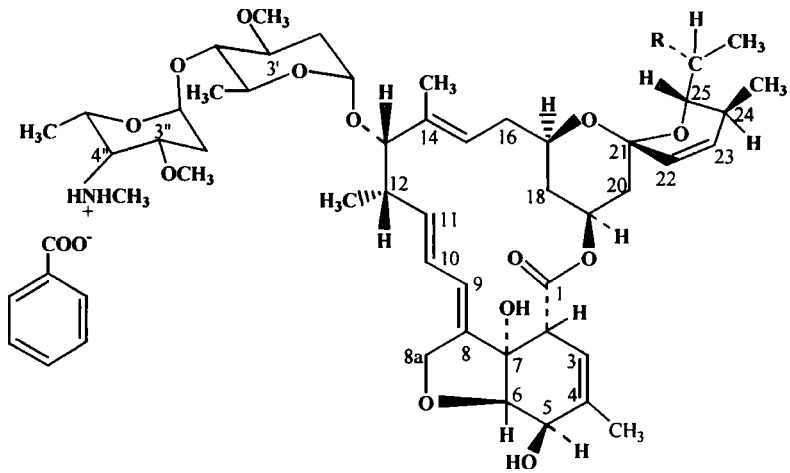
Establishment of an import tolerance is an action by the U.S. Food and Drug Administration (FDA) that requires preparation of an EA unless that action meets the criteria for categorical exclusion under FDA regulations at 21 CFR Part 25, Subpart C. Because the categorical exclusion criteria are not met, this EA has been prepared to address and evaluate the potential direct and indirect environmental impacts in the U.S. should the FDA establish an import tolerance for residues of emamectin benzoate in edible tissues of salmonids.

2. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Emamectin benzoate is a semi-synthetic avermectin. Avermectins are a class of macrocyclic lactones produced by *Streptomyces avermitilis*. Emamectin benzoate is synthetically derived from the natural product abamectin, which is made by a fermentation process. Emamectin benzoate is a member of the 4" amino avermectins (Mrozik et al. 1989) and is a mixture of two homologues: ≥90% of 4"-epimethylamino-4"-deoxyavermectin B_{1a} benzoate (MAB_{1a}) and ≤10% of 4"-epimethylamino-4"-deoxyavermectin B_{1b} benzoate (MAB_{1b}), as listed in Table 2-1. These components differ, in that the B_{1a} component has a sec-butyl group at the 25 position and the B_{1b} component has an isopropyl group at the 25 position (Budavari 1996). These compounds, which are the APIs, will be referred to, in combination, as emamectin benzoate (MAB1). The structural formula of emamectin benzoate is given in Figure 2-1.

Table 2-1. Identification of emamectin benzoate and physico-chemical characteristics

Drug Established (nonproprietary) Name	**Emamectin benzoate**	
Chemical Name	4"-epimethylamino-4"-deoxyavermectin B_{1a} benzoate (MAB_{1a})	4"-epimethylamino-4"-deoxyavermectin B_{1b} benzoate (MAB_{1b})
Chemical Abstracts Service Number	155569-91-8	138511-98-5
Composition	≥90%	≤10%
Empirical Formula	$C_{49}H_{75}NO_{13}C_7H_6O_2$	$C_{48}H_{73}NO_{13}C_7H_6O_2$
Molecular Weight	1008.26 g/mol	994.23 g/mol
Melting Point	141–146°C	
Dissociation Constants (pKa)	4.2 ± 0.1 (benzoic acid) 7.6 ± 0.1 (methylamino)	
Water Solubility (mg/L)	320 ± 30 (pH 5.03) 24 ± 2 (pH 7.04) 0.1 ± 0.1 (pH 9.05 5.5 (seawater)*	
UV Absorption Lambda Maxima (λ_{max})	244 nm (10 volume% methanol in water)	
Log Octanol-Water Partition Coefficient (Log P)	3.0 ± 0.1 (pH 5.07 ± 0.01) 5.0 ± 0.2 (pH 7.00 ± 0.03) 5.9 ± 0.4 (pH 9.04 ± 0.01)	
Vapor Pressure (mPa) (21.1 ± 0.1°C)	4×10^{-3}	
Reference: McCauley 1992 unless noted by * *Reference: Phillips 1996		



Emamectin B_{1a} R = CH_2CH_3; Emamectin B_{1b} R = CH_3

Figure 2-1. Structural formula of emamectin benzoate

The emamectin is made as its benzoate salt. Emamectin benzoate is not currently approved for use in the U.S., but it is approved for other countries in a product under the trade name of SLICE® (see Appendix B for specific information on SLICE®).

3. ECOSYSTEM AT THE SITE OF INTRODUCTION

This EA supports an import tolerance request relevant for the import of salmonid products from countries using emamectin benzoate but does not support the potential use of emamectin benzoate in the U.S. There are two potential pathways for introduction of emamectin benzoate residues to the U.S. environment that could result from establishing this import tolerance: 1) pathways arising from the release of drug residues, if present, from imported food derived from treated salmonids and 2) pathways arising from the use of the drug in salmonids in countries where it is legally authorized.

For the first pathway (following the import of food from treated salmonids), release of emamectin benzoate into the U.S. environment (e.g., soil, surface water, air) could potentially occur through points of introduction to the following ecosystems: (a) ecosystems where the residues of emamectin benzoate from consumed salmonid products might be introduced into surface water through wastewater from wastewater treatment plants (WWTPs); (b) ecosystems where biosolids from WWTPs are applied to soil; and (c) ecosystems where the residues of emamectin benzoate from unconsumed salmonid products, waste from fish processing plants, or sludge from WWTPs might be introduced through landfilling.

For the second pathway (following use of the drug in other countries), a potential point of introduction to the U.S. environment could consist of water flow or sediment transport from areas where fish are treated in countries adjoining the U.S. The only country that shares a border with the U.S. in which emamectin benzoate is used, i.e., for salmonid aquaculture, is Canada.

4. EXPOSURE ASSESSMENT

The potential exposures are evaluated based on the pathways previously described and environmental fate data for emamectin benzoate.

4.1 Environmental fate

Relevant environmental fate properties of emamectin benzoate are presented in Table 4-1. Values for adsorption coefficients normalized to organic carbon (K_{oc}) range from 8,687 to 728,913 L/kg, indicating that emamectin benzoate is likely to be adsorbed to soil, sediment, and suspended matter. Degradation times in soil (time to dissipation of 50% of original concentration of the test substance, DT_{50}) show a wide range, from 21 to 427 days (the latter being observed in anaerobic conditions). In aquatic systems, dissipation in water is rapid, with half-lives from less than 1 day to several days. Degradation in sediment is slow when investigated under laboratory conditions in the dark (Hurt et al. 2006) but fast when investigated in a microcosm study, resembling field conditions (Hand and Fleming 2007). With bioconcentration factors ranging from 33 to 90, emamectin benzoate has a low tendency to bioaccumulate.

Table 4-1. Environmental fate data for emamectin benzoate

Property	Result	Reference
Soil adsorption/desorption	K_{oc} for adsorption: 25,363 – 728,918 L/kg	Mushtaq 1993
	K_{oc} for adsorption: 8,687–125,808 L/kg	Wyeth and Ricketts 2005
Soil degradation	DT_{50}: 58 days	Clark 2003
	DT_{50}: 427 days (anaerobic)	Chukwudebe 1995
	DT_{50}: 21–348 days	Hand and Fleming 2006
	DT_{50}: 21–108 days	Jungmann and Nicollier 2006
Degradation in aquatic systems	Degradation/dissipation is rapid from water but no significant degradation occurred in sediment. Water DT_{50}: 0.4–1.7 days Sediment and total system DT_{50}: not calculated	Hurt et al. 2006
	Dissipation rapid from water, slow from sediment Water DT_{50}: 1.1–2.2 days Sediment DT_{50}: 0.4–48.8 days Total system DT_{50}: 3.5–3.9 days	Hand and Fleming 2007
Bioconcentration	BCF: 33–90	Drottar et al. 1994

BCF bioconcentration factor
DT_{50} time to 50% degradation
DT_{90} time to 90% degradation
K_{oc} organic-carbon normalized adsorption coefficient

4.2 Introduction from consumed salmonid products into U.S. ecosystems via wastewater

Emamectin benzoate was evaluated at the 78th meeting of the Food and Agriculture Organization (FAO)/World Health Organization (WHO) Joint Expert Committee on Food Additives (JECFA). The committee recommended Maximum Residue Limits (MRLs) for emamectin B_{1a} in salmon of 100 µg/kg in muscle and fillet and extended these MRLs to trout (JECFA 2014). It can therefore be assumed that all salmonid products imported into the U.S. that have been treated with emamectin benzoate would have residues of emamectin benzoate ≤100 µg/kg. Human consumption of these products will potentially result in the excretion of residues into wastewater. Based on the environmental fate properties previously discussed, these residues may not degrade during the wastewater treatment process; however, they are likely to dissipate from the aqueous stream and become sorbed onto solids. Residues in the solids from wastewater treatment are likely to be disposed of by land application, landfilling, or incineration, as discussed below. A qualitative assessment of the potential environmental impacts relating to discharge of wastewater from WWTPs is provided in Section 5.

4.3 Introduction from consumed salmonid products into U.S. ecosystems via land application of biosolids

An additional potential pathway of exposure related to wastewater treatment is the application of biosolids or residuals from wastewater treatment to agricultural soils as fertilizer. This pathway could introduce low levels of emamectin benzoate to the soil. A qualitative assessment of the potential environmental impacts relating to land application of biosolids is provided in Section 5.

4.4 Introduction from unconsumed salmonid products, waste from fish processing plants, or sludge from WWTPs into U.S. ecosystems via disposal in landfills

A small possibility exists of imported salmonid products ending up in U.S. landfills due to spoilage, rejection due to violative residues or other compliance parameters, or some other mismanagement of the products. The worst-case scenario (which would be rare) would be if a batch of imported salmonid products exceeding the MRL of 100 µg/kg was seized and disposed of at once in a landfill.

Wastes from processing plants that handle imported salmonid products could be another potential source of emamectin benzoate residues to the environment. If such wastes were not incinerated, they might be landfilled. Sludge from WWTPs is also typically disposed of in landfills. A qualitative assessment of the potential environmental impacts relating to landfills is discussed in Section 5.

5. ASSESSMENT OF ENVIRONMENTAL IMPACT

As stated previously, there are two potential pathways for introduction of emamectin benzoate residues to the U.S. environment that could result from establishing this import tolerance: 1) pathways arising from the release of drug residues, if present, from imported food derived from treated salmonids and 2) pathways arising from the use of the drug in salmonids in countries where it is legally authorized.

For the first pathway, there are three ecosystems considered for evaluation of the potential environmental impact due to the release of emamectin benzoate (following the import of salmonid products) into the U.S. environment: (a) ecosystems where residues from consumed

salmonid products might be introduced through wastewater; (b) ecosystems where residues from consumed salmonid products might be introduced through landfilled biosolids; and (c) ecosystems where residues from unconsumed salmonid products might be introduced through landfilling of noncompliant products, waste from fish processing plants, or sludge from WWTPs. These three ecosystems are discussed below under the headings wastewater, biosolids, and landfills.

For the second pathway, the relevant ecosystems are those in U.S. waters receiving water flow from areas where emamectin benzoate is used in Canadian aquaculture. This is discussed under Section 5.4 (Use in Canada or other foreign countries).

5.1 Wastewater

Consumption rates of salmonids in the U.S. are low compared to most other types of meats. In addition, the residues will be further reduced (diluted) by the excreta from other consumers who have not consumed emamectin benzoate treated salmonids. Due to these expected consumption patterns, only very low concentrations of emamectin benzoate are estimated to enter wastewater. In addition, the distribution of residues will likely be spatially and temporally variable. Emamectin benzoate is likely to dissipate in the wastewater treatment through partitioning to sludge, but substantial biodegradation may not occur. Because emamectin benzoate has a high sorption potential to solids (as indicated by the high K_{OC} in soils, ranging from 8,687 to 728,918 L/kg), it is likely that most of the substance will adsorb to sludge and will not be released with the aqueous effluent. Further dissipation, degradation, and dilution can be expected in the receiving water. Emamectin benzoate has a low tendency to bioaccumulate, and any accumulated residues are likely to be rapidly depurated; therefore, uptake through food chains eventually leading to secondary poisoning can be excluded. Taken together, these considerations indicate that adverse effects on the aquatic environment from discharged wastewater are unlikely.

5.2 Biosolids

Due to consumption patterns, residues of emamectin benzoate entering wastewater are likely to be very low. Partitioning will take place from the water to the solid phase, with residues in biosolids exceeding those in water (as indicated by the K_{oc} values). Nevertheless, due to the very low concentrations in wastewater, concentrations in soil following application of biosolids as fertilizer are anticipated to be very low as well. In this context, it is worth mentioning that <1% of agricultural lands use WWTP biosolids as a fertilizer (Lu et al. 2012). Due to the sorption properties of emamectin benzoate, these residues are unlikely to leach into groundwater.

5.3 Landfills

Disposal of spoiled, non-compliant, or mismanaged imported salmonid products into landfills is expected to be sporadic and rare.

Wastes from processing plants that handle imported salmonid products could be another potential source of emamectin benzoate residues to the environment. If such wastes were not incinerated, they might be landfilled. Assuming that the imported products contained levels of emamectin benzoate below the established MRL, leachates from these wastes would be at this level or lower and would be unlikely to pose a risk to the environment as discussed for wastewater.

Landfills would also be likely to receive sludge from WWTPs. Due to the low concentrations of emamectin benzoate predicted in wastewater and ultimately in sludge, it is unlikely that significant concentrations of the drug would be available for disposal into landfills. This pathway is also considered very minor.

Fish processing plants and municipal WWTPs can be expected to operate in compliance with applicable regulations regarding landfill disposal. Municipal solid waste landfills are regulated by EPA to restrict movement of waste into the environment, including location restrictions, composite liner requirements, leachate collection and removal systems, operating practices, groundwater monitoring requirements, and closure and postclosure care requirements (40 CFR Part 258). In addition, the K_{OC} of emamectin benzoate (8,687 to 728,918 L/kg) indicates strong sorption to soil, sediment, and other organic materials found in landfills and, thus, very slow migration potential to groundwater. Therefore, only a negligible amount of emamectin benzoate is expected to be available to potentially leach into groundwater (and from there to surface water) from landfill disposal. In conclusion, the potential environmental impact from landfill disposal of imported salmonid products, wastes from fish processing plants, or WWTP sludge containing emamectin benzoate is insignificant.

5.4 Use in Canada or other foreign countries

Canada is the fourth-largest producer of farmed salmon in the world,[1] with facilities located on both the Pacific and Atlantic coasts. Aquaculture facilities and activities in Canada are regulated under a number of acts, laws, regulations, and programs related to environmental management and shared use of aquatic resources. These instruments are administered by various federal, provincial, and territorial bodies. On June 29, 2015, the Aquaculture Activities Regulations came into effect. These regulations clarify rules on the deposit of pesticides and drugs in water for the purposes of aquaculture and impose new reporting requirements to make industry practices more transparent.[2] Emamectin benzoate is approved for use in Canada under prescription from a licensed veterinarian. Because emamectin benzoate may be used in Canadian aquaculture, and the proximity of Canada to the U.S., the potential impact to the U.S. environment due to emamectin benzoate use in Canada is evaluated.

As mentioned above, the operation of fish farms in Canada, including use of drugs, is regulated to prevent adverse impacts on the environment around the farms. It is thus unlikely that a drug being used on a Canadian fish farm would enter the environment of the U.S. at concentrations that could have adverse impacts to the U.S. environment. In addition, the fate of emamectin benzoate indicates it would primarily be associated with solids (uneaten feed and feces). In freshwater aquaculture these solids will be mostly removed by filtration and/or settling at the aquaculture facility prior to discharge or dissipate (e.g., partitioning, settling on solids) to the sediment phase in receiving waters, while in marine aquaculture the uneaten feed and feces will be deposited underneath and near the net pens. In either case, released emamectin benzoate would remain primarily, if not completely, within the country of use. This is further discussed below.

When emamectin benzoate enters the aquatic environment due to use in fish farming (as opposed to consumption of fish by humans, discussed earlier), it enters within uneaten feed or

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[1] http://www.dfo-mpo.gc.ca/aquaculture/sector-secteur/stats-eng.htm, accessed March 13, 2018

[2] http://www.dfo-mpo.gc.ca/aquaculture/management-gestion/aar-raa-bck-eng.htm, accessed March 13, 2018.

fish excreta. Once in the water column, emamectin benzoate is largely dissipated; this is supported by fate studies in the laboratory (Hurt et al. 2006) and in outdoor microcosms (Hand and Fleming 2007). Neither hydrolysis nor photolysis is expected to be an important fate process in the aqueous environment, and bioaccumulation is not a concern. Emamectin benzoate that leaches from uneaten food or from feces would tend to be incorporated into sediment, where it will degrade slowly. A laboratory study indicated no degradation in the sediment over a period of 120 days (Hurt et al. 2006), while a model outdoor microcosm study showed fast degradation with DT_{50} values of 0.4 to 48.8 days (Hand and Fleming 2007). Thus, sediment would provide the major route of potential exposure for non-target organisms, while concentrations in the water column would be extremely low. Furthermore, water flowing from the sites of Canadian fish farms would be subject to extremely large dilution, and thus the concentrations of emamectin benzoate in the water column would be rendered insignificant before reaching the U.S. It is therefore not expected that there would be any impact on pelagic non-target organisms in the U.S. environment.

The predominant fate of emamectin benzoate residues from marine fish farming is deposition directly underneath the net pens and to some extent around the vicinity of the farm, with incorporation in sediment over time. Solid residues from freshwater fish farming are removed by filtration and/or settling or would dissipate rapidly after discharge to the sediment phase. In either case, residues of emamectin benzoate would remain primarily, if not completely, in the country of use (i.e., Canada) and quantities that may enter the U.S. environment are considered insignificant and unlikely to have a significant impact on the U.S. environment.

These factors, together with the regulatory processes in place in Canada, indicate that sources of emamectin benzoate arising from Canadian salmonid farming activities should pose no unacceptable risk to the U.S. environment. Furthermore, because no significant impacts to the U.S. environment are expected from the use of emamectin benzoate in Canada, its use in countries further away from the U.S. (e.g., Chile) would also not be expected to result in any significant impacts to the U.S. environment.

6. MITIGATION MEASURES

Because the establishment of an import tolerance for salmonid products treated with emamectin benzoate in accordance with label directions in countries outside the U.S. would not have a significant effect on the environment in the U.S., no mitigation measures will be required.

7. ALTERNATIVES TO THE PROPOSED ACTION

The proposed action is to establish a tolerance for emamectin benzoate in salmonids imported into the U.S. for human consumption. The only alternative to the proposed action is the "no action" alternative, which would be the failure to establish a tolerance for residues of emamectin benzoate in edible salmonid tissues. However, based on our analysis in this environmental assessment, we do not believe that significant environmental impacts will occur from this action; therefore, the "no action" alternative was eliminated from consideration.

8. LIST OF PREPARERS

This document was prepared by Exponent, Inc., under the direction of Jane P. Staveley, and by Dr. Gregor Scheef of MSD Animal Health Innovation GmbH.

9. CERTIFICATION

The undersigned officials certify that the information presented in this Environmental Assessment is true, accurate, and complete to the best of their knowledge.

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05-Mar-2019

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APPENDIX A

Study Summaries

Reference:

Chukwudebe, A. (1995). Anaerobic soil metabolism of [^{14}C]4"-deoxy-4"-epimethylamino avermectin B1$_a$ benzoate ([^{14}C]MAB1a) in sandy loam soil. Merck & Co. Inc. Project No.: 93258. Report A-27958.

Title:

Anaerobic Soil Metabolism of [^{14}C]4"-Epimethylamino-4"-Deoxyavermectin B1a Benzoate [^{14}C]MAB$_{1a}$ in Sandy Loam Soil. Report Number A-27897.

Name of Sponsor Company:	**Study number:**	**Report date:**
Merck & Co., Inc.	Sponsor Study No.: 93258 PTRL No.: 588	25 September 1995

Study type:

Anaerobic Degradation in Soil (EPA-OPP, Subdivision N, Series 162-2 (1982): Anaerobic soil metabolism studies)

Name of test material:

Radiolabelled test item: [^{14}C]MAB$_{1a}$ (purity: 99.6%); Specific activity 23.9 µCi/mg.

Non-radiolabelled test item: MK-244 (97.9% pure), Lot # L656, 748-052S003

Test design:

The rate and route of degradation of [^{14}C]MAB$_{1a}$ was studied in a sandy loam soil according to EPA's Pesticide Assessment Guidelines (Subdivision N, Series 162-2). A test solution of [^{14}C]MAB$_{1a}$ was prepared in methanol. Aliquots of this solution containing 0.25 mg (5.96 µCi/49 µL) were applied directly to 50-g aliquots of air-dried sandy loam in separate 500-mL Erlenmeyer flasks to give a nominal concentration of 5.0 ppm. High-performance liquid-chromatography (HPLC)-grade water was added to obtain 75% of field moisture capacity at 0.33 bar and the flasks were sealed and placed in a dark incubator maintained throughout the study at a temperature range of 24.0–26.0°C, with a mean of 24.9 ± 0.3°C. The treated soils were aged aerobically for 30 days and then incubated for 60 additional days under anaerobic conditions. At intervals of 0, 30, 59, and 90 days the respective soil samples were removed for determination of total radioactive residues and [^{14}C]MAB$_{1a}$ levels. Duplicate flasks were sampled at 0 and 30 days (aerobic conditions) and 59 and 90 days (anaerobic conditions) following the initial [^{14}C]MAB$_{1a}$ application to soil.

At each sampling interval, soil samples (50 g each, 5.0-ppm concentration) were dried by lyophilization on a Labconco Freeze Dryer 4.5 (Labconco Corporation, Kansas City, Missouri). Following lyophilization, these bulk soil samples were thoroughly hand mixed to ensure uniform distribution of the total [^{14}C]MAB$_{1a}$-related residues throughout the sampled soil. Subsequently, the total radiocarbon present in each soil sample was determined prior to extraction by combustion of five separate 0.5-g aliquots followed by liquid scintillation counting (LSC). The soil samples were then extracted for reversed phase HPLC profiling and determination of [^{14}C]MAB$_{1a}$ levels by placing the bottles on a wrist-action shaker for approximately 45 minutes. Following extraction, the mixtures were centrifuged at approximately 10,000 rpm for 10 minutes and the supernatants decanted. Additional extractions were also carried out in an attempt to release more [^{14}C]MAB$_{1a}$-related residues from the extracted soil. The volatile traps were analyzed by LSC for determination [^{14}C]MAB$_{1a}$-related residues. Material balance was determined for each sample and is expressed as percent of applied radioactivity (%AR). Soil viability was evaluated by enumerating the total colony forming units (CFU) of aerobic bacteria, actinomycetes, and fungi.

Statistical analysis:

The rate of degradation of [^{14}C]MAB$_{1a}$ was determined using pseudo first-order kinetics. The suitability of the fit was evaluated by R^2.

Summary of findings:

The overall average material balance was 95.4 ± 4.7% of applied radiocarbon. At the end of the 90-day study period, the percentage of applied radiocarbon remaining as [^{14}C]MAB$_{1a}$ dropped to 60.6%. Conversely, the percentage of unextracted radiocarbon increased to an average of 15.6% of the initially applied radiocarbon. Following the initial 30 days of incubation (aerobic phase), an average of 21.8% of the initially applied [^{14}C]MAB$_{1a}$

was degraded. However, within the succeeding 60 days, (days 30–90, anaerobic phase), only about one-third that amount (average of 6.2%) of the initially applied [^{14}C]MAB$_{1a}$ was degraded. The calculated cumulative and anaerobic half-lives are 174.2 and 427.4 days, respectively. The results of this anaerobic soil metabolism study therefore demonstrate that [^{14}C]MAB$_{1a}$ will degrade relatively quickly in microbially viable soil under aerobic conditions but will be metabolized more slowly under anaerobic conditions similar to this study.	
Study conducted by: Merck Research Laboratories, Pesticide Metabolism and Environmental Safety Group, Drug Metabolism II Department and PTRL East, Inc. **Author:** Chukwudebe, A. **Address:** Hillsborough Road, Three Bridges, New Jersey, USA and 3945 Simpson Lane, Richmond, Kentucky, USA	**Compliance with GLP:** yes with minor exceptions **If no, justification:**

Reference:

Clark, A. (2003). Aerobic soil metabolism of ^{14}C-NOA-426007 and ^{14}C-NOA-4332990. Syngenta Crop Protection Study No. 1853-01

Title:

Aerobic Soil Metabolism of ^{14}C-NOA-426007 and ^{14}C-NOA-422390. Syngenta Crop Protection Study No. 1853-01

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta Crop Protection, Inc.	Sponsor Study No.: 1853-01 Lab Study No.: 1853-01	17 November 2003

Study type:

Aerobic Degradation in Soil (EPA-OPP, Subdivision N, Series 162-1 (1982): Aerobic soil metabolism studies)

Name of test material: [NOA-426007 is the same as MAB_{1a}; NOA-422390 is the same as MAB_{1b}]

Radiolabelled test items: ^{14}C-NOA-426007 (purity: 98.6%, Specific activity 58.9 µCi/mg) and ^{14}C-NOA-422390 (purity: 98.7%, specific activity 56.7 µCi/mg)

Non-radiolabelled test items: None

Test design:

A side-by-side aerobic metabolism study was conducted on a sandy loam soil with [23-^{14}C]-NOA-426007 (experiment 1) and [23-^{14}C]-422390 (experiment 2) to compare degradation under aerobic conditions at a rate of 0.138 ppm. NOA-426007 (MAB_{1a}) is the major component (≥90%) of emamectin benzoate and NOA-422390 (MAB_{1b}) is the minor component. Aerobic metabolism was also monitored on a bulk set (NOA-426007 experiment 3 and NOA-422390 experiment 4) for each test substance at higher rates (4.9–5.6 ppm). All samples were incubated in the dark at 25.0 ± 1°C for up to 100 days. Duplicate samples for each test substance were collected on days 0, 2, 4, 7, 14, 21, 30, 60, and 100 (experiments 1 and 2). The bulk samples (experiments 3 and 4) were collected on days 0, 30, and 60. The soil was extracted with a series of solvents, centrifuged for 15–30 minutes at 8,000 rpm, and a portion of the supernatants was radioassayed in triplicate by two-dimensional thin layer chromatography (2D-TLC) and representative samples confirmed by high-performance liquid chromatography (HPLC) to determine the percent extractable radiocarbon. The volatile traps were analyzed by liquid scintillation counting (LSC) for [23-^{14}C]-NOA-426007 and [23-^{14}C]-422390 residue determinations. Material balance was determined for each sample and is expressed as percent of applied radioactivity (%AR). Soil biomass was measured at the experimental start date and at the end of the incubation period to determine soil microbial viability.

Statistical analysis:

The percent total dose (parent) for each sampling time was used in the Origin program (Version 6.0) to calculate the half-life assuming exponential decay. The half-life values were confirmed by Modelmaker version 3.0. The suitability of the fit was evaluated by Chi^2 and R^2.

Summary of findings:

The average material balance ranged from 90.03 to 108.55% of applied radiocarbon. Microbial degradation of NOA-426007 and NOA-422390 led to formation of multiple metabolites. The kinetics indicate an exponential decline in extractable NOA-426007 and NOA-422390 with a half-life of 57.8 days for the former (experiment 1) and 63.0 days for the latter (experiment 2) by Origin. The DT_{50} values (53 days for NOA-426007 and 54 days for NOA-422390) were extrapolated from the Origin curve. Modelmaker confirmed the half-lives of 53.3 days and 54.6 days for NOA-426007 and NOA-422390, respectively. Therefore, no significant differences were observed between the degradation kinetics and pathways for NOA-426007 and NOA-422390.

Study conducted by: Syngenta Crop Protection, Inc. **Author:** Clark, A. **Address:** Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC, USA.	**Compliance with GLP:** yes with a minor exception **If no, justification:**

Reference:

Drottar, K., Swigert, J.P., and Jaber, M. (1994). MK 244: A bioconcentration test with the bluegill sunfish (*Lepomis macrochirus*). Wildlife International Ltd. Study No. 105A-119.

Title:

MK-244: A bioconcentration test with the bluegill (*Lepomis macrochirus*)

Name of Sponsor Company:	**Study number:**	**Report date:**
Merck Research Laboratories.	Report No. A-27972	22 September 1994

Study type:

U.S. EPA Pesticide Assessment Guidelines N-165-4

Name of test material:	**Name of formulated product:**
[^{3}H]-deoxy-4"-epimethylaminoavermectin B_{1a} (MAB_{1a}) benzoate, also referred to as [^{3}H]MAB_{1a} benzoate	MK-0244; containing 97.5% MAB_{1a}

Test design:

The study was designed to measure the bioconcentration of the test substance in the bluegill sunfish (*Lepomis macrochirus*). Following a pre-exposure equilibration period, test organisms in the treatment group were exposed to [^{3}H]MAB_{1a} at a nominal concentration of 1.6 µg/L using flow-through conditions during the 28-day uptake period. Fish in the control group were exposed to the solvent (methanol) at the same concentration as used in the treatment group. Following the uptake period, fish were maintained in untreated water for a 14-day depuration period. There were two replicate test chambers in both the treatment and control groups with 90 fish in each chamber. Fish had a total mean length of 45.9 ± 5.2 mm and mean weight of 1.48 ± 0.63 g. The test was conducted at a temperature of 22 ± 1°C with a photoperiod of 16 hours light:8 hours dark. On a daily basis, fish were fed flaked food, and the excess food was siphoned off. Dilution water was well water of medium hardness. Water samples were collected on uptake phase days 0, 1, 3, 7, 10, 14, 21, 23, and 28 and on depuration phase days 1, 3, 7, 10, and 14 and analyzed for total radioactivity using liquid scintillation counting (LSC). Two fish were collected from each test chamber at the same times (with the exception of day 23). Fish were divided into edible and nonedible portions. The two tissue fractions of each fish were weighed and pooled, homogenized, combusted and analyzed for total radioactivity by LSC. The concentrations of radioactivity in the water samples were converted to µg equivalents/L water; the Limit of Quantification (LOQ) in water was set at twice the background radioactivity (0.050 µg equivalents/L). Blank fish tissue samples were fortified with [^{3}H]MAB_{1a} and combusted with the study samples to evaluate recovery. Radioactivity measurements in tissue samples were converted to µg equivalents/kg tissue and were corrected for overall procedural recovery (79.7% in edible tissues and 77.9% in nonedible tissues); the LOQ was set at twice background or 2.5 µg equivalents/kg.

Statistical analysis:

Steady-state concentration was considered to be achieved when 3 consecutive sets of tissue samples were not statistically significantly different. Observed bioconcentration factor (BCF) values were calculated as the ratio of test substance concentration in fish tissues at steady state to the average test substance exposure concentration. However, steady state was not attained in edible tissues so this BCF was estimated based on the Day 28 tissue concentration. For nonedible tissues and whole fish, BCF values were calculated based on the mean tissue concentrations on days 7, 10, and 14. Predicted BCF values were calculated as the ratio of the uptake constant to the depurate rate constant.

Summary of findings:

Water quality parameters of temperature, conductivity, alkalinity, hardness, and pH measured throughout the test were within expected ranges. Dissolved oxygen dropped to 55% saturation on Day 5 but remained >60% saturation at all other days and the fish did not appear to be stressed. Two of the 368 fish used in the test died during the experiment; no clinical signs were noted.

Mean measured concentrations of [^{3}H]MAB_{1a} in water during the test indicated the concentration was <LOQ of 0.05 µg/L in the solvent control and 1.2 µg/L in the treatment (1.6 µg/L nominal).

The observed BCF values for edible tissue, non-edible tissue, and whole fish were 33, 90, and 62, respectively. This closely agrees with the predicted BCF values calculated from the uptake and depuration rate constants, which were 30, 116, and 80 for edible tissue, non-edible tissue, and whole fish, respectively. Non-edible tissues showed the greatest accumulation, but more than 50% clearance had occurred after about 4 days of depuration. Thus, it can be concluded that emamectin benzoate has a low tendency for bioaccumulation, and any accumulated residues are likely to be rapidly depurated.	
Study conducted by: Wildlife International Ltd. **Author**: Drottar, K., Swigert, J.P., and Jaber, M. **Address:** 8598 Commerce Drive, Easton, MD 21601	**Compliance with GLP:** Yes **If no, justification:**

Reference:

Hand, L.H., and Fleming, E.A. (2006). Emamectin benzoate: route and rate of degradation of NOA-426007 in three soils, under aerobic laboratory conditions, at 20°C. Syngenta Report T002559-04-REG.

Title:

Route and Rate of Degradation of NOA426007 in Three Soils, Under Aerobic Laboratory Conditions, at 20°C. Syngenta Report T002559-04-REG.

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta	Sponsor Study No.: 04JH008 Lab Study No.: 04JH008	12 April 2006

Study type:

Aerobic transformation in soil (OECD 307)

Name of test material: [NOA426007 is the same as MAB_{1a}]

Radiolabelled test item: [23-^{14}C]-NOA426007 (purity >98%); Specific activity 2.13 MBq/mg

Non-radiolabelled test item: None

Test design:

The route and rate of degradation of NOA426007 was investigated in 18 Acres, Gartenacker, and Marsillargues soils. Three sets of soil pots, containing 50 g (dry weight equivalent) of soil, were treated with [23-^{14}C]-NOA426007 at a rate of 0.13 mg kg^{-1}. The treated soil pots were maintained in a flow-through apparatus at 20 ± 2°C, and at moisture contents as close to pF2 values as practically feasible, for 120 days after application of the test substance. This system maintained aerobicity and flushed volatile degradation products into trapping systems.

Duplicate soil pots of each soil were taken for analysis immediately after treatment (zero time) and 7, 14, 21, 28, 60, 90, and 120 days after treatment. Soil samples were extracted, centrifuged, and the combined extracts were then concentrated to a low volume by rotary evaporation. The concentrated extracts were quantified by liquid scintillation counting (LSC). The sample was then analyzed by high-performance liquid chromatography (HPLC). The production of volatile degradates ($^{14}CO_2$) was also quantified at each time-point. Microbial biomass of the soils was also determined. The experiment was conducted in accordance with OECD Guideline 307 (OECD, 2002).

Statistical analysis:

The degradation of NOA426007 was determined using the simple first-order kinetics model and first-order multi-compartment kinetics using ModelManager version 1.1. The r^2, adjusted r^2, and the error mean square (EMS) values were used as indicators of the goodness-of-the-fit.

Summary of findings:

Microbial biomass findings were typical and confirmed a viable microbial population at the start of the study. Total mass balances (means of two replicates for each soil) from the samples analyzed immediately after treatment (zero time) ranged between 98.6 and 100.1% of the applied dose. Total mass balances for the remaining sampling intervals were generally ≥90% for all incubation soils. The mean mass balance was 94.2, 94.9, and 98.3% of the applied radioactivity for the 18 Acres, Gartenacker, and Marsillargues soils, respectively. The average total radioactive recovery for all conditions was 95.8%. The amount of extractable radioactivity was found to decrease with time under all conditions. It ranged from 95.3 to 97.3% on day zero to 47.3 to 56.2% by day 120. In addition, low levels of radioactivity were evolved as volatile products. The total amounts of volatile radioactivity evolved from soil pots incubated for 120 days were 7.8, 8.8, and 1.3% of the applied radioactivity for 18 Acres, Gartenacker, and Marsillargues, respectively. No metabolites of greater than 10% of applied radioactivity were observed in any of the three soils.

Degradation was relatively rapid in 18 Acres and Gartenacker but was significantly slower in Marsillargues. The simple first-order DT_{50} values were 46, 25, and 348 days for 18 Acres, Gartenacker, and Marsillargues soils, respectively. The best statistical fit to the data for the 18 Acres and Gartenacker soils was achieved with the FOMC model, which gave DT_{50} values of 30 and 21 days, respectively. The degradation kinetics are summarized below.

Soil	Type and % OC	Simple First-Order Model		First-Order Multi-Compartment Model	
		DT_{50} (days)	DT_{90} (days)	DT_{50} (days)	DT_{90} (days)
18 Acres	Sandy clay loam, 2.8%	45.8	152.2	29.6	449.2
Gartenacker	Loam, 3.1%	25.2	83.6	21.2	116.1
Marsillargues	Silty clay loam, 1.0%	347.9	155.8	348.1	1157.6

Study conducted by: Syngenta

Author: Hand, L.H., and E. A. Fleming

Address: Jealott's Hill International Research Centre, Bracknell, Berkshire, RG426EY, UK

Compliance with GLP: yes

If no, justification:

Reference:

Hand, L.H., and Fleming, E.A. (2007). Emamectin benzoate B1a (NOA-426007): Degradation in an aquatic microcosm study. Syngenta Report T013225-04-REG.

Title:

Emamectin-benzoate B1a (NOA426007) Degradation in an Aquatic Microcosm. T013225-04/Regulatory/Report

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta	Sponsor Study No.: T013225-04 Lab Study No.: T013225-04	6 July 2007

Study type:

Aquatic microcosm study (no established guideline)

Name of test material: [NOA426007 is the same as MAB_{1a}]

Radiolabelled test item: [23-^{14}C]-NOA426007; Specific activity 2.057 MBq/mg, Batch Number: BPM-XXXI-70; Radio purity: 100%.

Non-radiolabelled test item: None

Test design:

The objective of the study was to investigate the route and rate of dissipation/degradation of NOA426007 in aquatic systems under semi-natural conditions. The test system consisted of natural sediment and its associated overlying water in two plastic tanks (internal measurements of 1.2 × 1.8 × 0.7 m), one serving as a control and one for the exposure. Each tank was filled with sediment to a depth of 10 cm followed by water to a depth of 30 cm. The sediment and water were sampled from Calwich Abbey (as used in the study by Hurt et al. 2006).

During a 13-week period of stabilization, the systems were planted with the following macrophyte species: *Ceratophyllum demersum*, *Fontinalis* sp., *Typha laxmanni*, *Myriophyllum spicatum*, and *Elodea* sp. During equilibration, the systems became populated by a representative selection of both water and sediment dwelling macroinvertebrates. The taxa observed were Chironomidae, Culicidae, Dytiscidae, Daphnidae, Copopeda, *Asellus* sp., *Gerris* sp., Hydrophilidae, Ceratopogonidae, Corixidae, *Physa* sp., and *Lymnaea peregra*.

Radiolabeled NOA426007 was applied at an initial nominal aqueous phase concentration of 31.1 µg/L (assuming equal distribution throughout the water column). Water column samples were taken for analysis after 4, 10, 22, and 32 hours and 2, 3, 6, 14, 29, 58, and 90 days. Sediment cores were taken for analysis after 3, 6, 14, 29, 58, and 90 days. Representative macrophytes samples were also removed after l, 6, 29, 58, and 90 days. All samples were analyzed for total radioactivity by liquid scintillation counting (LSC); sediment and macrophyte samples were first combusted and extracted. High-performance liquid chromatography (HPLC) analysis with radio-detection was used to determine the purity of the radiolabeled test substance and for analysis of soil extracts. Liquid chromatography/tandem mass spectrometry (LC-MS/MS) was used to elucidate the structures of significant unknown degradates.

Statistical analysis: The values for the DT_{50} and DT_{90} were calculated using simple first-order, first-order multi-compartment, and hockey-stick models within ModelManager Version 1.1. The r^2, adjusted r^2, and the error mean square (EMS) values were used as indicators of the goodness-of-the-fit.

Summary of findings:

Total mass balances ranged between 90.7 and 61.1% of the applied dose, with a considerable reduction during the course of the study. This was considered indicative of significant mineralization. The level of total radioactivity in the water column decreased to 43% after 6 days, while the levels in the sediment increased to 48% after 3 days. Thereafter, the overall dissipation rate of total radioactivity slowed significantly from the water column but remained relatively constant in the sediment. The amount of radioactivity that could be extracted from sediment decreased with time, dropping to only 17% of the applied dose at 58 days. The decrease was attributed to binding or incorporation

into the sediment matrix. The amount of radioactivity in the macrophytes increased throughout the study to a maximum of 10.2% of that applied after 90 days. The proportion of this that could be extracted decreased significantly throughout the study such that after 90 days, only about 1.1% of the applied radioactivity could be extracted. Results are shown below.

Time after dosing	Percent of applied radioactivity as NOA-4267007		
	Water Column	Sediment Extracts	Total System
0	100.0	NA[1]	100.0
4 hr	63.0	NA	NC[2]
10 hr	60.6	NA	NC
22 hr	51.9	NA	NC
32 hr	46.9	NA	NC
2 days	41.6	NA	NC
3 days	32.7	29.6	62.3
6 days	12.2	14.1	26.3
14 days	1.0	15.2	16.2
29 days	0.2	10.1	10.3
58 days	0.0	12.0	12.0
90 days	0.0	8.2	8.2

[1] NA = not applicable (no sample taken)

[2] NC = not calculated (samples not taken)

Dissipation from the water column was very rapid, with a DT_{50} of 2.2 days using simple first-order kinetics, and no radioactivity was detected after 29 days. Partitioning to sediment was initially rapid, with the parent compound representing 29.6% of the total applied radioactivity 3 days after dosing. This was followed by a rapid decline in the sediment residues at 6 days and then a slower second phase of degradation. The DT_{50} for degradation in the whole system was 3.5 days using the hockey-stick model.

Compartment	Simple first-order model		Hockey-stick model	
	DT_{50} (days)	DT_{90} (days)	DT_{50} (days)	DT_{90} (days)
Water column (dissipation)	2.2*	7.3*	1.1	7.4
Sediment (degradation)	48.4	162.0	0.4*	261.2*
Total System	3.9	13.0	3.5*	61.5*

* best fit value

Many minor degradates (generally small, polar molecules) were observed in both water and sediment; only one (found in the water column) exceeded 5% of the total applied radioactivity at any time during the study. This was identified in the water phase as consisting of two components—i.e., (8-sec-butyl-4-hydroxy-9-methyl-1,7-dioxa-spiro[5,5]undec-10-en-2-yl)-acetic acid and (8-acetyl-4-hydroxy-9-methyl-1,7-dioxa-spiro[5,5]undec-10-en-2-yl)-acetic acid—which together constituted only 6% of applied radioactivity. One of the other minor degradates in the water column indicated that some direct photolysis had occurred. In sediment extracts, the most significant degradate reached a maximum of 4.7% of applied radioactivity after 6 days and then declined to 1.1% after 4 days. This was a highly labile, transient degradate and could not be identified.

The microcosm study showed that degradation of NOA426007 was rapid and extensive in the aquatic microcosm studied. This was driven primarily by dissipation from the water column. Degradation was by cleavage of the macrocycle to yield relatively small, polar degradates which did not partition significantly to the sediment and,

ultimately mineralization. Some photo-isomerism of the parent molecule was also implicated. Once in sediment, degradation was initially rapid but slowed significantly, as adsorption of NOA426007 became significant. No significant degradates were observed in the sediment. No accumulation of NOA426007 was observed in the macrophytes.	
Study conducted by: Syngenta **Author:** Hand, L.H., and Fleming, E.A. **Address:** Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK	**Compliance with GLP:** yes with minor exception **If no, justification:**

Reference:

Hurt, A.D., Grosjean, J., and Mason, G. (2006). Emamectin benzoate: aerobic degradation of NOA426007 in two aquatic systems under laboratory conditions. Syngenta Report T000308-06-REG.

Title:

Aerobic Degradation of NOA426007 in Two Aquatic Sediment Systems Under Laboratory Conditions. Syngenta Report T002559-04-REG

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta	Sponsor Study No.: 04JH026 Lab Study No.: 04JH026	26 April 2006

Study type:

Aerobic transformation in Aquatic Sediment Systems (OECD 308)

Name of test material: [note: NOA426007 is also known as MAB_{1a}]

Radiolabelled test item: [23-^{14}C]-NOA426007 *(purity:* 93.4–94.1%); *Specific activity* 2009 *Bq/µg*

Non-radiolabelled test item: NOA426007; Batch No. GAN-XL111-57; purity: 95.9% (w/w).

Test design:

The dissipation of [23-^{14}C]-NOA426007 was investigated in two laboratory-incubated sediments (Calwich Abbey and Haut Languedoc) and their associated waters. The water-sediment systems were set up in glass vessels (water:sediment ratio of 4:1 based on dry weight) under aerobic conditions at 20°C with the flow through gas being air and incubated in the dark for up to 120 days. The effluent gases were passed through a series of sodium hydroxide (NaOH(aq)) traps. ^{14}C-NOA426007 was applied into the water layer contained in each individual incubation vessel at a nominal rate of approximately 645 µg/L. Sediment and water parameters were characterized prior to being dosed with ^{14}C-NOA426007. The sediment from the Calwich Abbey system was classified as silt loam with 4.3% organic carbon content while the sediment from the Haut Languedoc was classified as loamy sand with 0.9% organic carbon content.

At each sampling interval at 0 (immediately after application), 14, 21, 28, 60, 90, and 120 days after the treatment, allocated duplicate water-sediment vessels were disconnected from the incubation system. The surface water was then removed via aspiration from the sediment and the weight of the water recorded. Aliquots of these samples were taken gravimetrically for quantification by liquid scintillation counting (LSC). When required, aliquots were concentrated by either turbo or rotor evaporation and re-analyzed by high-performance liquid chromatography (HPLC). The remaining sediment samples were transferred to centrifuge tubes, extracted, centrifuged at 3,000 rpm at 10°C for 10 min. and the aliquots of the supernatants analyzed as for the water layer samples. The remaining wet sediment pellet was air-dried at ambient temperature after extraction, grounded to a fine powder, combusted, and quantified by LSC.

Characterization and identification of NOA426007 was made by comparison of HPLC water layer and sediment extractable sample retention times with co-injected non-radiolabeled NOA426007. The water and extractable fractions at each sampling interval were spiked with non-radiolabeled NOA426007. The HPLC eluate was passed through the UV detector and then through the radioactive flow detector. The HPLC retention time of the non-radiolabeled NOA426007 by UV detection was then directly compared to the HPLC retention time of the test article by radiochemical detection.

The experiment was conducted in accordance with OECD Guideline 308 (OECD, 2002) with the exception that anaerobic degradation was not investigated.

Statistical analysis:

The degradation of NOA426007 in the water layer was determined using first-order multi-compartment kinetics using ModelManager (version 1.1). The r^2, adjusted r^2, and the error mean square (EMS) values were used as indicators of the goodness-of-the-fit.

Summary of findings:

The water-sediment systems were microbially active at 7 days before dosing and at 176 days after dosing. Total mass balances from the samples analyzed immediately after treatment (zero time) ranged between 93.1 and 103.1% of the applied dose. The levels of radioactivity in the surface waters declined rapidly due to adsorption of the [23-^{14}C]-NOA426007 onto the sediment. The dissipation from the water column for the Calwich Abbey and Haut Languedoc systems gave calculated DT_{50} values of 0.4 and 1.7 days respectively, and DT_{90} values of 67.5 and 21.0 days, respectively. Levels in sediments tended to either increase over time or decline only slightly towards the end of the test, precluding determinations of DT_{50} or DT_{90} values in either sediment. The DT_{50} and DT_{90} values for the total systems were not calculated. No discrete metabolites were detected in significant amounts (>4% of applied radioactivity) in the overlying water, nor the sediment, of either sediment types. The majority of the radioactive residue contained in the sediments was parent compound.

Study conducted by: Syngenta **Author:** Hurt, A.D., J. Grosjean, and G. Mason **Address:** Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK	**Compliance with GLP:** yes, with one minor exception **If no, justification:**

Reference:

Jungmann, V., and Nicollier, G. (2006). Rate of degradation of [^{14}C]emamectin benzoate B1a (^{14}C-NOA 426007) in one soil under various laboratory conditions at 20°C. Syngenta Report T000877-05 with addendum

Title:

Rate of Degradation of [^{14}C]Emamectin Benzoate B1a (^{14}C-NOA 426007) in one Soil under Various Laboratory Conditions at 20°C. Syngenta Report T000877-05 with addendum

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta Crop Protection AG	Sponsor Study No.: T000877-05 Lab Study No.: T000877-05	16 May 2006

Study type:

Rate of Degradation (Commission Directive 95/36/EC of 14 July 1995 amending Council Directive 91/414/EEC; OECD 307: Aerobic and Anaerobic Transformation in Soil (2002))

Name of test material:

Radiolabelled test item: ^{14}C-NOA-426007 (purity: 97.9%, Specific activity 2.0535 MBq/mg; Batch No. CL-LVII-87)

Non-radiolabelled test item: NOA-426007 (purity: 99 ± 2%; Batch No. KI-7238/3)

Test design:

The metabolism and rate of degradation of NOA 426007 were studied in the dark under various aerobic conditions in one soil (Gartenacker) at 20°C for 119 days. Two application rates (0.031 mg/kg and 0.307 m/kg) and two soil moisture contents (20 or 40% of mean water content [MWC]) were included in three tests in the study. Duplicate soil samples were taken at 0, 3, 7, 14, 28, 56, 91, and 119 days after treatment. The soil samples for the determination of the microbial biomass were taken before application and on day 119. The soil samples for the determination of residues of NOA 426007 and its metabolites were extracted; the supernatants were then processed and analyzed by liquid scintillation counting (LSC), two-dimensional thin layer chromatography (2D-TLC), and high-performance liquid chromatography (HPLC). The residual radioactivity remaining in the soil after the last extraction step was determined by combustion and LSC. The radioactivity in the trapping solutions (NaOH) was determined by LSC without further preparation of the samples. Isolation and purification of metabolites were performed by HPLC, HPLC with nuclear magnetic resonance detection, and mass spectroscopy. The study was conducted in accordance with the Commission Directive 95/36/EC (1995) amending Council Directive 91/414/EEC and the OECD 307: Aerobic and Anaerobic Transformation in Soil (2002).

Statistical analysis:

The degradation rates of NOA 426007 were calculated assuming simple first-order kinetics (SFO) or first-order two-compartments kinetics (FOTC). The rate constants were calculated by applying MicroCal Origin least squares parameter estimation program version 6.0. Half-life and DT_{50} values were calculated by iteration using the solver module of MS-Excel 2000. In addition, the degradation rates of the three metabolites in Tests 1 and 3 were estimated by fitting unweighted simple first order (SFO) kinetics to the average data using ModelManager, version 1.1.

Summary of findings:

The overall mean recovery comprising the soil extracts, non-extractable residues and volatile products was between 97.9 and 109.3% (Test 1), 104.1 and 108.4% (Test 2), and 99.5 and 106.9% (Test 3). NOA-426007 was rapidly degraded in aerobic soil with a half-life of 20.6 (Test 3) to 23.1 (Test 1) days at 40% MWC at an application rate of 230 or 23 g a.i./ha, respectively. At 20% MWC, the half-life was much longer (107.6 days) (Test 2). Two major metabolites, NOA 459720 (maximum of 15.3%) and NOA 438306 (maximum of 9.7%) were observed. Formation of bound residues was also a significant pathway for the disappearance of NOA 426007 with non-extractables reaching 19.7–27.4% at the end of the study. Volatiles in the form of carbon dioxide were always below 5.2%. Assuming simple first-order degradation kinetics (SFO) or first-order two-compartment kinetics, the following half-lives (DT_{50}) and DT_{90} values of NOA 426007 were calculated:

Test	Simple First-Order (SFO)			First-Order Two-Compartments (FOTC)		
Soil	DT_{50} (days)	DT_{90} (days)	R2	DT_{50} (days)	DT_{90} (days)	R2
Gartenacker Test 1	39.8	161.0	0.9245	23.1	204.8	0.9904
Gartenacker Test 2	108.8	361.5	0.9789	107.6	394.5	0.9889
Gartenacker Test 3	32.3	107.3	0.9432	20.6	183.1	0.9956

The simple first-order DT_{50} and DT_{90} values of three metabolites (NOA 459720, NOA 438306, and NOA 415692) were also calculated as follows:

Test	Compounds	DT_{50} (days)	DT_{90} (days)
Gartenacker Test 1	NOA 459720	14.1	46.8
	NOA 438306	14.0	46.5
	NOA 415692	39.4	131.0
Gartenacker Test 3	NOA 459720	19.0	63.2
	NOA 438306	14.1	46.9
	NOA 415692	75.6	251.0

Study conducted by: Syngenta Crop Protection AG **Author:** Jungmann, V., and G. Nicollier **Address:** Syngenta Crop Protection AG, Global Environmental Fate and Exposure, Ecochemistry, 4002 Basel, Switzerland.	**Compliance with GLP:** yes **If no, justification:**

Reference:

McCauley, J.A. (1992). Determination of Physical-Chemical Properties of MK-244. Merck Research Laboratories. & Co. Inc. SPAH Report A-27951.

Title:

Determination of Physical-Chemical Properties of MK-244

Name of Sponsor Company:	**Study number:**	**Report date:**
Merck and Co., Inc.	SPAH Report A-27951	17 December 1992

Study type:

Physical-chemical properties

Name of test material:	**Name of formulated product:**
MK-244	

Test design:

Studies were conducted to determine various physical-chemical properties of MK-244. Those properties discussed in the EA are summarized here.

The octanol-water partition coefficient was determined at pH 5, 7, and 9 by the shake-flask method. At each pH, triplicate determinations, at initial octanol concentrations differing by about a factor of 10, were made. After equilibration, the concentration of MK-244 in the various phases was determined by high-performance liquid chromatography (HPLC).

The water solubility was determined in aqueous buffers at pH 5, 7, and 9 by HPLC analysis on successive days of the filtrates from saturated solutions, which were maintained in a water bath at 25°C.

The melting point was determined by differential scanning calorimetry (DSC) using various heating rates and atmospheres.

The sublimation (vapor) pressure was determined with the gas saturation method using nitrogen gas, C18 as the adsorbent, and HPLC to analyze for adsorbed MK-244. A Gilmont flowmeter with a gas float was used to measure the gas flow rate. The C18 adsorbent was extracted with phosphoric acid in methanol. The resulting slurry was centrifuged, and an aliquot of the methanol extract was evaporated to dryness, redissolved, and analyzed with HPLC.

Two dissociation constants were expected, one for the epi-methylamino (basic salt component) and one for the benzoate (acid salt component). To determine the dissociation constants, solutions of MK-244 in various methanol/water mixed solvents were titrated potentiometrically with standardized solutions of sodium hydroxide and hydrochloric acid. The observed dissociation constants were extrapolated to zero methanol concentration.

The ultraviolet (UV) absorption spectrum of MK-244 was determined in basic (10 volume % methanol in 0.1 M NaOH), neutral (10 volume % methanol), and acidic (10 volume % methanol in 0.1 M HCl) media using a Perkin-Elmer Lambda 5 spectrophotometer.

Statistical analysis:

Linear regression analysis.

Summary of findings:

The average octanol-water partition coefficients (as Log P) were 3.0 ± 0.1, 5.0 ± 0.2, and 5.9 ± 0.4 at pH values of 5.07 ± 0.01, 7.00 ± 0.03, and 9.04 ± 0.01, respectively.

The average values for water solubility were 0.32 ± 0.03 mg/mL at pH 5.03 ± 0.01, 0.024 ± 0.002 mg/mL at pH 7.039 ± 0.04, and 0.0001 ± 0.0001 mg/mL at pH 9.05 ± 0.1.

The melting point was determined to be 141–146°C, based on the DSC run at 2°C/min and under nitrogen.

The calculated sublimation (vapor) pressure from the gas saturation method was $3 \pm 1 \times 10^{-8}$ torr (equivalent to 4×10^{-3} mPa) at 21.1 ± 0.1°C.

The acidic pKa was 4.2 ± 0.1 (benzoic acid component) and the basic pKa was 7.6 ± 0.1 (methylamino component).

The UV absorption maximum was 244 nm in basic and neutral media and 236 nm in acidic media.	
Study conducted by: Merck Research Laboratories **Author**: McCauley, J.A. **Address:** P.O.B. 2000, Rahway, NJ, 07065	**Compliance with GLP: Yes** **If no, justification:**

Reference:

Mushtaq, M. (1993). Sorption and desorption of [^{3}H]-deoxy-4"-epimethylaminoavermectin B1A (MAB1A) benzoate with soils. Merck & Co. Inc. Project ID: ENC-5. SPAH Report A-27911.

Title:

Sorption and desorption of [^{3}H]-deoxy-4"-epimethylaminoavermectin B1a (MAB1a) benzoate with soils

Name of Sponsor Company:	**Study number:**	**Report date:**
Merck and Co., Inc.	ID: ENC-5. SPAH Report A-27911	29 June 1993

Study type:

U.S. EPA Pesticide Assessment Guidelines N-163-1

Name of test material:	**Name of formulated product:**
[^{3}H]-deoxy-4"-epimethylaminoavermectin B_{1a} (MAB_{1a}) benzoate, also referred to as [^{3}H]MAB_{1a} benzoate	MK-0244; containing 91.1% MAB_{1a} and 5.1% MAB_{1b}

Test design:

Preliminary Adsorption Test: A preliminary adsorption test to determine the optimum equilibration time was performed with [^{3}H]MAB_{1a} in sandy loam soil (Lufkin, Texas) using 1.00 g soil and 5.0 mL of 0.01 M $CaCl_2$. Analyses were conducted at time intervals of 2, 4, 6, and 22 hours. The test article concentration was approximately 130 ng/mL. Following equilibration and centrifugation in both the sorption and desorption phases, triplicate aliquots were analyzed for radioactivity by liquid scintillation counting (LSC). Soil samples were extracted with organic solvents, combusted, and analyzed to determine the mass balance. Results indicated that sorption and desorption equilibria were reached within 2 hours. MAB_{1a} did not bind to glass surfaces.

Definitive Test: The definitive test was similar to the experiment used to determine the equilibrium time in the preliminary adsorption test, except four soil types and four concentrations of [^{3}H]MAB_{1a} were used in the definitive test. The soil types were sandy loam (Lufkin, Texas), sand (Lakeland, Florida), clay loam (Houston, Texas) and silt loam (Three Bridges, New Jersey). Test article concentrations ranged from approximately 2 to 130 ng/mL. Sampling was conducted at 5 hours for adsorption. In addition, a portion of the post-treatment samples from the adsorption samples of each soil were used to analyze desorption, using 0.01 M $CaCl_2$ solution. Sampling for desorption was conducted at 13.5 hours.

Statistical analysis:

Regression analysis to determine the values of the Freundlich distribution constant (K_d)

Summary of findings:

At equilibrium (5 hours in the adsorption phase), [^{3}H]MAB_{1a} adsorbed by ≥99% in each of four soil types. Desorption ranged from 0.1 to 1.28%. The K_d values were 2,037, 219, 665, and 295 for sandy loam, sand, clay loam, and silt loam, respectively. The K_{des} values were 4,088, 127, 2,591, and 245, respectively. Extrapolated to 100% organic carbon content, the corresponding sorption K_{oc} values were 278,983 for sandy loam, 728,918 for sand, 25,363 for clay loam, and 28,325 for silt loam. The corresponding desorption K_{oc} values were 559,986 for sandy loam, 424,013 for sand, 98,878 for clay loam, and 23,570 for silt loam.

During the determination of adsorption and desorption kinetics, the average mass balance ranged from 97 to 107%. No metabolite/degradate peaks were detected in the high-performance liquid chromatography (HPLC) analyses of the test compound and organic extracts from each soil type, indicating that MAB_{1a} was not metabolized or degraded in soils during the experiment.

Study conducted by: Merck Research Laboratories	**Compliance with GLP: Yes**
Author: Mushtaq, M.	
Address: Hillsborough Road, Three Bridges, NJ, 08887-0450	**If no, justification:**

Reference:

Phillips, M. (1996). Adsorption/desorption of [^{3}H]-MK-244 in marine sediments. IRI Project No. 384746. Inveresk Research International. Report No. 12618

Title:

Adsorption/desorption of [^{3}H]-MK-244 in marine sediments

Name of Sponsor Company:	**Study number:**	**Report date:**
Schering Plough Animal Health	IRI Project No. 384746	18 July 1996

Study type:

Adsorption/desorption but includes data on water solubility in seawater (summarized herein)

Name of test material:

Radiolabelled test material: [^{3}H]-MK-244 (purity: 99%, Specific activity 13.74 mCi/mg; Batch No. L-683, 825-005J006)

Non-radiolabelled test item: MK-244 (purity: 94.62%; Batch No. L-656, 748-052S005)

Test design:

As part of this study, the solubility of [^{3}H]-MK-244 in seawater was determined. These are the only results discussed in this summary, as the other data are not cited in the EA.

To determine solubility, radiolabelled and non-radiolabelled test material was dissolved in ethanol, mixed and made up to a final volume of 5 mL in a volumetric flask. Homogeneity and radioactivity content were determined by liquid scintillation counting. An aliquot of the solution was transferred to a 25 mL volumetric flaks and the ethanol evaporate off under nitrogen. The volumentric flask was made up to volume with seawater and placed on a magnetic stirrer. Aliquots of seawater were taken after 1, 2, 4, and 24 hours, centrifuged at 3,000 r.p.m. for 10 minutes and aliquots of the supernatant collected for liquid scintillation counting.

Statistical analysis:

None

Summary of findings:

The maximum solubility of [^{3}H]-MK-244 in seawater was calculated to be 5.5 µg/g (obtained with 4 hours of stirring).

Study conducted by: Inveresk Research International	**Compliance with GLP: Yes**
Author: Phillips, M.	
Address: Tranent, EH33 2HE, Scotland	**If no, justification:**

Reference:

Wyeth, K., and Ricketts, D.C. (2005). ^{14}C emamectin benzoate B1a (NOA 426007): Adsorption/desorption properties in soil. Syngenta Report RJ3566B. Syngenta Study No. 04JH009

Title: ^{14}C-Emamectin Benzoate B1a (NOA426007): Adsorption/Desorption Properties in Soil

Name of Sponsor Company:	**Study number:**	**Report date:**
Syngenta	04JH009	27 May 2005

Study type:

OECD 106: Adsorption – Desorption Using a Batch Equilibrium Method

Name of test material:

Radiolabelled test item: ^{14}C-Emamectin benzoate B_{1a} (NOA426007), also referred to as ^{14}C-MAB_{1a} benzoate; specific activity of 2.1275 MBq/mg.

Non-radiolabelled test item: NOA426007; Batch No. GAN-XL111-57; purity: 95.9% (w/w).

Test design:

Preliminary Test: A preliminary test was performed with ^{14}C-MAB_{1a} benzoate to determine the optimal "definitive" phase conditions for the adsorption/desorption study. The time to adsorption equilibrium was studied over 24 hours, as was the time to desorption equilibrium. The optimal soil water ratio was investigated at a single treatment rate of 2.0 µg/mL, and the optimal test vessel material and size were investigated at different treatment rates. Stability of the test compound was investigated for all four soil types (see Definitive Test). Analyses were conducted over each 24-hour period at time intervals of 0, 1, 3, 6, and 24 hours. Following equilibration and centrifugation in both the sorption and desorption phases, aliquots were analyzed for radioactivity by liquid scintillation counting (LSC) for the higher concentrations and liquid chromatography/tandem mass spectroscopy (LC-MS/MS) for the lower concentrations. Soil samples were extracted with organic solvents, combusted, and analyzed to determine the mass balance. Results indicated that sorption and desorption equilibria were reached within 24 hours. MAB_{1a} did not degrade during the entire period of the study.

Definitive Test: The definitive test was conducted in four soil types at five concentrations of ^{14}C-MAB_{1a} benzoate (0.0025, 0.01, 0.025, 0.1, and 0.5 µg/mL) using a soil:aqueous ratio of 1:20 in silanized vessels. The soil types were loamy sand (Borstel soil, Germany), sandy clay loam (18 Acres soil, UK), loam (Gartenacker soil, Les Barges, Switzerland) and loam (Marsillargues soil, La Paluzette, France). Sampling was conducted at 24 hours for adsorption. In addition, a portion of the post-treatment samples from the adsorption samples of each soil were used to analyze desorption by 3 consecutive desorption steps of approximately 3, 18, and 3 hours.

Statistical analysis:

Regression analysis to determine the values of the soil equilibrium adsorption partition coefficient (K_d) and the Freundlich distribution constant (K_F)

Summary of findings:

MAB_{1a} benzoate gave very high adsorption to all of the soils studied. Average adsorption partition coefficients (K_d values) ranged from 176 in the Gartenacker soil to 1,037 in the 18 Acres soil. After correction for measurable analytical losses arising from sticking to glassware during quantification the Freundlich equation showed a good fit for all the soils with 1/n values ranging from 0.91 (Marsillargues soil) to 0.99 (18 Acres soil). Average K_d values adjusted for the organic carbon content of soil (K_{oc} values) ranged from 8,687 in the Gartenacker soil to 125,808 in the Marsillargues soil. Similarly, the corresponding Freundlich adsorption coefficient (K_{FOC} values) ranged from 6,666 (Gartenacker soil) to 55,761 (Marsillargues soil). The binding properties of MAB_{1a} benzoate appear to correlate to the cation exchange capacity of the soils (K_d vs CEC plot gave an r^2 correlation of 0.96). No other specific soil properties show any correlation to the binding properties (e.g., pH, clay, or organic matter content). According to the McCall Classification scale to assess a chemical's potential mobility, MAB_{1a} benzoate is classified as "immobile" for all the soils studied.

Soil	Freundlich Adsorption Coefficients			Adsorption Partition Coefficients (a)		pH	%OM	USDA Textural Classification
	K_F	K_{FOC}	1/n	K_d	K_{oc}			
Borstel	133.92	13,581	0.93	212.01	21,500	5.1	1.7	Loamy Sand
18 Acres	910.51	31,394	0.99	1,036.98	35,755	5.9	5.0	Sandy Clay Loam
Gartenacker	135.33	6,666	0.96	176.37	8,687	7.1	3.5	Loam
Marsillargues	323.44	55,761	0.91	729.74	125,808	7.8	1.0	Loam

Three desorption steps showed roughly similar binding patterns and average K_{FOC} values for the desorption steps ranged from 16,909–27,428 (Borstel soil), 20,673–51,963 (18 Acres soil), 5,037–10,504 (Gartenacker soil), and 51,168–79,854 (Marsillargues soil). These results show that the binding properties are roughly the same between the adsorption and three desorption steps and the binding is reversible.

Study conducted by: Syngenta

Author: Wyeth, K., and D. C. Ricketts

Address: Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK.

Compliance with GLP: Yes, with two minor exceptions

If no, justification:

APPENDIX B

Label from United Kingdom

SLICE®

2 mg/g premix for medicated feeding stuff

FOR ANIMAL TREATMENT ONLY
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

2.5 kg

Each 2.5 kg pouch of SLICE contains 5 g of emamectin benzoate (equivalent to 2 mg/g) and 0.25 g butylated hydroxyanisole (equivalent to 0.1 mg/g) as a preservative.

Premix for medicated feeding stuff. A white to off-white free flowing powder.

Target species: Atlantic salmon (*Salmo salar*)

Indications:
For the treatment and prevention at group level of infestations of all parasitic stages of sea lice (*Lepeophtheirus* sp. and *Caligus* sp.) on Atlantic salmon (*Salmo salar*) ranging in size from smolts in freshwater (just prior to transfer to seawater) to market weight fish in seawater.

Dosage and method of administration: Administer medicated feed to fish at the recommended feeding rate of 0.5% biomass/day for 7 days which will yield a dose rate of 50 micrograms/kg biomass/day. If the feeding rate differs from 0.5% biomass/day, then the concentration of SLICE in feed must be adjusted proportionately. The following table is provided for reference.

Feeding rate (% biomass of fish)	Concentration of emamectin benzoate in feed medicated with SLICE (mg/kg)	Quantity of SLICE per 1,000 kg of medicated feed (kg)	Quantity of SLICE-medicated feed per 1,000 kg of fish per day (kg)
0.25	20.0	10.0	2.5
0.5	10.0	5.0	5.0
1.0	5.0	2.5	10.0
2.0	2.5	1.25	20.0
3.0	1.67	0.833	30.0
4.0	1.25	0.625	40.0

Directions for use:
SLICE-medicated fish feed is to be prepared only at commercial fish feed mills and not at fish farms. SLICE is to be coated onto feedstuff of the following type: Extruded cylindrical pellets of varying thickness and length, e.g., 3.5 mm, 5.0 mm, 7.0 mm and 10.0 mm.

Recommended method of incorporation:
SLICE may be coated onto the surface of non-medicated fish feed in the following manner:

a. Standard feed is transported by a conveyor belt to a fractioning sieve where dust and fragments are sorted out.
b. The sorted pellets are transferred to an intensive mixer.
c. The pellets are dry-mixed/coated with a predetermined amount of SLICE for up to 2 minutes.
d. 0.5% to 1% fish or vegetable oil is added and mixing continued for up to 5 minutes. The added oil seals the premix powder to the feed pellet.
e. At the completion of mixing, the product is transferred to a feeder tank for packaging into sacks.

The recommended maximum number of marine treatments is 5 per 2 year growth cycle and not more than 3 per 12 month period.
Smolts should only be treated when raised either in tanks or in flowing waterways (see contra-indications).
Smolts should be transferred to seawater 1-2 days after the seven day treatment period has ended.
To reduce the possibility of resistance development in sea lice it is recommended that emamectin benzoate is used in integrated control programmes with the following considerations:

- Administration of the correct dosage rate over the full seven day period
- Medication of an appropriate amount of feed to ensure complete and homogeneous consumption
- Careful feeding practices to monitor feeding behaviour
- Use of the product in the absence of any intercurrent disease affecting appetite
- Simultaneous medication of all fish on a site
- Coordination of treatments of all farms in a loch or bay system to reduce cross-infestation
- Use of good management practices such as single age sites, all-in-all-out systems and fallowing between production cycles
- Use in rotation with other authorised therapeutic agents and/or in collaboration with other natural agents such as cleaner fish.

It is important that the level of infestation and the effectiveness of control measures are monitored by routine counting of sea lice stages on samples of representative fish. Counts should be conducted on at least five fish from each of 20% of cages on the farm at weekly intervals in summer and every second week in winter. Treatment should only be initiated when the number of sea lice per fish reach a level so that effective sea lice population control can be established.

Withdrawal period:
Zero days.
To ensure that tissue residues do not exceed the MRL, fish must not be treated more than once in the 60 days prior to the first fish being harvested for human consumption.

Special warnings:
Do not use in adult Atlantic salmon intended for broodstock.
Do not use for treatment of smolts in freshwater cages due to potential environmental risks.
Wear gloves, protective work clothing, dust mask and safety glasses with side shields when handling SLICE in the preparation of medicated fish feed.
Wash hands thoroughly with soap and water after handling the product or medicated feed and before eating or smoking.
Do not smoke or eat while handling the medicated feed.
At the recommended dose emamectin benzoate produced no undesirable effects in the clinical trials, apart from a slight reduction in appetite during the medication period in two trials. A change in the source and pellet size of the medicated diet may have contributed to this effect.
Emamectin benzoate administered to Atlantic salmon smolts in freshwater at 5.4 times the recommended dose produced dark skin colouration and incoordination during the treatment period.
Emamectin benzoate administered to Atlantic salmon in seawater at seven times the recommended dose produced lethargy, dark skin colouration and incoordination commencing on the fifth day of medication and inappetance commencing two days after treatment.
Recovery was not evident in the week following treatment, in either fish treated in freshwater or in seawater. There is no known antidote.

Special storage conditions:
This veterinary medicinal product does not require any special storage conditions.
Shelf life after incorporation into meal or pelleted feed: 6 months
Do not use after the expiry date stated on this label.

Disposal advice:
Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

Further information:
In UK - it is essential to obtain a discharge consent from the local regional office of the Environment Agency or SEPA before using this product.

To be supplied only on veterinary prescription

UK Only	IE Only
Vm 01708/4580	VPA 10996/257/001
POM-V	POM

MA holder in the UK: Intervet UK Ltd., Walton Manor, Walton, Milton Keynes MK7 7AJ, UK
VPA holder in IE and distributor in Northern Ireland: Intervet Ireland Ltd. Magna Drive, Magna Business Park, Citywest Road, Dublin 24, Ireland

Manufacturer responsible for batch release:
Intervet GesmbH Vienna, Siemensstrasse 107
1210 Vienna, Austria

MSD Animal Health

Imprint area/Varnish free