IMIDACLOPRID FOR SALMONIDS

ENVIRONMENTAL ASSESSMENT
IN SUPPORT OF AN
IMPORT TOLERANCE REQUEST

Final: Original signed and on file

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BMK	Benchmark Animal Health Ltd
CAKE	Computer Assisted Kinetic Evaluation
CAS	Chemical Abstracts Service
CVMP	Committee for Medicinal Products for Veterinary Use
CFR	Code of Federal Regulations (U.S.)
DAT	Days after treatment
DFOP	Double first-order in parallel
DPT	Days post treatment
DT_{50}	Estimated time for 50% biodegradation or disappearance
INN	International Nonproprietary Name
DT_{90}	Estimated time for 90% biodegradation or disappearance
EMA	European Medicines Agency
EPA	Environmental Protection Agency
GLP	Good Laboratory Practice
HPLC	High pressure liquid chromatography
INN	International Nonproprietary Name
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	Soil adsorption coefficient
LLOQ	Lower limit of quantification
MRL	Maximum residue level
nAChRs	Nicotinic acetylcholine receptors
P_{ow}	Octanol water partition coefficient
OECD	Organisation for Economic Cooperation and Development
SFO	Single first-order
SCBP	Standing Committee on Biocidal Products
TOC	Total organic content
TRR	Total radioactive residue
U.S.	United States of America
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WWTP	Wastewater treatment plants

1.0 General information

Sponsor: Benchmark Animal Health Ltd
1 Pioneer Building
Edinburgh Technopole
Milton Bridge
Near Penicuik
EH26 0GB
UK

Established Name: Imidacloprid

Proprietary Name: Ectosan® Vet for salmonids

2.0 Purpose and need for the proposed action

Benchmark Animal Health Ltd (BMK) is requesting establishment of an import tolerance for imidacloprid so that meat from salmonids treated with imidacloprid may be imported into the United States (U.S.) for human consumption. Imidacloprid is the active ingredient and only component in Ectosan® Vet 1000 mg/g powder for treatment solution for fish (hereafter referred to as Ectosan® Vet)[1], which has a marketing authorization in Norway. Ectosan® Vet is indicated for the treatment of pre-adult and adult salmon lice (*Lepeophtheirus salmonis)* infestation in Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). Fish to be treated are immersed in an enclosed bath of seawater containing imidacloprid at a concentration of 20 mg/L for one hour on a wellboat. The safety to consumers of fish treated with imidacloprid has been assessed by the European Medicines Agency (EMA) who have adopted a maximum residue level (MRL) of 600 μg/kg for fin fish muscle and skin in natural proportions (EMA, 2021).

No drug products containing imidacloprid are currently approved or conditionally approved for use in fish or other food animals in the U.S.; therefore, an import tolerance needs to be established. The establishment of an import tolerance is an action by the U.S. Food and Drug Administration (FDA) that requires the preparation of an environmental assessment (EA) unless it meets the criteria for categorical exclusion under FDA regulations in the U.S. Code of Federal Regulations (21 CFR Part 25, Subpart C). Because there are currently no such categorical exclusions that apply for the establishment of an import tolerance, the current EA has been prepared. The environmental impact on the U.S. environment from imidacloprid residues in salmonid flesh, and from imidacloprid residues that may be transported by water into the U.S. environment, was evaluated herein based on the expected exposure pathways and physical-chemical properties and environmental fate data for the drug.

3.0 Identification of the substance

Imidacloprid is in the N-nitroguanidine group of neonicotinoids (IRAC, 2021). Neonicotinoid insecticides are synthetic derivatives of nicotine, an alkaloid compound found in the leaves of

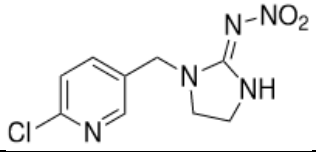
[1] See Appendix A for the product label and package leaflet.

many plants including tobacco which acts on the insect, and crustacean, nicotinic acetylcholine receptors (nAChRs) of the nervous system via competitive modulation. At low concentrations, neonicotinoids cause excessive nervous stimulation and at high concentrations, insect paralysis and death.

Imidacloprid is not currently approved or conditionally approved for use in food animals in the U.S. However, imidacloprid is registered by the U.S. Environmental Protection Agency (EPA) for use as an insecticide on a wide variety of agricultural crops, as well as numerous non-agricultural uses (EPA, 2016).

The identity and physicochemical properties of imidacloprid are summarized in Table 3.0.1. Given the chemical properties shown below, imidacloprid is highly water soluble with low vapor pressure and Henry's Law Constants, suggesting that imidacloprid is likely to remain in and be mobile in the water phase. Data suggest that imidacloprid is relatively stable to multiple routes of degradation other than photolysis in aqueous solution (EPA, 2016).

Table 3.0.1: Identity and physicochemical and environmental fate properties

International Nonproprietary Name (INN)	Imidacloprid
International Union of Pure and Applied Chemistry (IUPAC) Name	1-(6-chloro-3- pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine
Chemical Abstracts Service (CAS) Name	1-[(6-chloro-3- pyridinyl)methyl]- N-nitro-2-imidazolidinimine
CAS Registry Number	138261-41-3
Structure	
Empirical formula	$C_9H_{10}ClN_5O_2$
Molecular weight	255.7 g/mol
Water solubility [A] (at 20 °C)	580-610 mg/L
Melting point [B]	144°C
Boiling point [B]	Decomposes before boiling
Thermal degradation point [B]	230°C
Vapor pressure (Pa at 20°C) [B]	4×10^{-10}
Henry's Law constant (Pa m^3 mol^{-1} at 20 °C) [B]	1.7×10^{-10}
Octanol/water partition coefficient (log P_{ow} at 20°C) [B]	0.57
Soil adsorption coefficient (K_{oc}) [A]	266 L/Kg (average)
Maximum ultraviolet absorption [B]	212 nm (extinction coefficient = 13346), 270 nm (extinction coefficient = 22054)
Hydrolysis half-life (DT_{50})	stable at pH 5 and 7 [B] 11.4 days at 12°C (marine water) [C, D]
Photolytic degradation half-life (DT_{50})	0.2 days at 20°C (aqueous) [B] 16.3 hours at 12°C (marine) [C]
Water-sediment aerobic degradation half-life (DT_{50})	118 days at 12°C (marine) [E]

[A] EPA, 2016
[B] IUPAC, 2021
[C] Mould, 2020*
[D] The hydrolysis half-life of 11.4 days was estimated by extrapolation from the non-irradiated control sample recoveries over a 48-hour test period in Mould, 2020*.
[E] Sutcliffe, 2020*
* Summaries of proprietary studies referenced in this table are provided in Appendix B below.

4.0 Sites of introduction and exposure pathways

There are two general types of exposure pathways for imidacloprid to enter the U.S. environment that could potentially exist due to the establishment of an import tolerance for this drug in salmonid tissues: 1) pathways arising from the release of drug residues, if present, from

imported food derived from treated fish, or 2) pathways arising from use of the drug on salmonids in countries adjoining the U.S. where it could be authorized.

With respect to the first of the two general types of exposure pathways, potential points of introduction into the U.S. environment arising from the release of drug residues, if present, from imported food derived from treated fish include:

- disposal in landfills of seized fish, waste from the processing of treated fish, or waste from unconsumed treated fish;
- effluent from wastewater treatment plants containing residues of the drug via human excreta following the consumption of food derived from treated fish;
- application of biosolids containing drug residues to soil following wastewater treatment; and
- disposal of solid waste or biosolids containing drug residues via incineration.

With respect to the second of the two general types of exposure pathways, a potential point of introduction to the U.S. environment could consist of water flow or sediment transport from treatment of fish in countries adjoining the U.S., specifically Canada, where aquaculture of salmonids is common.

The environmental exposure and likelihood of imidacloprid to cause impacts on U.S. ecosystems at the sites of introduction are evaluated in Section 5.0.

5.0 Analysis of exposure and risk

The potential exposures due to the pathways listed in Section 4.0 are evaluated based on existing regulatory frameworks and metabolism and environmental fate data for imidacloprid.

5.1 Metabolism and residues in fish

Residue levels of imidacloprid in salmon tissues declined rapidly following a one-hour treatment with imidacloprid (20 mg/L at 15°C), with maximum imidacloprid residue levels of 349 µg/kg in fillet and 644 µg/kg in liver detected the day after treatment (Longshaw, 2020*). Imidacloprid residue levels dropped below the lower limit of quantification (LLOQ) of 4 µg/kg in fillet and liver at 21- and 28-DPT, respectively (Longshaw, 2020*).

5.2 Metabolism and excretion in mammals

The metabolization rate of imidacloprid in the rat, as a representative mammal, was high, with only between 10-16% of the originally applied dose excreted as unchanged parent compound (SCBP, 2015). Two major routes of metabolism responsible for the degradation of imidacloprid can be derived, with the predominant metabolic pathway involving oxidative cleavage followed by conjugation or de-chlorination, and a minor pathway entailing hydroxylation of the imidazolidine ring (SCBP, 2015). Excretion from the organism is fast and complete (> 95% within 48 h), and there is no indication of any bioaccumulation potential of the parent compound and/or its metabolites (SCBP, 2015). In studies using methylene group-labelled (^{14}C) test substance, on average at least 75% of the administered radioactivity were excreted with the urine, while the

remainder was found in the feces. In the study with imidazolidine ring-labelled (^{14}C) imidacloprid, excretion with urine exceeded 90% of dose, while only approximately 8% were excreted with the feces (SCBP, 2015).

5.3 Environmental fate

In aquatic environments, imidacloprid may undergo degradation via photolysis and to a lesser extent hydrolysis. As shown in Table 3.0.1, a direct aqueous photolysis half-life of 0.2 days is reported (EPA, 2016), and a photolytic half-life of 16.3 hours was determined in seawater (Mould, 2020*). A hydrolytic half-life of 11.4 days has been estimated by extrapolation for imidacloprid in sea water (Mould, 2020*), while an aerobic degradation half-life of 118 days was determined in the marine water-sediment system (Sutcliffe, 2020*).

With water solubilities ranging from 580 to 610 mg/L and an average K_{oc} of 266 L/Kg, imidacloprid is expected to be moderately mobile in soils and have the potential to leach to groundwater (EPA, 2016). In the surface water environment, imidacloprid is likely to remain in the water phase and not preferentially move to sediment, as supported by data from Sutcliffe (2020*), which reported a slow dissipation from the water phase into sediment, with <18% transferred from water into the sediment phase over the first 7 days.

5.4 Analysis of environmental exposure and risk from potential pathways arising from the release of drug residues, if present, from imported food derived from treated fish

5.4.1 Landfill disposal of seized fish, waste from U.S. processing of treated fish, or waste from unconsumed treated fish

Any treated fish and fish products that are discarded from U.S. processing plants or households, or that are seized by U.S. authorities for non-compliance with Federal or local regulations, might be disposed of as solid waste in a landfill. Solid waste may also be incinerated (see Section 5.4.4). Disposal to landfills could create a potential route for imidacloprid to enter groundwater or be washed out as surface run-off. As an MRL of 0.6 mg/kg has been set by the European authorities (EMA, 2021), it is considered unlikely that levels above this will be found in salmonid flesh imported into the U.S., although this will be dependent on concentrations set in the US. Furthermore, fish metabolism data described in Section 5.1 suggest that residue levels decline rapidly after treatment. However, if fish were condemned for exceeding a set import tolerance, it must be considered possible that this residue level might be exceeded in fish flesh sent for disposal.

Landfill disposal events due to the seizure of noncompliant goods are expected to be sporadic and rare, and therefore, only a negligible amount of imidacloprid is expected to be available to potentially leach from seized salmonid products disposed of to landfills. Solid waste from U.S. processing plants or consumers are expected to be geographically and temporally dispersed and would contain levels of imidacloprid below the established MRL. Therefore, any potential introductions into landfill leachate are expected to be diffuse and at low levels.

Furthermore, landfills in the U.S. are regulated by local, state, and Federal authorities to prevent environmental contamination. For example, U.S. EPA regulates municipal solid waste landfills (40 CFR Part 258) to restrict the movement of contaminants into the environment through requirements related to composite liners, leachate collection and removal systems, operating practices, groundwater monitoring, and closure and post-closure practices. As a result of these controls, there is expected to be minimal or no movement of imidacloprid out of U.S. landfills and into the adjacent U.S. environment (groundwater or surface water). In addition, because imidacloprid has a low vapor pressure (4×10^{-10} Pa at 20°C; see Table 3.0.1 above), it is not expected to volatilize from landfills or enter air to any significant extent.

Therefore, based on lack of exposure, significant environmental impacts on the terrestrial and aquatic environments are not expected from residues of imidacloprid in imported food derived from treated salmonids that are disposed of in U.S. landfills.

5.4.2 Effluent from wastewater treatment

Wastewater treatment plants (WWTP) may receive inputs of excreta containing imidacloprid at low concentrations arising from human consumers of imidacloprid-treated fish or from inputs of industrial effluent from factories processing fish previously treated with imidacloprid.

The excretion of low levels of imidacloprid is expected relatively quickly following human consumption of treated fish according to the metabolism and excretion data for rat (see Section 5.2 above). Within the WWTP, it can be expected that there will be negligible degradation of imidacloprid within the transit time through the plant. However, the low concentrations expected in human excreta following consumption of treated fish will be further diluted by the excreta from other consumers who had not eaten imported salmonid products previously treated with imidacloprid. It should also be noted that consumption rates of salmon in the U.S. are low (i.e., 1%) compared to those for most other types of meats (Knapp et al., 2007), and the distribution of the excreted residues in the U.S. environment will be spatially and temporally variable following the patterns of U.S. consumers. For both effluent from factories processing fish and human consumption, the low concentrations in the input streams will be further diluted by other WWTP waste streams not containing imidacloprid. The relatively low K_{oc} value for imidacloprid (see Table 3.0.1 above) indicates that imidacloprid will remain largely in the water phase and not be adsorbed to the organic matter or inorganic filtration matrices of the treatment plant. As such, there will be little transfer to biosolids which could be disposed of in landfills, applied to land, or incinerated (see Sections 5.4.1, 5.4.3, 5.4.4).

On the basis of these low inputs and expected levels of dilution from other waste streams, it is considered unlikely that the effluent from WWTPs will contain imidacloprid at levels that would pose risk in the receiving waters. In addition, any imidacloprid present in receiving waters could be susceptible to photolysis and, to a lesser extent, hydrolysis.

5.4.3 Application of biosolids as fertilizer to soil

If biosolids from WWTPs are applied to soil as fertilizer, the exposure to imidacloprid from this pathway is expected to be *de minimis* for the reasons described in Section 5.4.2 above (e.g., low concentrations expected in biosolids), as well as considerable dilution in the soil. Furthermore, the land application of biosolids is regulated by the U.S. EPA under 40 CFR Part 503, Standards

for the Use or Disposal of Sewage Sludge. Therefore, the application of biosolids containing imidacloprid should pose no unacceptable risk to the environment.

5.4.4 Disposal by incineration

Solid waste streams containing seized or discarded fish or fish materials containing imidacloprid (see Section 5.4.1) or biosolids derived from wastewater treatment (see Section 5.4.3) could be sent for final disposal by incineration. With a thermal degradation point of 230°C for imidacloprid (see Table 3.0.1), it is considered unlikely that incineration would release parent imidacloprid to the receiving environment. Therefore, incineration of imidacloprid should pose no unacceptable risk to the environment.

5.5 Water flow from treatment of fish in foreign countries adjoining the U.S.

Although use of imidacloprid on salmonids is not currently approved in Canada, it is reasonably foreseeable that it could be approved there because salmon farming is a major industry in Canada. Therefore, for this reason and because of Canada's close proximity to the U.S., the potential impact to the environment of the U.S. from the potential use of imidacloprid in Canada is evaluated.

In Canada, the administration of medicines and subsequent discharges of the active ingredients are regulated by national and local agencies. Under Sections 35 and 36 of the Canadian Fisheries Act (R.S.C., 1985, c. F-14), The Aquaculture Activities Regulations (AAR) clarify conditions for aquaculture operators (e.g., operation and maintenance of an aquaculture facility, treating fish for disease and parasites, deposition of organic matter, environmental monitoring requirements) to minimize and mitigate any potential detriments to fish and fish habitat. Therefore, the operation of fish farms in Canada is regulated to prevent adverse impacts on the environment around the farms. In addition to these controls, any imidacloprid released to the marine environment is expected to disperse primarily in the water, undergo substantial and rapid dilution, and may also undergo photolysis and, to a lesser extent, hydrolysis (see Section 3.0 and 5.3). On this basis, it is considered that waters, and sediments, arising from Canadian farms using imidacloprid should pose no unacceptable risk to U.S. waters.

6.0 Description of any alternatives to the proposed use

BMK is proposing to establish an import tolerance for imidacloprid in muscle with adhering skin for 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 an import tolerance for imidacloprid in salmonids. However, based on our analysis in this EA, we do not believe that significant environmental impacts will occur from this action; therefore, the preferred alternative is the establishment of a tolerance for imidacloprid in salmonids imported into the U.S. and the no action alternative was eliminated from consideration.

7.0 Conclusions

Based on the available information on the metabolism, environmental fate, and exposure of imidacloprid, and the potential exposure pathways presented in the EA, there is expected to be little or no exposure to imidacloprid residues in the U.S. arising from the import of salmonids treated with imidacloprid in other countries. Therefore, it is concluded that the proposed action of establishing an import tolerance for imidacloprid residues in salmonids will not result in significant impacts to the U.S. environment.

8.0 Agencies and persons consulted

This EA was prepared with input and assistance from members of Environmental Team 1 in the Office of New Animal Drug Evaluation in the United States Food and Drug Administration's Center for Veterinary Medicine.

9.0 Author

John G McHenery

BSc, PhD, FRSB.

JGM-Env Consult

10.0 Signature

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

Date: 25 April 2022

11.0 References

European Medicines Agency. (2021). European public MRL assessment report (EPMAR): Imidacloprid (fin fish) (EMA/CVMP/223046/2021). Committee for Medicinal Products for Veterinary Use. https://www.ema.europa.eu/en/documents/mrl-report/imidacloprid-fin-fish-summary-report-committee-veterinary-medicinal-products_en.pdf

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* Proprietary study; see Summaries in Appendix B below.

Appendix A

Drug information
Translations of Norwegian:
Labeling and Package Leaflet

A. LABELING

MINIMUM REQUIREMENTS TO APPEAR ON SMALL INNER PACKAGES
Water Soluble Film:
100g and 1000g

1. NAME OF THE VETERINARY PREPARATION

Ectosan Vet 1000 mg/g powder for treatment solution for fish
imidacloprid

2. AMOUNT OF ACTIVE SUBSTANCE(S)

Each gram contains:
Active substance:

Imidacloprid 1000 mg

3. PACKAGE SIZE INDICATED BY WEIGHT, VOLUME OR NUMBER OF DOSES

100g
1000g

4. ADMINISTRATION ROUTE(S)

5. RETENTION PERIOD(S)

Retention time(s): 98 degrees.

If fish under treatment are exposed to imidacloprid for a significantly extended period due to delays in, for example, pumping out treated fish, a longer retention time should be considered.

6. PRODUCTION NUMBER

Batch:

7. EXPIRY DATE

EXP:

8. THE TEXT "FOR ANIMALS"

For animals.

INFORMATION TO APPEAR ON THE INNER PACKAGING

100 g and 1000 g
Dose bag label

1. NAME OF THE VETERINARY PREPARATION

Ectosan Vet 1000 mg/g powder for treatment solution for fish
imidacloprid

2. DECLARATION OF ACTIVE SUBSTANCE(S)

Each gram contains:
Active substance:

Imidacloprid	1000 mg

3. PHARMACEUTICAL FORM

powder for treatment solution for fish.

4. PACKAGE SIZE

100g
1000g

5. ANIMAL SPECIES FOR WHICH THE MEDICINAL PRODUCT IS INTENDED (Target species)

Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*).

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Retention time(s): 98 degrees

If fish under treatment are exposed to imidacloprid for a significantly extended period due to delays in, for example, pumping out treated fish, a longer retention time should be considered.

9. SPECIAL WARNING(S), IF NECESSARY

To be used only in well boats. Treatment and rinsing water must be cleaned before discharge. Read the package leaflet before use.

10. EXPIRY DATE

EXP {month / year}

Shelf life after dilution according to the instructions for use: 24 hours after dilution in the well.

11. STORAGE CONDITIONS

Store the bags in a dry place in the aluminium dose bag.

12. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS, RESIDUES AND PACKAGING

Disposal: read the package leaflet.

13. THE TEXT "FOR ANIMALS" AND ANY TERMS OR LIMITATION WITH REGARD TO DELIVERY AND USE, IF RELEVANT

For animals. Prescription required.

14. THE WORDS "KEEP OUT OF THE REACH OF CHILDREN"

Keep out of reach of children.

15. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Benchmark Animal Health Norway AS
Bradbenken 1
5003 Bergen
Norway
Tel: + 47 94177810
ectosanvet@bmkanimalhealth.com

16. MARKETING AUTHORIZATION NUMBER(S)

MT no. 20-13358.

17. MANUFACTURER'S PRODUCTION NUMBER

Batch {number}

Health hazard

Environmental hazard

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard box
2 x 100g and 1 x 1000g

1. NAME OF THE VETERINARY PREPARATION

Ectosan Vet 1000 mg/g powder for treatment solution for fish
imidacloprid

2. DECLARATION OF ACTIVE SUBSTANCE(S)

Each gram contains:
Active substance:
Imidacloprid 1000 mg

3. PHARMACEUTICAL FORM

powder for treatment solution for fish.

4. PACKAGE SIZE

2 x 100 g
1 x 1000 g

5. ANIMAL SPECIES FOR WHICH THE MEDICINAL PRODUCT IS INTENDED (Target species)

Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*).

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Retention time(s): 98 degrees

If fish under treatment are exposed to imidacloprid for a significantly extended period due to delays in, for example, pumping out treated fish, a longer retention period should be considered.

9. SPECIAL WARNING(S), IF NECESSARY

To be used only in well boats. Treatment and rinsing water must be cleaned before discharge. Read the package leaflet before use.

10. EXPIRY DATE

EXP:

Shelf life after dilution according to the instructions for use: 24 hours after dilution in the well.

11. STORAGE CONDITIONS

Store the bags in a dry place in the aluminium dose bag.

12. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS, RESIDUES AND PACKAGING

Disposal: read the package leaflet.

13. THE TEXT "FOR ANIMALS" AND ANY TERMS OR LIMITATION WITH REGARD TO DELIVERY AND USE, IF RELEVANT

For animals. Prescription required.

14. THE WORDS "KEEP OUT OF THE REACH OF CHILDREN"

Keep out of reach of children.

15. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Benchmark Animal Health Norway AS
Bradbenken 1
5003 Bergen
Norway
Tel: + 47 94177810
ectosanvet@bmkanimalhealth.com

16. MARKETING AUTHORIZATION NUMBER(S)

MT no. 20-13358.

17. MANUFACTURER'S PRODUCTION NUMBER

Batch {number}

Health hazard

Environmental hazard

INFORMATION TO APPEAR ON THE INNER PACKAGING

10 x 1000 g
Label for plastic container

1. NAME OF THE VETERINARY PREPARATION

Ectosan Vet 1000 mg/g powder for treatment solution for fish
imidacloprid

2. DECLARATION OF ACTIVE SUBSTANCE(S)

Each gram contains:
Active substance:

Imidacloprid	1000 mg

3. PHARMACEUTICAL FORM

powder for treatment solution for fish.

4. PACKAGE SIZE

10 x 1000 g

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Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*).

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

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If fish under treatment are exposed to imidacloprid for a significantly extended period due to delays in, for example, pumping out treated fish, a longer retention period should be considered.

9. SPECIAL WARNING(S), IF NECESSARY

To be used only in well boats. Treatment and rinsing water must be cleaned before discharge. Read the package leaflet before use.

10. EXPIRY DATE

EXP:

Shelf life after dilution according to the instructions for use: 24 hours after dilution in the well.

11. STORAGE CONDITIONS

Store the bags in a dry place in the plastic container.

12. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS, RESIDUES AND PACKAGING

Disposal: read the package leaflet.

13. THE TEXT "FOR ANIMALS" AND ANY TERMS OR LIMITATION WITH REGARD TO DELIVERY AND USE, IF RELEVANT

For animals. Prescription required.

14. THE WORDS "KEEP OUT OF THE REACH OF CHILDREN"

Keep out of reach of children.

15. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Benchmark Animal Health Norway AS
Bradbenken 1
5003 Bergen
Norway
Tel: + 47 94177810
ectosanvet@bmkanimalhealth.com

16. MARKETING AUTHORIZATION NUMBER(S)

MT no. 20-13358.

17. MANUFACTURER'S PRODUCTION NUMBER

Batch:

Health hazard

Environmental hazard

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Ectosan Vet 1000 mg/g powder for treatment solution for fish

1. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER AND OF THE MANUFACTURER RESPONSIBLE FOR BATCH RELEASE IF THEY DIFFERENT

Marketing Authorization Holder:
Benchmark Animal Health Norway AS
Bradbenken 1
5003 Bergen
Norway

Manufacturer responsible for batch release:
Freja Transport and Logistics AS
Viborgvej 52
DK-7800 Skive

2. NAME OF THE VETERINARY PREPARATION

Ectosan Vet 1000 mg/g powder for treatment solution for fish
imidacloprid

3. DECLARATION OF ACTIVE SUBSTANCE(S) AND EXCIPIENT(S)

Each gram contains:
Active substance:
Imidacloprid 1000 mg

White or whitish powder

4. INDICATION(S)

For the treatment of infestation with pre-adult and adult salmon lice (*Lepeophtheirus salmonis*) on Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). The preparation should only be used as part of a total control strategy against fish lice, which also includes other control measures.

5. CONTRAINDICATIONS

None.

6. SIDE EFFECTS

A slight increase in ventilation rate was commonly observed during treatment in one laboratory trial.

Increased mortality was observed on day 1 after the treatment procedure in all field trials.

The frequency of adverse reactions is indicated by the following criteria:

- Very common (more than 1 in 10 animals treated gets side effect (s))
- Common (more than 1 but less than 10 out of 100 treated animals)
- Uncommon (more than 1 but less than 10 out of 1000 treated animals)
- Rare (more than 1 but less than 10 out of 10,000 treated animals)
- Very rare (less than 1 in 10,000 treated animals, including isolated reports)

If you notice any side effects, including those not already mentioned in this leaflet, or you think the medicine has not worked, you should report this to your veterinarian or fish health biologist.

7. ANIMAL SPECIES FOR WHICH THE PREPARATION IS INTENDED (TARGET SPECIES)

Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*).

8. DOSAGE FOR EACH TARGET SPECIES, SUPPLY ROUTE(S) AND SUPPLY

Bath treatment.

Dose: 20 mg imidacloprid per litre of seawater.

Duration of treatment: 60 minutes.

A starvation period of at least 48 hours before treatment is recommended.

9. CORRECT USE INFORMATION

Requirements for well boat:

- Mixing tanks that meet the following minimum criteria:
    - Sufficient volume capacity to accommodate a solution of 50:1 (1000 l capacity is recommended).
    - Mixing equipment sufficient to produce a vortex in the mixing tanks.
    - One mixing tank per well.
- Suitable dewatering system that is suitable for separating fish from water both at the inlet and at the outlet of the well boat.
- Adequate filters to remove organic material, including fish lice, throughout the treatment process (recommended ≤ 150 µm) to maintain water quality.
- A suitable system for monitoring water quality (O_2, CO_2, and pH).
- A rinsing system mounted above the dewatering system to rinse fish with clean seawater as it is unloaded from the well boat (recommended 30m^3/h). The rinsing water must be retained for cleaning.
- Pipe system compatible with the water purification system.

Dose preparation:
Estimate the volume of water in the treatment well as accurately as possible by calculating the required amount of product to avoid under- or overdose.

To achieve a final concentration of 20 mg Imidacloprid /l, the following amount (litres) of seawater is required to achieve the recommended dose with the respective pack sizes:

Pack size	Capacity (m^3)	Litre of water (l)
200 g (2 x 100 g)	10	10,000
1000 g (1 x 1000 g)	50	50,000
10 kg (10 x 1000 g)	500	500,000

Well boat capacity (m^3)	Ectosan Vet needed to achieve 20 mg/l (kg)	Recommended package size
2500	50	5 x 10 kg
3000	60	6 x 10 kg
3500	70	7 x 10 kg
> 3500	10 kg per 500 m^3 over 3500	1 x 10 kg

The dose must be prepared separately for each well.

Use the mixing tanks on board to premix the required amount of the preparation into a suspension. This requires vigorous stirring. This mixing process must be done not less than 30 minutes and not more than 4 hours before feeding to the well.

Mixing tanks and piping must be rinsed with clean seawater to ensure that there are no product residues in the system.

Initial dose monitoring should be done to demonstrate that consistent dosing can be achieved for each new well boat that will use the drug and be repeated every 6 months.

After treatment, fish must be dewatered and rinsed before being returned to the sea.

All treatment and rinsing water must be stored in the treatment vessel for cleaning.

All treatment and rinsing water must be filtered and purified before returning to the sea

Treatment procedure:

Well boat Instructions:

1. Fill the well or wells of the well boat with the required amount of water and fish (density must be determined by the responsible fish health personnel).

2. Prepare the suspension with the required amount of the preparation while filling the wells. Fill the mixing tank one third full with clean seawater (one mixing tank per well to be treated). Prepare a suspension with a maximum concentration of 50: 1 (50 g Ectosan Vet for each litre of seawater).

a. For 2 x 100 g and 1 x 1000 g packages: Open the box and remove the dose bag. Open the first sachet by tearing along the top edge of the sachet. Do not damage the inner water-soluble bag. Insert the inner water-soluble bag into the mixing tank without touching it. Repeat the procedure until the correct amount of drug is added to the mixing tank.

b. For 10 x 1000 g packages: Break the seal on the plastic container, remove the lid and insert the contents into the mixing tank. Be careful not to touch the water-soluble bags. Repeat until the correct amount of drug has been added to the mixing tank.

c. Complete the filling of the mixing tank with the required amount of seawater and start mixing.

3. The treatment suspension can be administered into the treatment well from the mixing tank via the gravity driven system when the following criteria are met:

   - Water quality parameters are as described in Special Warnings.
   - The wells are closed to ensure that water cannot enter or leave the boat.

4. After emptying the mixing tanks, they should be rinsed with clean seawater to ensure that all drug residues are washed out of the mixing tank and into the treatment well. The drug should be mixed in using the circulatory and oxygenation system as well as the movement from fish.

5. Once the full dose has been administered, the treatment time starts at 60 minutes.

6. At the end of the treatment (60 minutes), the fish should be pumped from the treatment well and dewatered and rinsed using a suitable system. All treatment and purification water must be retained in the treatment well.

7. After emptying, the wells must be rinsed and the rinsing water sent for filtration and cleaning.

<u>Cleaning procedure:</u>

1. All treatment water and rinsing water must be treated using a validated cleaning process before discharge back to the sea. The system must contain a suitable validated analytical laboratory or equivalent analytical monitoring system at the facility.

2. The system used must be able to purify the treatment water to ≤ 0.30 µg imidacloprid/l (measured by a validated analytical method).

3. The treatment water must be filtered (≤ 50 µm) to remove lice, lice eggs and other organic material before cleaning.

4. Once the water has been filtered, purified and disinfected in accordance with local regulations (e.g. UV-treated), it can be discharged into the sea.

5. The active substance and its metabolites collected after the purification process must be disposed of as special waste in accordance with the relevant rules.

10. WITHDRAWAL PERIOD(S)

98 degrees

If fish under treatment are exposed to imidacloprid for a significantly extended period due to delays in, for example, pumping out treated fish, a longer retention period should be considered.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of reach of children.

This veterinary medicinal product does not require any special temperature storage conditions.

Store the bags in a dry place in the aluminium dose bag/plastic container

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP. The expiration date refers to the last day of that month.

Shelf life after dilution according to the instructions for use: 24 hours after dilution in the well.

12. SPECIAL WARNINGS

Special warnings for the individual target species:

The drug does not prevent reinfestation with fish lice after treatment.

Avoid treating fish with a significant number of trapped lice.

To prevent the development of resistance, it is important that the treatment is carried out with the correct dose and duration of treatment.

It is recommended to test the sensitivity of the lice before treatment according to local / national procedures in order to determine the most suitable treatment alternative.

Avoid repeated treatment of the same fish population with this medicine.

Unilateral use of the same class of therapeutic agents may cause parasites to develop resistance to the class to which the active substance belongs.

Special precautions for use in animals:

Should only be used in accordance with benefit / risk assessment performed by the responsible veterinarian / fish health biologist, and which takes into account fish welfare, fish health and local salmon lice conditions.

Avoid treatment if there is a suspicion of an acute outbreak of infectious disease such as PD, HSMB or CMS as stress related to the treatment procedure can then lead to increased mortality.

Avoid unnecessary handling of fish less than 7 days before treatment with this medicine.

Cleaning fish must be separated from the treatment population before the treatment procedure is initiated. No safety information for cleaner fish is available for this medicine.

During treatment, fish should be monitored for, but not limited to, signs of stress (lethargy, gaping, orientation problems, balance problems and abnormal swimming behaviour). The treatment water must be monitored for oxygen (target: at least 90%) CO_2 and pH to ensure that the water quality is within acceptable limits, as used in the risk assessment by the responsible veterinarian / fish health biologist. Interruption criteria must also be included in this risk assessment.

Special precautions to be taken by the person handling the veterinary medicinal product:

Personal protective equipment consisting of coveralls, waterproof gloves and appropriate face protection should be worn when handling the veterinary product. When opening the packages, respiratory protection in accordance with EN:149 should be used. Care should be taken not to puncture the inner water-soluble gaskets when opening the outer gasket.

When handling suspension or solution, a face shield should be used to prevent splashes from entering the eye, nose or mouth.

When samples are analysed in the laboratory, a laboratory coat, goggles and gloves must be worn.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

In case of contact with skin, wash exposed skin with soap and water. If the product gets into the eyes, rinse the eyes with large amounts of water.

Other precautions

Excretion from treated fish is the main source of emissions of imidacloprid into the environment. Environmental modelling performed for this product was done for the treatment of fish kept at aquaculture facilities with locality condition 1 (very good) at the last MOM-B survey at maximum production load. It has not been shown that there is a positive environmental risk assessment for the use of the preparation for fish kept at sites with other site conditions, and the preparation should therefore not be used for fish kept at such sites.

Only completely closed treatment vessels (well boats) must be used to prevent suboptimal dosing and unintentional discharges of unfiltered and untreated treatment water into the environment.

The treatment water must be filtered (≤ 50 µm) before the cleaning process to remove lice and lice eggs.

All treatment water and treatment water must undergo a validated treatment process before discharge.

All waste collected during the filtration and purification process must be treated as special waste.

Do not discharge treatment water and purification water containing> 0.30 µg imidacloprid / l into the sea.

All discharge sites must have a minimum depth of 30 meters to ensure sufficiently safe emissions to the environment.

The treatment system must be able to operate with an emission concentration ≤ 0.30 µg / l with an emission velocity up to 500 m^3/h.

The purification system must contain a suitable analytical laboratory capable of analysing the imidacloprid concentration before discharging water. See Environmental Properties for more information.

Effect on fertility:

The safety of the veterinary medicinal product for brood stock has not been established.

Overdose (symptoms, first aid, antidotes):

No adverse reactions were observed during treatment in laboratory studies when the product was administered to salmon at one, three and five times the recommended therapeutic dose for three times the recommended duration of treatment.

Increased ventilation rate was associated with treatment when the product was administered to salmon at the recommended therapeutic dose for up to six times the recommended treatment time in a laboratory study.

Incompatibilities:

No one familiar.

13. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS, RESIDUES AND PACKAGING

Any unused product or waste material should be disposed of in accordance with local requirements.

Water and watercourses must not be contaminated with Ectosan Vet, as the preparation may be harmful to fish and other aquatic organisms.

Do not discharge treatment and rinsing water containing >0.30 micrograms imidacloprid/l.

All waste collected during the filtration and cleaning process must be disposed of as special waste.

14. DATE OF LAST APPROVED PACKAGE LEAFLET

29 June 2021

15. FURTHER INFORMATION

Pharmacological properties
Pharmacotherapeutic group: Other ectoparasite agents for topical use, Imidacloprid, 1- (6-chloro-3-pyridylmethyl) -N-nitroimidazolidin-2-ylidenamine, belong to the chloronicotinyl group of compounds.
ATC vet code: QP53AX17

Pharmacodynamic properties
Imidacloprid is an insecticide in the group of neonicotinoids, which acts by binding to the nicotinic acetylcholine receptors in arthropods. In arthropods, these receptors are located only in the central nervous system. After binding to the nicotinic receptor, the nerve impulse is first spontaneously discharged, and then the neuron is no longer able to conduct signals. Sustained activation of the receptor is due to the fact that acetylcholinesterase is unable to break down the active substance since binding is irreversible. Neonicotinoids have low toxicity in mammals but are highly toxic to arthropods and crustaceans.

Pharmacokinetic information
Studies in Atlantic salmon have shown that after exposure at 7 °C, imidacloprid was found in muscle, liver, skin and fillet (muscle and skin). The mean concentration in these tissues varied on day 1 of exposure, and the concentration dropped to approximately 50% on day 7. At day 60, the concentrations were not measurable.

After exposure at 15 °C, a higher average concentration was found on day 1 compared to the results at 7 °C.

Imidacloprid is absorbed by fish during treatment. The elimination takes place via urine, mucus and faeces and over the gills.

Studies in Atlantic salmon showed that exposure at low temperature resulted in a lower absorbed concentration of imidacloprid and slower excretion compared to exposure at high temperature.

Environmental properties
Imidacloprid is water soluble (601 mg / l) and has an octanol/water partition coefficient (log K_{ow}) of 0.60–0.63. Photolysis (DT_{50} 21.9 hours) and hydrolysis (DT_{50} 15.2 days) have been shown in seawater in laboratory experiments. Imidacloprid is

biodegradable in seawater at a rate classified as persistent (P). Imidacloprid is classified as toxic (T) for marine arthropods and annelids.

No treatment water must be discharged into the sea until the level of imidacloprid is ≤ 0.30 µg/l. There shall be systems in place to monitor discharge concentrations and discharge rate at all discharges of treated treatment water. In case of discharge of concentrations> 0.30 µg / l to the sea, contact local regulatory authorities immediately.

The choice of discharge site must follow relevant regulatory guidelines and permits must be obtained when needed. The selected discharge site must have a minimum depth of 30 meters. Purified treatment water must contain ≤ 0.30 µg / l and can be discharged at <500 m^3/h at a location.

No information is available on the environmental impact of this veterinary medicinal product used on fish kept in facilities with a MOM-B sediment classification of 2, 3 or 4. See Special Warnings under Other Precautions.

Inner packaging, type and composition

Heat-sealed water-soluble polyvinyl alcohol (PVOH) bag with 100 g or 1000 g of product, packed either in a heat-sealed aluminium sachet or in a 10-bag polypropylene container (plastic container) with a polypropylene lid.

Packed for sale as:

2 × 100 g or 1 x 1000 g water-soluble bags packed in aluminium foil sachets which in turn are packed in a secondary cardboard box.

10 × 1000 g water-soluble bags packed in a polypropylene container.

Not all pack sizes may be marketed.

For further information on this veterinary medicinal product, please contact the Marketing Authorization Holder.

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Appendix B

Executive summaries of proprietary studies

Reference:
Longshaw 2020*. Extended ECTOSAN® bath exposure and sampling of Atlantic salmon (*Salmo salar*) for residue analysis. Benchmark Animal Health: ARD0014 p. 292. OECD Good Laboratory Practice (GLP) Compliant. Unpublished Benchmark Animal Health Report.

Test Design:
The objective of the study was to provide samples for residue analysis of salmon fillet and liver from fish exposed to imidacloprid at 20 mg/L as Ectosan® for extended periods of time and was based on VICH Guideline (GL) 48 and VICH GL 57.

Groups of 72 fish, and 36 untreated control fish, were exposed to the bath treatment.

Behavior was observed during treatment and at daily husbandry checks for external pathology. Fish round weights and lengths (i.e., the weight and length of the whole fish before processing) and fillet and liver weights were recorded at sampling points on Study Days 1, 7, 14, 21, 28 and 33 post treatment.

Statistical Analysis:
Data from the in-life phase was tabulated using Microsoft Excel for Office 365. Means and standard deviations were calculated using Microsoft Excel for Office 365. Raw data was 100% quality control (QC) checked by study personnel for transcription accuracy. No other statistical analysis was conducted.

Summary of Findings:
Salmon (408.8 g ± 2.70 g standard errors of the mean [SEM]) were exposed to between 20.9 - 21.8 mg/L Ectosan® for 60, 196 and 360 minutes at 15.2–16.0°C. The time to deplete to below the LLOQ (4 µg/kg) in fillet was 21 days (313.2 degree days) after a 60-minute exposure, 28 days (422.1 degree days) after a 180-minute exposure and 33 days (508.6 degree days) after a 360-minute exposure. A similar pattern was seen in the liver samples, LLOQ was reached at 28 days following the 60-minute exposure, 33 days for 180-minute exposure and 33 days for the 360-minute exposure. It was concluded that no adverse effects attributable to Ectosan® exposure were observed in fish during treatment, husbandry checks or external pathology assessments at sampling.

This study showed concentrations of the test item depleted to below LLOQ in fillet and liver tissues after 33 days (508 degree days). A clear concentration/exposure time relationship was shown with concentrations increasing with increasing exposure time.

* Proprietary study

Reference:
Mould, 2020*. Imidacloprid – Aqueous Photolysis in Marine Water. Smithers ERS Limited: 3202592 82 p. The Department of Health of the Government of the United Kingdom GLP Compliant. Unpublished Benchmark Animal Health Report.

Test Design:
The study was conducted in compliance with the Organization for Economic Cooperation and Development (OECD) Test Guideline 316 to determine the photolysis rate of imidacloprid in marine water under sterile conditions at an initial concentration of 1 µg/mL.

Water samples were collected from Sandsend beach, North Yorkshire, United Kingdom. Water temperature, pH, oxygen content, depth above sediment and visual quality were measured at the time of sampling. Suspended solids, electrical conductivity, pH and oxygen content were measured at the test facility.

Test vessels containing sterilized marine water were treated with an acetonitrile solution of imidacloprid at a rate of 1 µg/mL. The amount of organic material present in each test vessel was < 1 % of the total volume. The treated samples were continuously irradiated for 48 hours at 12 ± 2°C. Samples were analyzed at regular intervals up to 48 hours post exposure by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

Dark control samples (i.e., samples that were treated with imidacloprid but were not exposed to irradiation) were incubated in the dark at 12 ± 2°C and analyzed at the same intervals as the irradiated samples.

Sterility of the test systems for the duration of the incubation period was confirmed using a plate count method.

Statistical Analysis:
Determination of Degradation Rates

The concentration of test substance was plotted against the incubation time. Curves were constructed through the data points using non-linear regression analysis to give lines of best fit. Light and dark data was fitted to single first-order (SFO) kinetics using the following equation:

$$y = C_0 \times e^{-kt}$$

Where y is the percent of test substance at time t days, C_0 is the computed initial concentration and k is the rate constant (slope). DT_{50} and DT_{90} values were calculated from the equation of the lines as the value of t which gave a value equal to 50% (DT_{50}) and 10% (DT_{90}) of test substance originally present (intercept on the y-axis).

All calculations were performed using CAKE (version 2.0).

Determination of Rate Constants

Determination of the photolysis rate constant (k_d) was calculated according to the following formula:

* Proprietary study

$k_{photolysis} = k_{irradiated} - k_{dark}$

Where $k_{photolysis}$ is the photolysis rate constant, $k_{irradiated}$ is the rate constant for the irradiated samples, and k_{dark} is the rate constant of the dark control samples.

DT_{50} and DT_{90} values were then determined using the following formulae:

$DT_{50} = \ln (2) / k_{photolysis}$
$DT_{90} = \ln (10) / k_{photolysis}$

Summary of Findings:
The degradation of imidacloprid was studied in marine water at 12 ± 2 °C, at an application rate of 1 µg/ mL. Samples were continually irradiated over a period of 48 hours, equivalent to *ca* 48 hours of summer sunlight at 30-50° N latitude.

The concentration of the test compound in the application solution was checked three times and the mean value was found to be 499 µg/mL.

The pH of the marine water was 7.85 before sterilization and 7.93 after sterilization. Incubated samples had pH measurements of 7.71 (irradiated) and 7.79 (dark control) and were proven to be sterile. The temperature of the water bath containing dark control samples ranged from 11.3–12.6°C. The irradiated samples were maintained at temperatures ranging from 11.3–12.5°C.

The mean recovery of imidacloprid was ≥ 90% at all sampling intervals for in the dark controls. The mean recovery of imidacloprid in irradiated samples, decreased from 101% immediately after application to 7% at the end of the incubation period. The degradation rates were determined by SFO kinetics (best fit) and were determined to be 273 hours (DT_{50}) in the dark and 14.4 hours (DT_{50}) irradiated.

The photolysis rate constant, DT_{50} and DT_{90} were determined and corrected for the irradiance of the artificial sunlight. The corrected values were 16.3 hours ($DT_{50\ sun}$) and 54.2 hours ($DT_{90\ sun}$).

* Proprietary study

Reference:
Sutcliffe, R. (2020).* [^{14}C]-Imidacloprid: Degradation in Water-Sediment Systems under Aerobic Conditions. Smithers ERS Limited (Study No. 3202636).

Test Design:
The study was conducted in compliance with OECD 308 to determine the route and rate of degradation of [^{14}C]-Imidacloprid in water-sediment systems sourced from a marine environment at 12 ± 2°C in the dark. An aerobic test design was followed (air was drawn over the surface of the overlying water) and a redox gradient was established whereby oxidizing conditions predominated in each of the surface waters with lower redox potentials in the sediments. The redox conditions in the Cage Edge sediment were more reducing than in the Unimpacted sediment. The application rate was 40 µg/vessel. Two sediment/water test systems were selected, one sampled from the edge of a salmon cage and the other from an unimpacted area within the same geographical location. The characteristics of the two water-sediment systems were as follows:

Sediment	pH ($CaCl_2$)	OC %	Sand %	Silt %	Clay %	Classification	Biomass (µg C/g sediment)
Cage Edge	8.1	3.2	32	44	24	loam	1838
Unimpacted	8.2	2.2	30	46	24	loam	755
OC = organic carbon							

Water	pH in H_2O (upon arrival)	TOC (mg/L)	Suspended solids (mg/L)
Cage Edge	8.5	1.5	2
Unimpacted	8.6	1.3	3
TOC = total organic carbon			

The test system consisted of individual glass vessels, containing sediment to a depth of 3 cm and associated water to a depth of 9 cm above the sediment, through which moistened air was drawn. The vessels were incubated under experimental conditions for 19 days prior to test substance application. After application, the air drawn over the surface of the vessels was passed through a series of sodium hydroxide traps to collect evolved radiolabelled carbon dioxide.

[^{14}C]-Imidacloprid was applied dropwise in Milli-Q water to the water surface. The concentration in surface water was equivalent to 0.29 µg/mL.

Microbial biomass of the sediment was determined on samples removed from incubation at treatment and at the end of the incubation period. Samples were removed for analysis immediately after application of [^{14}C]-Imidacloprid and at 7, 14, 30, 61 and 100 DAT (days after treatment). The water was separated from the sediment and the two phases were analyzed separately.

The surface water was aspirated from each sample using a glass pipette and then transferred into a glass vessel. The sediment was then extracted using solvent, before being air dried and

* Proprietary study

subject to combustion analysis. Bound residue fractionation was performed on the 100 DAT sediment samples from each water-sediment system

Statistical Analysis:
The percentage of applied radioactivity present as Imidacloprid in the surface water, and total system were used for kinetic calculations, combining the data for each radiolabel and test system.

Kinetics were determined from values of [^{14}C]-Imidacloprid and any degradation products, assayed by HPLC, plotted against days of incubation and fitted to single first-order (SFO) and double first-order in parallel (DFOP) kinetics using CAKE version 2.0 software. The software calculated the degradation rates and associated parameters.

Summary of Findings:
The total mean recovery of applied radioactivity (AR), for samples treated with [^{14}C]-Imidacloprid, ranged from 95.7 to 100.4 %.

Radioactivity dissipated slowly from the water phase into the sediment in both water-sediment systems. As the incubation progressed, the amount of non-extractable residue associated with the sediment increased.

The 100 DAT non-extractable residue samples were subject to bound residue fractionation. In both Unimpacted and Cage Edge, over half of the radioactivity remained in the humin fraction with approximately a third in the fulvic acid and a small amount in the humic acid.

Levels of radioactivity recovered in the sodium hydroxide traps was very low (≤ 0.5 % AR) from both water-sediment systems.

Chromatographic analysis of the surface water and sediment extracts was performed. In the total test system, [^{14}C]-Imidacloprid decreased to 53.1 % and 54.1 % AR for Cage Edge and Unimpacted respectively by the end of the incubation period. One degradation product was present at > 5 % AR in both the Cage Edge and Unimpacted total system. This was confirmed as desnitro-imidacloprid by LC-MS/MS. No other individual degradation product was present at ≥ 0.9 % AR in surface water or sediment extracts.

Disappearance of [^{14}C]-Imidacloprid from the surface water had DT_{50} values determined by DFOP of 49.3 and 52.1 days in the Cage Edge and Unimpacted systems, respectively.

The degradation rate of [^{14}C]-Imidacloprid in the total test system had DT_{50} values determined by SFO of 118 days for both Cage Edge and Unimpacted water-sediment systems.

The distribution and transformation rate of [^{14}C]-Imidacloprid was similar between the two water-sediment systems tested.

* Proprietary study