Environmental Assessment

in Support

of an Import Tolerance

for

Azamethiphos in Food Derived from Salmonids

FVG Ltd.

22 Carsegate Road

Inverness,

Scotland

IV3 8EX

February 2016

1. General Information

Requestor: FVG Ltd.
22 Carsegate Road
Inverness, Scotland
IV3 8EX

Drug Established Name: Azamethiphos

2. Purpose and Need for the Proposed Action

Azamethiphos is the active pharmaceutical ingredient (API) in several drug products (e.g., Salmosan®, Salmosan® Vet, Byelice®) used as ecto-parasiticides for treatment and control of pre-adult to adult stages of sea lice (*Lepeophtheirus salmonis* or *Caligus* species) on farmed Atlantic salmon and other salmonids (e.g., coho salmon, steelhead trout, sea trout) that are reared in seawater[1]. Drugs containing azamethiphos are currently approved for marketing and use in the United Kingdom (UK), Norway, Faroe Islands, and Chile, and at times may also be used in other countries, including Canada, under emergency or temporary authorizations. Treatments of sea lice on salmon in seawater occur by bathing or immersing infested fish *in-situ* for up to one hour. Bath treatments are typically given to fish reared in sea cages or net pens by enclosing the pen or cage with a tarpaulin and then dosing the drug into the enclosed volume of water via a concentrated stock solution.

Azamethiphos is currently not approved nor is it conditionally approved in the United States (U.S.) as a drug substance for use in or on any fish species; therefore, FVG Ltd is requesting establishment of an import tolerance of 0.02 parts per million (ppm) for residues of azamethiphos in salmonids so that imported food derived from salmonids treated with, and containing residues of, azamethiphos may be legally marketed in the U.S. for human consumption[2]. The act of establishing an import tolerance is an agency action requiring preparation of an environmental assessment (EA) unless the action is one that meets criteria for categorical exclusion under FDA regulations in 21 CFR Part 25, Subpart C, which is currently not the case. Therefore, this EA has been prepared to address and evaluate any potential direct and

[1] Atlantic salmon and some other salmonid species (e.g., rainbow trout) may be reared in freshwater for their entire lifecycle, although the great majority of production for food use occurs in seawater. The currently approved drugs that contain azamethiphos are limited to use on fish in seawater.
[2] Although the currently approved drugs that contain azamethiphos limit drug use to fish in seawater, this could change in the future; therefore, the import tolerance would apply to all salmonids regardless where they are reared.

indirect environmental impacts in the U.S. due to the action of establishing an import tolerance for residues of azamethiphos in food derived from salmonids.

The impact on the environment of the U.S. arising from the occurrence of azamethiphos residues in salmonid tissues will be evaluated herein based on the primary pathways for environmental exposure and the available physical-chemical property and fate data for the drug (Section 6). In addition, because azamethiphos treatments occur in the tarped net pens/cages or wellboats, with subsequent direct release to the marine environment, and because drug use could potentially occur in countries adjacent to the U.S., Canada in particular, consideration will also be given to the potential for effects on the U.S. environment as a result of azamethiphos use in these other countries. Because azamethiphos is currently authorized only for use on salmonids in seawater, and because use in seawater is expected to represent a worst-case scenario for environmental exposures and risks to non-target aquatic life in the U.S. (due to direct release from the site of use without prior treatment), the risk evaluation herein will focus solely on that exposure scenario.

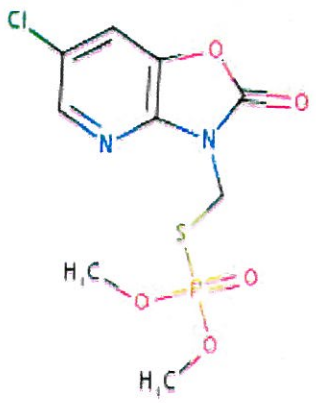
3. Identification of the Substance

Azamethiphos is an organophosphorus insecticide, which acts by inhibiting cholinesterase activity. Table 1 summarizes the most relevant physical-chemical properties of azamethiphos. It is typically present in drug products (e.g., Salmosan®, Salmosan® Vet, Byelice®) at a concentration of 50% (w/w) and is used at a final treatment concentration of 0.1 mg azamethiphos per liter water. The withdrawal period, i.e., the minimum time period following treatment before fish may be slaughtered for human consumption, is either 24 hours or 10 degree days depending on the specific product and country. See Appendix 1 for additional information on a typical azamethiphos product (Salmosan® Vet) and how it is used.

Table 1. Physico-chemical properties of azamethiphos[3]

Drug established (nonproprietary) name	Azamethiphos
CAS Registry Number	35575-96-3

[3] Data from ChemIDplus, a TOXNET database (http://chem.sis.nlm.nih.gov/chemidplus/rn/35575-96-3), accessed December 30, 2015. Data provided to ChemIDplus by Syracuse Research Corporation.

Chemical structure	
Molecular formula	C9-H10-Cl-N2-O5-P-S
Molecular weight	324.68 g/mole
Melting point	89 °C
Log P (octanol-water partition coefficient)	1.05
Water solubility	1100 mg/L
Vapor pressure	3.76 X 10^{-8} mm HG

Azamethiphos has a low volatility (low vapor pressure) and a moderate solubility in water (1100 mg/L)(Table 1). Based on its relatively low octanol-water partition coefficient (log P) of 1.05, significant bioaccumulation in aquatic life is not expected.

4. Sites of Introduction and Exposure Pathways

There are two general types of exposure pathways for azamethiphos to 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 where it is legally authorized. With respect to the first of the two general types of exposure pathways, i.e., following the importation of food derived from azamethiphos-treated salmonids, release of azamethiphos into the U.S. environment (e.g., soil, surface water, air) may potentially occur through two points of introduction:

- through landfills that may hold seized materials (fish or food-derived from treated fish) containing residues of the drug;
- through wastewater treatment plants and their effluents that may contain residues of the drug in human excreta as a result of consumption of imported food from treated fish.

The potential introduction of drug residues into soils and surface waters from landfills and wastewater treatment facilities strongly depends on the inherent physicochemical and fate properties of the respective drug (e.g., water solubility, adsorption coefficients, biodegradation

rates, etc.), as well as on numerous factors specific to the landfills (e.g., liner thickness, soil type, proximity to surface water) and wastewater treatment facilities themselves (e.g., removal efficiencies, flow rates, dilution factors). In general, only in cases where the substance is volatile or highly mobile (i.e., will migrate out of the compartments at the site of introduction), and present at concentrations high enough to cause effects, is it possible that environmental impacts on the circumjacent ecosystems could become evident.

The environmental exposure and likelihood of azamethiphos to cause impacts on the ecosystems at the sites of introduction is evaluated in Section 5.

5. Analysis of Exposure and Risk

The potential exposures due to the pathways listed in Section 4 will be evaluated based on the available metabolism and environmental fate data for azamethiphos, which is described below. Information on the metabolism of azamethiphos in salmon will help to determine the types and magnitude of residues, if any, that could potentially be present in imported fish tissues (which could be potentially be disposed of in landfills in the U.S.), as well as the amount of the drug (and/or its potential metabolites) consumed by humans in the U.S., which could then be present in sewage, be processed by wastewater treatment facilities, and subsequently be discharged to surface waters. The environmental fate information will help to determine if azamethiphos is likely to migrate out of landfills, and whether it will likely be persistent in terrestrial and aquatic environments if it does.

A. Metabolism and Fate of Azamethiphos

Metabolism and Residues in Atlantic Salmon

Several studies have been conducted examining the metabolism and residues in Atlantic salmon that have been treated with azamethiphos. In one study using radiolabeled compound (Lonsdale, 1992), residues of azamethiphos in fish muscle and skin depleted quickly and were below the limit of detection (0.02 ppm) within one hour after immersion for one hour in a bath containing 0.2 ppm azamethiphos, which is twice the maximum recommended treatment concentration. In another study with the same exposure scenario (0.2 ppm azamethiphos for one hour), total residues in muscle with adhering skin (90% muscle, 10% skin) at zero withdrawal (i.e., the time that treatment was stopped and salmon were removed) were 0.03 ppm (Mucke, 1992). Total residues in tissues were too low for characterization of the metabolites, but the major metabolite in bile was the glucuronic acid conjugate of 2-amino-3-hydroxy-5 chloro-pyridine. Based on this collective information, the FVG Ltd has requested an import tolerance of 0.02 ppm for

azamethiphos in salmonid tissues. Because there is a minimum withdrawal period of either 24 hours or 10 degree days following azamethiphos treatment, and the actual withdrawal period may be much longer than this, perhaps days to weeks longer, the actual concentrations of azamethiphos in imported foods, if any, are likely to be much lower than the requested tolerance limit of 0.02 ppm and below the limit of detection.

Adsorption and Mobility

Adsorption/desorption data are not currently available for azamethiphos, but a soil adsorption coefficient (Koc) of 21.38 L/kg is predicted by KOCWIN (V2.00). Based on this Koc estimate and the reported water solubility (1100 mg/1 @20 degrees C) and log Kow (1.05) for azamethiphos, it is predicted that azamethiphos present in the aqueous environment as a result of bath treatments is likely to remain largely in solution rather than adsorb to sediments or suspended solids. Likewise for residues present in terrestrial environments, significant adsorption to soil is not expected and moderate mobility in soil is predicted.

Degradation and Persistence in Water

Azamethiphos has a measured decay half-life of 8.9 days in seawater (Mucke, 1992), with further and relatively rapid degradation of its primary degradation products (mineralization half-life of 50.2 days). Because of its moderately high solubility in water, 1100 mg/L, azamethiphos is expected to remain largely in the aqueous phase until it is degraded. According to one report (Lewis et al., 1998), hydrolysis appears to be the most important degradation process, with reported half-lives in the range of a few hours to a few days depending on environmental conditions. Calculated half-lives for dissipation (DT50) of azamethiphos in water are reported as follows by Tomlin (1997): 800 h (pH 5), 260 h (pH 7), and 4.3 h (pH 9). Seawater has a pH of approximately 8.3, so azamethiphos would be expected to have a half-life between 0.18 and 10.8 days based on these estimates. In addition, estimates from the software program BIOWIN v4.10 shows a high probability of rapid degradation with primary degradation predicted in 3.85 days using the Primary Survey Model and ultimate degradation predicted in 2.17 months using the Ultimate Survey Model. These estimates are in good general agreement with the measured dissipation/degradation data from the Mucke (1992) study, indicating that azamethiphos will not persist for long periods of time in seawater.

B. Exposure and risks for pathways arising from the release of azamethiphos residues from imported food derived from treated salmon

As discussed previously, there are two theoretically possible pathways to the environment at large for azamethiphos residues originating in imported food (e.g., salmon steaks and filets):

- through release from landfills that may hold seized materials (fish or food-derived from treated fish) containing residues of the drug;
- through discharges from wastewater treatment plants via effluents that may contain residues of the drug in human excreta as a result of consumption of imported food from treated fish.

The amounts of azamethiphos introduced into the U.S. environment from both of these pathways are expected to be extremely low because the residues of azamethiphos in Atlantic salmon muscle and skin are very low immediately after treatment (0.02 and 0.117 ppm respectively, on average [Mucke, 1992]), and will continue to decline thereafter in tissues as a result of fish metabolism and excretion during the withdrawal period (24 hours or 10 degree days depending on the product and country of use) applied to the product; therefore, the amounts of residues in salmon tissues at the time of slaughter and import into the U.S. are expected to be *de minimus* and below detection limits.[4]

The potential for impacts to the U.S. environment through these two exposure pathways is evaluated further below.

Landfill Pathway

Landfills in the U.S. are highly regulated by local, state and federal authorities to prevent environmental contamination. For example, most landfills are required to have caps and liners of clay or an impermeable membrane to prevent leaching of water or fluids therein (and any contaminants they may contain) to groundwater and/or local surface waters (e.g., rivers and lakes). As a result of these controls and the fact that the amounts of residues in fish tissue will be extremely small to begin with, there is expected to be minimal or no movement of azamethiphos out of U.S. landfills and into the adjacent U.S. environment (groundwater or surface water). In addition, because azamethiphos has a low vapor pressure (0.0049 mPa; Tomlin 1997) and moderately high water solubility, it is not expected to volatilize from landfills and enter air to any significant extent. Therefore, based on a lack of exposure, significant environmental impacts on the terrestrial and aquatic environments are not expected from residues of azamethiphos in imported food derived from treated salmon that are disposed of in U.S. landfills.

[4] The European Medicines Agency has declined to establish a maximum residue limit (MRL) for azamethiphos residues in fish tissues because residues are expected to be below the limit of detection even shortly after treatment.

Wastewater Discharge Pathway

The concentrations of drug residues introduced into the U.S. environment from wastewater treatment facilities as a result of human consumption of imported food containing residues of azamethiphos, is expected to be extremely low for several reasons. First, as previously described, the residues of azamethiphos in Atlantic salmon muscle and skin are very low to begin with (0.02 and 0.117 ppm respectively on average immediately after treatment) and will continue to decline rapidly thereafter during the withdrawal period due to fish metabolism and excretion, therefore, the amounts of residues in salmon tissues at the time of import into the U.S. are expected to be *de minimus* and below detection limits. Although the import tolerance itself is expected to be set at 0.02 ppm for residues in muscle, the actual tissue concentrations are likely to be much lower due to declines after treatment, which would typically occur days to weeks (or more) before fish are sacrificed and brought to market. Additional reasons why this exposure pathway is not expected to be significant include: 1) consumption rates of salmon in the U.S. are low compared to those for most other types of meats; 2) further metabolism of azamethiphos residues, if present, is likely to occur in humans after consumption; 3) the distribution of the excreted residues, if any, in the U.S. environment will likely be spatially and temporally variable (i.e., it is very unlikely that enough salmon will be consumed in the same region on the same day to have a detectable level occurring in the same wastewater treatment facility); and 4) additional degradation and removal of azamethiphos in wastewater treatment facilities. As a result, the expected concentrations of azamethiphos in effluents entering aquatic systems as a result of discharge from wastewater treatment facilities are expected to be extremely low, approaching zero (and likely undetectable), with further dilution and degradation of azamethiphos expected to occur in effluent receiving waters. As a result, it is very highly unlikely that azamethiphos will ever be present at concentrations in water that would cause effects on aquatic life. Therefore, no significant environmental impacts on the aquatic environment are expected from this exposure pathway.

C. Exposure and risk to the U.S. environment from use of azamethiphos on salmonids in seawater in countries where it is legally authorized

Typical Use Conditions

Treatments of sea lice on salmonids in seawater occur by bathing or immersing infested fish in-situ for a period of between 30 to 60 minutes in concentrations of 0.1 mg azamethiphos/L. Bath treatments are typically given to Atlantic salmon reared in sea cages or net pens by enclosing the pen or cage with a tarpaulin and then dosing the drug into the enclosed volume of water via a

concentrated stock solution. In some locations, treatments made also be made using well boats at a concentration of 0.1 mg azamethiphos/ L. At the end of the treatment, the tarpaulin is removed and the treated water is allowed to dissipate from the cage and disperse with the prevailing current. For well boat treatments, the treatment water is discharged via a pump to the surrounding environment after completion of the treatment. There may be two or more net pen treatments per day at a particular fish farm until the entire farm (i.e., all net pens or cages) has been treated.

Relevant Research and Analysis of Potential Impacts on the U.S. Environment

As azamethiphos has been approved for use on Atlantic salmon and other salmonids in seawater in other countries, it has undergone an evaluation as part of the approval processes in those countries to determine its potential impact on the aquatic (marine) environment. For example, for authorization in Scotland, the potential effects of azamethiphos use were extensively evaluated in both laboratory and field studies, and environmental (water) quality standards were developed for this compound (by the Scottish Environmental Protection Agency (SEPA, 1998)[5]. Field and laboratory studies on azamethiphos have also been conducted in Canada by Environment Canada and Fisheries and Oceans Canada (DFO), see discussion in Burridge and Van Geest (2014). The field studies conducted in Canada are most relevant for evaluating the potential effects of azamethiphos on the U.S. environment because of the proximity of the use sites in Canada to the U.S. border. Salmosan is currently used under emergency authorization in New Brunswick and Newfoundland[6], with several potential use sites, i.e., fish farms, located in Passamaquoddy Bay (New Brunswick) near the Canadian/U.S. border and the state of Maine.

Toxicity tests conducted in conjunction with dispersion studies on azamethiphos in 1996 at three farm sites in eastern Canada showed that most samples collected after releases of azamethiphos were not toxic to test organisms (Amphipod *Eohaustorius estuaries*) in 48-hr exposures, with no toxicity in those samples collected 20 minutes or later after release of the drug (Ernst et al., 2001). Concentrations of azamethiphos were not measured in these tests, but a florescent dye (Rhodamine) was used as a surrogate for azamethiphos in subsequent dispersion studies conducted in 1997. Concentrations of this dye showed a three order of magnitude reduction

[5] Maximum acceptable concentrations (MACs) for azamethiphos are 250 ng/L, 150 ng/L, and 40 ng/L for time periods of 3, 24 and 72 hours, respectively.

[6] According to Burridge and Van Geest (2014), Salmosan had full registration status with the Canadian Pest Management Regulatory Agency (PMRA) during the period from 1995 through 2000. Subsequently, the registrant did not apply to have its PMRA registration renewed. However, after the subsequent development of resistance to emamectin benzoate (SLICE) by sea lice, an emergency authorization for use of azamethiphos in eastern maritime Canada was granted in 2009.

between 3 and 5 hr post-release under conditions described as moderately dispersive. The authors concluded that the results "showed a low risk for azamethiphos to non-target organisms when released from net pens under the conditions used in this study."

Additional studies conducted by Chang and McClelland (1996, 1997) of Fisheries and Oceans Canada (DFO) support the conclusions of the research by Ernst et al., 2001. These studies are briefly described in Burridge and Van Geest (2014). Chang and McClelland (1996) investigated the effects of azamethiphos treatments on juvenile and adult American lobsters, shrimp, clams, and scallops suspended at two depths and varying distances from the treatment cage. During two of the treatments, all of the lobsters held within the treatment tarpaulin died, but no other treatment-related mortalities were observed. In addition, no mortalities were observed with lobsters that were suspended at three depths at 20 sites surrounding a salmon cage site that was conducting operational treatments with Salmosan.

Additional studies by Chang and McClelland (1997) at four farm sites and a control site in New Brunswick support the results of their earlier work. Survival of lobsters suspended at mid-depth and near the bottom at these sites was monitored for nine weeks during August to October 1996. There were no apparent differences in lobster survival between the experimental and control sites and no residues of azamethiphos were detected in water samples collected weekly from the five sites (limit of detection = 50 pg/L). Additional surveys conducted by divers confirmed the lack of effects on lobster populations in a lobster nursery area near another salmon farm.

These Canadian field study results, plus those from field studies conducted in Scotland, support a conclusion that significant effects of azamethiphos on marine organisms in the vicinity of treated cages are highly unlikely. With a moderately high water solubility (1100 mg/L) and degradation half-life of 8.9 days, azamethiphos should remain in the water column, disperse relatively rapidly with the current and tide, and not accumulate to any significant extent in sediments or aquatic organisms. Therefore, if there are no significant effects on sensitive aquatic life (i.e., juvenile and adult American lobsters) in Canada from use of azamethiphos, there should also be no resulting effects from this use in waters of the U.S. due to additional dispersion and dilution of any treatment plumes before they would reach the U.S./Canadian border. The same should also be the case from use in other countries, such as Norway and Scotland, where use of azamethiphos is currently authorized.

6. Description of Any Alternatives to the Proposed Use

The FVG Ltd. is proposing to establish a tolerance for azamethiphos in food derived from salmon that is 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 azamethiphos 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 azamethiphos in salmonids imported into the U.S. and the no action alternative was eliminated from consideration.

7. Conclusions

Based on the available information on the metabolism, environmental fate, and exposure of azamethiphos, there is expected to be little or no exposure to azamethiphos residues in the U.S. environment for the three exposure pathways evaluated. Therefore, it is concluded that the proposed action of establishing an import tolerance for azamethiphos residues in salmonids will not result in significant environmental impacts in the U.S.

8. Agencies and Persons Consulted

This EA was prepared with input and assistance from members of the Environmental Safety Team in the Office of New Animal Drug Evaluation in FDA's Center for Veterinary Medicine.

9. Preparer(s)

John Marshall, Director, FVG Ltd.

10. Signature of Responsible Official

John Marshall.
Director

10. References

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APPENDIX 1

Drug Information for Salmosan Vet®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Salmosan® Vet, Azamethiphos 50%w/w powder for suspension for fish treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azamethiphos 500mg/g

For full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Powder for suspension for fish treatment.

Light beige to beige powder.

4. CLINICAL PARTICULARS

4.1 Target species

Farmed Atlantic salmon (*Salmo salar*)

4.2 Indications for use (specifying the target species)

For treatment of pre-adult to adult sea-lice (*Lepeophtheirus salmonis* or *Caligus* species)

on farmed Atlantic salmon.

4.3 Contraindications

Do not use the product in cases of known hypersensitivity to the active substance or any of the excipients.

4.4 Special warnings (for each target species)

The product does not treat juvenile attached sea lice which may be present with the pre-adult and adult stages. These juvenile stages will develop into pre-adults and adults in 10 to 20 days when the population count should show whether a second treatment is necessary. All fish on the site should be simultaneously treated.

Resistance is known to occur where incomplete treatments are carried out. To help prevent resistance occurring ensure the correct dose and duration of treatment is accomplished. Only fully enclosed treatments should be used. Repeated use of the same class of chemotherapeutic agent may result in the development of resistance. In order to reduce the risk of resistance to the product developing, the product should be used as part of a rotational strategy in the medicinal treatment of sea lice.

Where there are concerns of decreasing sensitivity of lice to Azamethiphos based products the maximum treatment time (60 minutes) should be used to achieve optimum efficacy and limit the opportunity for resistance development (see also section 4.5)

Do not use the product prophylactically. Only use when infestation with mature lice has been diagnosed.

4.5 Special precautions for use

i. Special precautions for use in animals

For external use only.

Vigorous oxygenation of the water must be provided during treatment. It is recommended that oxygen addition begins before the tarpaulins are fitted to the pens. During treatment, careful observation of fish behaviour should be maintained. If signs of distress, e.g., fish suffering balance problems during or shortly after treatment occur flush the treatment area with clean sea water and ensure vigorous oxygenation.

The product should be applied to salmon suffering from infestations with pre-adult and adult sea lice before the stage at which serious skin damage is evident.

A laboratory study was conducted to determine the safety of treatment at temperatures above 10°C for the maximum recommended treatment duration of 60 minutes. Salmon (with bodyweights from 350g) appeared to tolerate exposure to Salmosan® Vet at up to three times the recommended dose rate (i.e. 0.6ppm), for up to three times the recommended treatment time (i.e. 180 minutes), at both 6°C and 15°C.

ii. **Special precautions for the person administering the veterinary medicinal product to animals**

This product contains azamethiphos. Azamethiphos is an organophosphorus compound. DO NOT USE if under medical advice not to work with such compounds.

THIS PRODUCT MAY CAUSE SENSITISATION (ALLERGY) BY SKIN CONTACT OR INHALATION.

AVOID ALL CONTACT WITH MOUTH, SKIN OR EYES.

ACCIDENTAL SPLASHES ON EXPOSED SKIN OR EYES should be washed off immediately with plenty of water.

WEAR SUITABLE PROTECTIVE CLOTHING SUCH AS WATERPROOF COVERALLS,

HEAVY DUTY GAUNTLET STYLE NITRILE GLOVES of at least 300 mm length and 0.5 mm thickness, FACE SHIELD AND RESPIRATORY PROTECTION, both when handling the concentrate and when applying the diluted chemical to the pen.

RENEW PROTECTIVE CLOTHING AND EQUIPMENT REGULARLY and certainly when cracking or damage has occurred.

WASH ALL PROTECTIVE CLOTHING thoroughly after use, especially the insides of gloves.

REMOVE HEAVILY CONTAMINATED CLOTHING IMMEDIATELY after a spill; wash or destroy.

Ensure that the drum/container is securely closed during the dissolving process.

DO NOT EAT, DRINK OR SMOKE without first withdrawing from the work area, removing protective clothing and washing hands, face and exposed skin.

WASH HANDS, FACE AND ANY EXPOSED SKIN immediately after leaving the work area.

KEEP AWAY FROM FOOD, DRINK AND ANIMAL FEEDINGSTUFFS.

RINSE APPLICATION EQUIPMENT AND CONTAINERS AFTER USE.

MEDICAL ADVICE TO USERS

- If you have previously felt unwell after using a product containing an organophosphorus compound, consult your doctor before working with this product and show your doctor the product label.
- If you feel unwell after using this product, consult your doctor and show your doctor the product label.
- Treat any cases of heavy contamination as an emergency. You should go straight to hospital after removing contaminated clothing, and rinse areas of skin which came into contact with the product with plenty of water.
- If the product has been swallowed go straight to hospital and take the product label with you.

MEDICAL ADVICE TO DOCTORS

Poisoning from organophosphorus compounds results from blockage of acetylcholinesterase, with a resulting over-activity of acetylcholine.

Symptoms include headache, exhaustion and weakness, mental confusion together with blurred vision, excessive salivation and sweating, cramp-like abdominal pain, chest tightness, diarrhoea, constricted pupils and bronchorrhea. These may develop for up to 24 hours after exposure.

Severe poisoning can include general muscle twitching, loss of coordination, extreme difficulty with breathing and convulsions which may lead to unconsciousness in the absence of medical treatment. Treat symptomatically and seek urgent hospital transfer if poisoning is suspected.

Advice on clinical management is available from the National Poisons Information Service.

REPORTING INCIDENTS

In the UK:

Illness suspected to be a result of working with this product may be reportable under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1985. If in doubt contact your local Health and Safety Executive Officer.

Report suspected adverse reactions to the Fish Vet Group, 22 Carsegate Road, Inverness, IV3 8EX, Scotland. Tel: +44 (0) 1463 717774, 24 hour emergency number 0845 0093342, or directly to the Veterinary Medicines Directorate online at http://www.vmd.defra.gsi.gov.uk/adversereactionreporting/

In Norway:

Adverse reactions, including human reactions, should be reported to the Norwegian Medicines Agency, www.noma.no.

Further advice can be obtained from: Fish Vet Group, 22 Carsegate Road, Inverness, IV3 8EX, Scotland. Tel: +44 (0) 1463 717774, info@fishvetgroup.com

iii **Other precautions**

The product is very dangerous to crustaceans and is dangerous to fish and other aquatic organisms; therefore the product should not be used in sea farms where crabs and lobsters are kept in close proximity of the treated cages.

Frequent use and/or use on a larger scale may pose an increased risk to the environment. In order to ensure safe use (including large scale and multiple treatments) of the product under a combination of different environmental conditions (e.g. low water current speeds, shallow waters, short distance to the shore etc.), local environmental regulations governing discharges, where applicable, must be adhered to. **If there is any doubt about safe use, relevant competent authorities should be consulted or professional advice sought accordingly.**

The most important mechanism for removal of the product in coastal waters is dilution which is increased by water movements including the flushing effects in sea lochs. After treatment, care should be taken to provide sufficient water exchange through the net to dilute residual azamethiphos. The water movements from a boat's propeller may be used to increase water exchange in cases where low water exchange rates cannot be avoided. These measures will help to prevent possible adverse effects on aquatic life.

From a practical use position, 'restrictive tarpaulins' are commonly available now and can be used to reduce the volume of larger net pens for bath treatments. Depending on biomass, these tarpaulins can reduce the size of larger pen nets by >60%. This is good practice which not only allows for better measurement of the water volume to be treated but also reduces the amount of product needed to be used and therefore released at the end of treatment.

For countries where an environmental authorisation is not required at each individual site, the following risk mitigation measures should be followed:

At sites with cages ≥ 150 m in circumference, a maximum of one cage should be treated per day.

At sites with cages 120-149 m in circumference, a maximum of two cages should be treated per day.

4.6 Adverse reactions (frequency and seriousness)

Signs of hyperactivity or distress may be seen if fish are not adequately oxygenated during treatment.

4.7 Use during pregnancy, lactation or lay

The safety of the product with regard to reproduction toxicity has not been assessed. Therefore, only use in maturing brood stock in accordance with the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

None known

4.9 Amount(s) to be administered and administration route

READ THE OPERATOR PRECAUTIONS AND ENVIRONMENTAL WARNINGS (see sections 4.5.ii and 5.3 of the SPC).

Fish affected by sea-lice should be bathed in 0.2 ppm the product (0.1 ppm azamethiphos) for a period of not less than 30 minutes and not more than 60 minutes. Assess water volume as accurately as possible when calculating the amount of product needed for treatment to avoid under- or over- dosing.

To achieve a final concentration of 0.1ppm azamethiphos, 0.2g of the product must be added per cubic metre of water, i.e., 1 x 100g sachet treats 500 cubic metres.

Oxygenation must be provided during treatment, ideally continuously while the fish are crowded in the net and the tarpaulin is fitted to and removed from the cage. Vigorous oxygenation is recommended in the treatment cage. Where several cages are to be treated a large reservoir of oxygen bottles should be available.

Initial preparation of the treatment concentrate should take place in a dry and sheltered location, not more than 48 hours prior to treatment. Operators wearing suitable

equipment and protective clothing, (See Section 4.5.ii of the SPC), should place the number of water soluble bags of the product required for the dosage of an individual cage into a labelled screw-topped polyethylene container, together with a quantity of fresh water (1 litre or more of water for every 200g of the product). Screw the lid tightly onto the container and gently shake this intial dilution for up to 5 minutes.

When fish are ready to be treated, the diluted suspension of the product should be further diluted into approximately 200 to 1000 litres of sea water and gently stirred for 5 minutes. The polyethylene container, in which the first dilution was prepared, should be rinsed with sea water and the rinsing from this should be added to the sea water dilution tank. This latter mixture should then be immediately and carefully added to the cage by pouring or pumping the mixture into the water as evenly and efficiently as possible using the Bath Technique.

THE BATH TECHNIQUE

In this technique, the depth of the fish cage net is reduced to a known depth at the centre and a tarpaulin placed around the net so that it is totally enclosed. Ensure the base of the cage is not drooping when in the raised position as fish may congregate and come to harm. The volume of water to be treated should be estimated as accurately as possible, restrictive tarpaulins can be used to give a better management of water volume and reduce the amount of product needed depending on biomass of fish to be treated. Oxygenation should begin before the tarpaulin is fitted and continue until the tarpaulin is fully removed after treatment. Once the tarpaulin is in place the product (in the seawater dilution) should be immediately added. When the addition of product diluted in seawater to the tarpaulined cage is completed the treatment time begins. At the end of the treatment time the tarpaulin should be removed as quickly as possible allowing the exchange of clean seawater into the cage. The Bath Technique is designed to ensure the product is used in a totally enclosed volume of water.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

During a study exposing salmon to up to three times the recommended dose rate for up to 180 minutes no adverse events were observed during the treatment period. However, a small percentage of fish showed reversible changes in colour after the 180 minute treatment period and a very small percentage of fish showed an irreversible loss of equilibrium (at doses of two and three times the recommended treatment dose). It is reported that prolonged exposure to azamethiphos at concentrations in excess of

0.1ppm signs of stress, stupor and in extreme cases death may occur. If acute toxicity is seen the treatment should be stopped and oxygenation increased and the tarpaulin removed to aid recovery.

4.11 Withdrawal period(s)

Withdrawal period: 10 degree days.

5. PHARMACOLOGICAL PROPERTIES

ATC Vet Code: QP53AF17

Ectoparasiticides for topical use, organophosphorus compounds.

5.1 Pharmacodynamic properties

Organophosphorus insecticide, acting by anticholinesterase activity. Resistance to azamethiphos and other organophosphates has been demonstrated in some sea-lice populations. Although the mechanism is not fully elucidated, it is probable that resistance is due to a genetic alteration of the enzyme acetylcholinesterase influenced by natural selection.

5.2 Pharmacokinetic properties

Radiolabelled metabolism studies in salmon have shown azamethiphos residues in tissues and organs are depleted quickly and are below the limit of detection 1 hour after immersion for 60 minutes in a bath containing the maximum recommended dose.

Environmental properties

5.3

Azamethiphos is highly soluble in water (>1g/l) with a low octanol/water partition coefficient (log K_{ow}) of 1.0 g/ml. These characteristics indicate that azamethiphos will remain in the aqueous phase and will not enter the sediments. Azamethiphos has a moderate propensity to adsorb to suspended organic matter; however it is unstable in salt water, degrading with a half-life of <8.9 days (at 12°C), producing non-toxic transformation products. Hydrolytic degradation is the primary breakdown route but photolysis and microbial action will also hasten the process.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Lauryl Sulphate

Kaolin Light

Silicic Acid Precipitated

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale:

24 months

6.4 Special precautions for storage

Do not store above 25ºC

Store in the original unopened packaging

Store in a dry place

Store away from food, drink and animal feedingstuff

6.5 Nature and composition of immediate packaging

Heat-sealed PVA water soluble bag containing 20g or 100g of product contained in a sealed polyethylene lined paper sachet.

5 x 20g or 2 x 100g packages in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

The product is dangerous to fish and other aquatic organisms in the concentrated form. Do not contaminate ponds, streams, lochs or inlets with product or used packaging.

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

FVG (Fish Vet Group) Limited

22 Carsegate Road

Inverness

IV3 8EX

Scotland

8. MARKETING AUTHORISATION NUMBER

UK - Vm 33459/4001

9. DATE OF FIRST AUTHORISATION

10 December 2014

10. DATE OF REVISION OF THE TEXT

December 2014

Approved: **10/12/2014**