Proposed Registration Decision PRD2016-25

# Azamethiphos

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# Overview

## Proposed Registration Decision for Azamethiphos

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Azamethiphos Technical and Salmosan Vet containing the technical grade active ingredient azamethiphos, to control sea lice on Atlantic salmon.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Azamethiphos Technical and Salmosan Vet.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "… the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on azamethiphos, the PMRA will consider any comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on azamethiphos, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

## What Is Azamethiphos?

Azamethiphos, an organophosphate pesticide, is the active ingredient of Salmosan Vet, which works mainly by contact. Salmosan Vet is applied as a bath treatment to control pre-adult and adult sea lice (*Lepeophtheirus salmonis*) in farmed Atlantic salmon (*Salmo salar*).

## Health Considerations

### Can Approved Uses of Azamethiphos Affect Human Health?

**Salmosan Vet, containing azamethiphos, is unlikely to affect your health when it is used according to label directions.**

Potential exposure to azamethiphos may occur through the diet or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, azamethiphos was of slight to moderate acute toxicity via the oral route of exposure; consequently, the signal word and hazard statement "WARNING – POISON" are required on the label. It was of low acute toxicity via the dermal route, and slightly acutely toxic following inhalation exposure. Azamethiphos was not irritating to skin but was mildly irritating to eyes and caused an allergic skin reaction. Therefore, the hazard statements "EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the label of the technical product.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The end-use product, Salmosan Vet, was slightly acutely toxic via the oral and inhalation routes of exposure and was of low acute toxicity via the dermal route. It was minimally irritating to the eyes and skin. Salmosan Vet has potential to cause an allergic skin reaction, and therefore the hazard statement "POTENTIAL SKIN SENSITIZER" is required on the label for Salmosan Vet.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of azamethiphos to cause neurotoxicity, immuno-toxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the nervous system and bodyweight. It was not possible to completely characterize potential sensitivity of the young. The risk assessment takes this into account and is protective against the above-noted effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal tests.

**Residues in Water and Food**

**Dietary risks from food are not of a health concern.**

The dietary intake estimates (food alone) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most azamethiphos relative to body weight, are expected to be exposed to less than 2% of the acceptable daily intake. Dietary intake estimates from food plus drinking water were not calculated since there is no expectation of azamethiphos residues in drinking water from the proposed use (for example, farmed salmon). Based on these estimates, the chronic dietary risk from azamethiphos is not of concern for all population subgroups.

Acute dietary (food alone) intake estimates for the general population and all population subgroups were less than 8% of the acute reference dose, and are not of health concern. The highest exposed subpopulation was adults 50 years and older.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Fish residue trials conducted in a closed system treatment tank using azamethiphos on farmed salmon are acceptable. The MRL for this active ingredient can be found in the Science Evaluation section of this consultation document.

### Occupational Risks from Handling Salmosan Vet

**Occupational risks are not of concern when Salmosan Vet is used according to the proposed label directions, which include protective measures.**

Workers mixing, loading, or applying Salmosan Vet, as well as workers re-setting cage nets, entering water at treated sites, and cleaning and repairing equipment can come in direct contact with Salmosan Vet residues on the skin. Therefore, the label specifies that anyone mixing, loading, applying Salmosan Vet**,** and during clean-up and repair must wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks with chemical-resistant footwear, and a faceshield. The label also requires that workers do not enter treated cages for 12 hours after the treatment is completed. Taking into consideration these label statements, the number of applications and the exposure duration for handlers and workers, risks to these individuals are not a concern.

Bystander exposures are considered negligible, as treatments will not occur in swimming areas. Therefore, health risks to bystanders are not of concern.

## Environmental Considerations

### What Happens When Azamethiphos is Introduced into the Environment?

**When used according to label directions azamethiphos is not expected to pose risks of concern to the environment.**

Azamethiphos can enter the environment when it is used to control sea-lice on salmon in open ocean aquaculture net pens. Azamethiphos breaks down in water, in the presence of light and in the presence of microorganisms. Azamethiphos is not expected to remain in the environment for long periods of time, nor is it expected to move from the water into the sediment. Azamethiphos is unlikely to enter the atmosphere and be transported to areas far away from where it was applied. Azamethiphos is not expected to build up in the tissues of organisms.

Azamethiphos formed four major degradation products in control laboratory studies. Degradation products of azamethiphos are not expected to build up in the tissues of organisms.

When used according to the label directions, azamethiphos presents a negligible risk to birds, small mammals, fish, algae, earthworms, bees and invertebrates. The use of the end-use product, Salmosan Vet, may pose a risk to non-target aquatic invertebrates. To minimize potential risks to non-target aquatic invertebrates use restrictions such as buffer zones and minimum water depths will be proposed on the label.

## Value Considerations

### What Is the Value of Salmosan Vet?

**Salmosan Vet has value as it provides a new active ingredient to control pre-adult and adult sea lice (*Lepeophtheirus salmonis*), which are a major pest of farmed Atlantic salmon (*Salmo salar*).**

Sea lice are a significant and chronic problem in aquaculture and injuries to farmed Atlantic salmon caused by sea lice are an animal welfare concern. Untreated infestations of sea lice in farmed Atlantic salmon can lead to complete loss of fish stock. Salmosan Vet controls pre-adult and adult sea lice when applied as a bath treatment. Other available alternatives have use limitations such as they only control certain life stages or they can only be applied at certain water temperatures. Salmosan Vet has value as it can be used to control sea lice in situations where other products are not effective or cannot be used. Salmosan Vet may contribute to resistance management as it can be used in rotation with other sea lice control products.

## Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label Salmosan Vet to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

### Human Health

There is a concern with users coming into direct contact with Salmosan Vet on the skin or through inhalation of spray mists; therefore, anyone mixing, loading, applying Salmosan Vet, and during clean-up and repair must wear chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant-gloves, socks with chemical-resistant footwear, and a faceshield. The label also requires that workers do not enter treated cages for 12 hours after the treatment is completed.

### Environment

To minimize potential risks to non-target aquatic invertebrates and lobster held in active lobster holding facilities, use restrictions such as maximum number of tarped and skirted net pens that may be treated simultaneously, minimum water depths and no-use buffer zones of 1 kilometer down current from active lobster holding facilities as well as label statements to inform users of potential risks to the environment are required.

## Next Steps

Before making a final registration decision on azamethiphos, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please note that, to comply with Canada's international trade obligations, consultation on the proposed MRLs will also be conducted internationally via a notification to the World Trade Organization. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

## Other Information

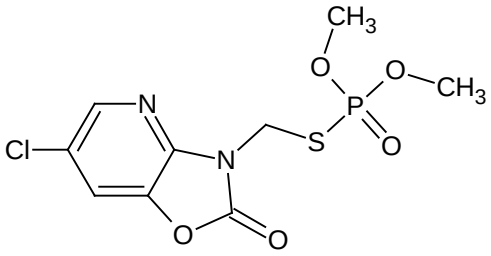
When the PMRA makes its registration decision, it will publish a Registration Decision on azamethiphos (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

# Science Evaluation

## Azamethiphos

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| Active substance | Azamethiphos |
| Function | acaricide |
| Chemical name | |
| 1. International Union of Pure and Applied Chemistry (IUPAC) | S-[(6-chloro-2-oxo-1,3-oxazolo[4,5-*b*]pyridin-3(2*H*)-yl)methyl] *O,O*-dimethyl phosphorothioate |
| 2. Chemical Abstracts Service (CAS) | S-[(6-chloro-2-oxooxazolo[4,5-*b*]pyridin-3(2*H*)-yl)methyl] *O,O*-dimethyl phosphorothioate |
| CAS number | 35575-96-3 |
| Molecular formula | $C_9H_{10}ClN_2O_5PS$ |
| Molecular weight | 324.7 |
| Structural formula |  |
| Purity of the active ingredient | 99.5 % |

### 1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

**Technical Product—Azamethiphos Technical**

| Property | Result |
|---|---|
| Colour and physical state | beige to light grey |
| Odour | weak aromatic |
| Melting range | 89°C |
| Boiling point or range | Not applicable for a solid |
| Specific Gravity | 1.60 |
| Vapour pressure at 20°C | 0.0049 mPa |
| Ultraviolet (UV)-visible spectrum | Absorption maxima at 230 and 295 nm, negligible absorbance was observed above 320 nm |

| Property | Result |
|---|---|
| Solubility in water at 20°C | 1.1 g/L |
| Solubility in organic solvents at 20°C | Solvent — Solubility (g/kg)<br>dichloromethane — 610<br>benzene — 130<br>methanol — 100 |
| *n*-Octanol-water partition coefficient ($K_{ow}$) | log $K_{ow}$ = 1.05 |
| Dissociation constant (p$K_a$) | p$K_a$ < 0 (molecule will be predominantly uncharged in the environmental pH range) |
| Stability (temperature, metal) | unstable in acid and alkali |

**End-Use Product—Salmosan Vet**

| Property | Result |
|---|---|
| Colour | light beige to beige |
| Odour | onion-like |
| Physical state | solid (powder) |
| Formulation type | WP (wettable powder) |
| Guarantee | 49.8% |
| Container material and description | PVA water soluble sachet inside a laminated pouch |
| Density | 0.10–0.20 g/cm$^3$ (bulk density) |
| pH of 1% dispersion in water | 4–7 |
| Oxidizing or reducing action | the product is expected to react with strong oxidizers |
| Storage stability | stable on accelerated storage at 54°C for 14 days |
| Corrosion characteristics | not corrosive to commercial packaging materials |
| Explodability | not expected to be explosive |

## 1.3 Directions for Use

Salmosan Vet is used to control pre-adult and adult sea lice in farmed Atlantic salmon when applied as a bath treatment with an application duration of 30 to 60 minutes at 0.2 ppm product (0.1 ppm azamethiphos) in well boats and fully enclosed tarped net pens, or at 0.3 ppm product (0.15 ppm azamethiphos) in open-bottomed skirted net pens.

## 1.4 Mode of Action

Azamethiphos is an organophosphate pesticide (IRAC Mode of Action Group 1) that affects the nervous system of the pest, causing paralysis and death. Organophosphate pesticides inhibit acetylcholinesterase, interfering with nerve function. Salmosan Vet is mainly active through contact.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

### 2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

### 2.3 Methods for Residue Analysis

A high performance liquid chromatography method with ultraviolet detection (HPLC-UV) was proposed for data gathering and enforcement purposes. This method fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in salmon muscle and skin. The proposed enforcement method was successfully validated in salmon matrices by an independent laboratory. Adequate extraction efficiencies were not demonstrated for salmon treated with radiolabelled azamethiphos, as residues present in edible fish (for example, muscle) were too low for further analysis. Furthermore, extraction solvents used in the method were similar to those used in the metabolism studies; thus, further demonstration of extraction efficiency with radiolabelled matrices is not required. For details, see Appendix I, Table 1.

## 3.0 Impact on Human and Animal Health

### 3.1 Toxicology Summary

Azamethiphos is an organophosphate insecticide. The mode of action is through the inhibition of the enzyme acetylcholinesterase in the central and peripheral nervous system. Enzyme inhibition, through phosphorylation, leads to accumulation of the neurotransmitter acetylcholine and signs of neurotoxicity.

A detailed review of the toxicological database for azamethiphos was conducted. The database contains a wide array of toxicology studies currently required for hazard assessment purposes. The majority of studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. In addition, results of toxicology studies reported in other regulatory documentation supplemented the assessment. The scientific quality of the data was good and overall, the database is considered adequate to define the majority of the toxic effects for the purpose of the current assessment.

Oral toxicokinetic studies in rats were available with radiolabelled azamethiphos using either single low or high dose, or repeated low dose administration. $^{14}$C-pyridine-labelled azamethiphos was well absorbed and rapidly metabolised and excreted within 24 hours. The major route of elimination was via the urine, with only minor amounts excreted via the feces and expired air. The excretion pattern was not significantly influenced by dose level or sex of the animal. Tissue

retention of administered $^{14}$C-pyridine-labelled azamethiphos was low. When the radiolabel was in the methylene group instead of the pyridine moiety, urine was also the predominant route of excretion and faecal elimination remained low. Elimination via expired air was approximately 35%. Tissue retention of radioactivity from the methylene-labelled azamethiphos, 6-7 days after oral administration, was high (approximately 20% of the administered dose), with detectable activities in the liver, kidneys, spleen, fat, muscle, ovary, testis, brain, and blood. The high radioactivity in tissues was assumed to be caused by the incorporation of radioactive $CO_2$, via the $C_1$-pool. The major metabolic pathway involved degradation to 2-amino-3-hydroxy-5-chloropyridine followed by glucuronic and sulphuric acid conjugation. No unchanged parent compound was detected in the excreta.

Azamethiphos was of slight to moderate acute toxicity in rats via the oral route of exposure. Clinical signs of toxicity resembled those of cholinergic poisoning and included dyspnea, sedation, exophthalmos, curved position, ruffled fur and tonic-clonic muscle spasms. Azamethiphos was of low acute toxicity in rabbits via the dermal route, and slightly acutely toxic following inhalation exposure in rats. Clinical signs including decreased activity, piloerection, salivation and piloerection were observed with inhalation exposure. It was mildly irritating to the eyes and minimally irritating to the skin of rabbits. Clinical signs including salivation and muscle spasms were observed in one strain of rabbits following instillation to eyes and application to the skin, and one rabbit died six days following instillation to the eye. Azamethiphos was not irritating to rabbit skin. In guinea pigs, negative results were obtained in a sensitization study using the Buehler protocol; however, positive results were observed in two studies using the Optimization protocol. In view of these results, azamethiphos is considered to be a potential skin sensitizer.

Salmosan Vet was slightly acutely toxic in rats via the oral and inhalation routes of exposure and was of low acute toxicity in rats via the dermal route. It was minimally irritating to rabbit eyes and skin. In the absence of a skin sensitization study with Salmosan Vet, this end-use product was considered to be a dermal sensitizer based on the findings for azamethiphos.

Regardless of the route of exposure, the primary effect observed in the azamethiphos database following repeated dosing was the inhibition of cholinesterase activity in plasma, erythrocyte and brain. In all studies, cholinesterase inhibition was the most sensitive endpoint and, when measured, was observed in all species at the dose levels that defined the lowest observed adverse effect level (LOAEL). Effects on body weight were also noted consistently throughout the azamethiphos database.

Following repeated oral dietary administration of azamethiphos to rats and dogs, cholinesterase activity was inhibited in erythrocytes and brain. Generally, the degree of inhibition increased with dose and duration of dosing. In studies conducted via the oral dietary and gavage routes, there were no overt cholinergic signs of intoxication.

In a 21-day dermal toxicity study in rabbits with azamethiphos, the decreases in cholinesterase activity that defined the LOAEL were accompanied by clinical signs of toxicity at the next highest dose, including dyspnea, tremors, diarrhea, sedation, and ruffled fur. The study was considered supplemental due to limitations in group size and sampling. In a 21-day inhalation

toxicity study in rats with Salmosan Vet, inhibition of cholinesterase activity (brain only) was observed at the lowest dose tested. A similar spectrum of clinical signs as noted following repeated dermal exposure with azamethiphos was observed at the next highest dose level. In addition, histopathological changes in the lungs and an increase in lung weight were observed.

Chronic dietary dosing in rats and mice with azamethiphos did not result in any evidence of oncogenicity. The effects noted following chronic dietary dosing in rats and mice were similar in nature to those reported following shorter durations of exposure. Decreased body weight gain was observed in both species and cholinesterase inhibition was observed in rats. Cholinesterase inhibition was not measured in mice. In mice, alterations in blood parameters, hematopoiesis in the spleen and liver, bone marrow hyperplasia and an increase in mucosal lesions in the gastrointestinal tract were also noted. In rats, an increased incidence of uterine distention and hydrometra was considered related to treatment.

The mutagenic potential of azamethiphos was investigated in an extensive battery of in vitro and in vivo tests. Results from in vivo studies were negative; however, mixed results were obtained in the in vitro test systems. Overall, azamethiphos was not considered genotoxic.

Azamethiphos produced no adverse effects on mating or reproduction in two dietary multigeneration reproduction studies in rats. Reductions in body weight and body weight gain were noted in the parental animals and offspring. Cholinesterase activity was measured in only one of the studies, and only in the first generation parental animals. Depression of erythrocyte cholinesterase activity was observed; however, brain cholinesterase activity was not affected and clinical signs of toxicity were not observed. In guideline oral gavage developmental toxicity studies in rats and rabbits, there were no adverse effects in the developing young at dose levels producing overt maternal toxicity. Delayed fetal ossification at maternally toxic dose levels was reported in both rats and Chinchilla rabbits in two additional supplemental oral gavage studies. There was no evidence of increased sensitivity of the young in any of the available studies; however, comparative measurements of cholinesterase activities in the young and adult animal were not available.

A 90-day oral gavage neurotoxicity study in rats yielded decreased erythrocyte cholinesterase activity as the most sensitive endpoint; brain cholinesterase activity was not affected. There were no treatment-related neuropathological findings or effects on measured Functional Observational Battery (FOB) parameters. The study was considered supplemental due to limitations in the FOB and reporting. Azamethiphos did not produce delayed neurotoxicity in hens; however, neurotoxic esterase was not measured in the study.

Although the database is lacking an acute neurotoxicity study, developmental neurotoxicity (DNT) study and a comparative cholinesterase assay (CCA) in young and adult animals, current knowledge of the organophosphate class of pesticides indicates that, typically, the CCA is the most pivotal study in risk assessment to address concerns regarding susceptibility of the young. Consequently, it was considered appropriate to apply a database uncertainty factor of 3-fold in the risk assessment.

Additionally, consideration was given to the fact that the end-use product is restricted for use only by licenced Pest Control Operators and, more importantly, that exposure is anticipated to be low. It should be noted, however, that the requirement to fill the identified gaps in the toxicology database will be revisited for any future submissions involving azamethiphos.

Results of the toxicology studies conducted on laboratory animals with azamethiphos and its associated end-use product are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

**Incident Reports**

As of 1 February 2016, there was one minor animal incident involving azamethiphos and (Z)-9-tricosene in which it was reported that a dog ingested a fly bait product and then experienced diarrhea and vomiting. This incident was considered to be possibly associated with the reported exposure; however, it did not affect the risk assessment.

### 3.1.1 *Pest Control Products Act* Hazard Characterization

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

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, developmental toxicity studies in rats and rabbits and two reproductive toxicity studies in rats were available for azamethiphos. In addition, supplemental developmental toxicity studies in rats and rabbits were available. With respect to potential pre-and post-natal toxicity, the available studies provided no indication of increased susceptibility of the young; however, cholinesterase inhibition was not assessed in offspring in the reproduction studies, or in dams and their fetuses in the developmental toxicity studies. In the reproduction studies, decreases in body weight and/or body weight gain were observed in both parental animals and offspring. In the guideline developmental toxicity studies, effects in the parental animals included clinical signs and decreased body weight/body weight gain or body weight loss in both rats and rabbits, and mortality in rabbits. No effects on the developing fetuses were observed. In the supplemental developmental toxicity studies, maternal toxicity was evident as increased mortality and decreased food consumption and bodyweight gain in rabbits and decreased food consumption in rats. In these studies, delayed fetal ossification was reported in both rats and rabbits at the same dose levels at which the maternal effects were observed.

As noted above, the database for azamethiphos is lacking several studies, notably, a DNT study and a CCA in young and adult animals. However, based on current knowledge of the organophosphate class of pesticides, typically, the CCA is pivotal in addressing concerns regarding potential sensitivity of the young. In its absence a database uncertainty factor of 3-fold was applied for risk assessment.

Consideration was given to the fact that the end-use product is restricted for use only by licenced Pest Control Operators and, more importantly, that exposure is anticipated to be low. As residual concern for potential sensitivity of the young is subsumed by the application of a database uncertainty factory, the *Pest Control Products Act* factor was reduced to 1-fold.

### 3.2 Determination of Acute Reference Dose

To estimate acute dietary risk, the 52-week dietary dog study with a no observed adverse effect level (NOAEL) of 0.24 mg/kg bw/day was selected for risk assessment. This NOAEL was based on a depression of erythrocyte cholinesterase activity at the next highest dose (2.72 mg/kg bw/day) and above. Although depression of erythrocyte cholinesterase activity was not measured earlier than week two in the study, this effect is known to result following a single exposure to an organophosphate compound, and is not dependent upon repeated exposure. As such, the NOAEL is considered relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. In addition, for the reasons noted above, a database uncertainty factor of 3-fold was applied to account for the absence of a CCA in young and adult animals. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is therefore 300.**

The Acute Reference Dose (ARfD) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.24 \text{ mg/kg bw}}{300} = 0.0008 \text{ mg/kg bw of azamethiphos}$$

### 3.3 Determination of Acceptable Daily Intake

To estimate the risk following repeated dietary exposure, the 52-week dietary dog study with a NOAEL of 0.24 mg/kg bw/day was selected for risk assessment. This NOAEL was based on a depression of erythrocyte cholinesterase activity at the next highest dose (2.72 mg/kg bw/day) and above. This study provides the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. In addition, as noted above, a database uncertainty factor of 3-fold was applied to account for the absence of a CCA in young and adult animals. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The CAF is therefore 300.**

The Acceptable Daily Intake (ADI) is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{0.24 \text{ mg/kg bw/day}}{300} = 0.0008 \text{ mg/kg bw/day of azamethiphos}$$

**Cancer Assessment**

There was no evidence of oncogenicity; therefore, a cancer risk assessment was not necessary.

## 3.4 Occupational and Residential Risk Assessment

### 3.4.1 Toxicological Endpoints

Occupational exposures to Salmosan Vet are characterized as short-term duration for fish farm operators to intermediate-term duration for well boat operators, and are via the dermal and inhalation routes.

**Short- and intermediate-term dermal exposure:**

Although a 21-day dermal toxicity study in rabbits was available, the study was deemed to be supplemental due to limitations in group size and sampling, and therefore it was not considered further in endpoint selection. For short- and intermediate-term occupational exposures via the dermal route, the NOAEL of 0.24 mg/kg bw/day from the 52-week dietary dog study was selected for risk assessment. This NOAEL was based on a depression of erythrocyte cholinesterase activity at the next highest dose (2.72 mg/kg bw/day) and above. This study provides the lowest NOAEL in the database and is based upon the most sensitive endpoint (cholinesterase inhibition). The target Margin of Exposure (MOE) for these scenarios is 300, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, and an additional database uncertainty factor of 3-fold as outlined above. The selection of this study and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

**Short- and intermediate-term inhalation exposure:**

A repeat-dose inhalation toxicity study conducted with azamethiphos was not available. For short- and intermediate-term exposures via the inhalation route, the NOAEL of 0.24 mg/kg bw/day from the 52-week dog study was considered the most appropriate for use in the risk assessment. This NOAEL was based on a depression of erythrocyte cholinesterase activity at the next highest dose (2.72 mg/kg bw/day) and above. This study provides the lowest NOAEL in the database and is based upon the most sensitive endpoint (cholinesterase inhibition). The target MOE for these scenarios is 300, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, and an additional database uncertainty factor of 3-fold as outlined above. The selection of this study and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

#### 3.4.1.1 Dermal Absorption

The study was considered to be conducted in an acceptable manner. The stock and dilutions were made with blank Alfacron 10WP. The low dose (9.6µg/cm$^2$), at the time of the review, was considered higher than what would be experienced in the field (fish farms/aquaculture sites).

Skin washes were conducted after each of the exposure periods, but no monitoring was conducted beyond the exposure periods (i.e. rats were sacrificed). Dermal absorption was greater in the 24-hour exposure period than in the 10-hour exposure. Therefore, residue remaining in the skin from the application site (skinbound residue) after a wash is considered to be available for

absorption. Combining the absorbed dose (20%) with the skinbound residue (22%) is a total of 42% for the 10-hour exposure. Also, at the 2, 4, and 24-hour exposure durations, skin from the application sites contained levels of residue that were not significantly different, suggesting that approximately 20% of the dose would be skinbound residue and would be available for absorption. Considering the doses applied, exposure durations, radioactivity recoveries, and skinbound residue, a dermal absorption value of 42% is considered appropriate for risk assessment purposes.

### 3.4.2 Occupational Exposure and Risk

#### 3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Salmosan Vet during mixing, loading and application. Dermal and inhalation exposure estimates for workers were generated from the Pesticide Handlers Exposure Database (PHED).

Exposure of fish farm operators mixing, loading and applying Salmosan Vet is expected to be short-term duration for fish farm operators and intermediate-term duration for well boat operators, and are via the dermal and inhalation routes. Exposure estimates were derived for mixers/loaders/applicators applying Salmosan Vet using closed pumping equipment for large cages and on well boats, or open pouring methods for large cages. The risks of treating multiple small cages, using pumping equipment or open-pouring is considered to be over-estimated by the skirted treatment of two large cages. The exposure estimates are based on mixers/loaders/applicators wearing chemical-resistant coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Dermal exposure was estimated by coupling the PHED unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight. Exposure estimates were compared to the NOAEL to obtain the MOE. The target MOE is 300. See Table 3.4.2-1 for details of the assessment.

**Table 3.4.2-1 Mixer/Loader/Applicator Risk Estimates for handling Salmosan Vet**

| **PHED unit-exposures** | | | | **Amount of active (µg/kg a.i.)** | |
|---|---|---|---|---|---|
| | | | | **Dermal [a]** | **Inhalation [b]** |
| Wettable powder, in water soluble packaging (WSP) closed mixing and loading (PHED Scenario 6a) | | | | 5.18 | 0.18 |
| All liquids, open mixing and loading (PHED scenario 3a) | | | | 29.09 | 1.6 |
| **Maximum application rate (mg a.i./m$^3$)** | **Number and cage size (circumference)** | **Application method** | **Active ingredient handled per day [c] (kg a.i.)** | **Daily Exposure [d,e] (mg a.i./kg-bw/day)** | **MOE [f] (Target = 300)** |
| Wettable powder, WSP mix-load, closed transfer [g] | | | | | |
| 150 | 2 × 150 m | skirt | 3.22 | 9.48 × 10$^{-5}$ | 2530 |
| 100 | 2 × 150 m | tarpaulin | 2.15 | 6.33 × 10$^{-5}$ | 3790 |
| | 3 × 150 m | well boat | 0.504 | 1.48 × 10-5 | 16200 |

| Wettable powder, WSP mix-load + open-pour liquid mix-load (open transfer) [h] | | | | | |
|---|---|---|---|---|---|
| 100 | 2 × 150 m | tarpaulin | 2.15 | $4.35 \times 10^{-4}$ | 553 |
| 150 | 2 × 150 m | skirt | 3.22 | $6.51 \times 10^{-4}$ | 368 |

[a] Worker wearing chemical-resistant coveralls over long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant footwear;
[b] light work;
[c] A maximum of two net pens (cages) of maximum 150 m circumference, at dry-up depth of 6 m are expected to be treated by skirt or tarpaulin methods (expected to address more than two pens of less than 150 m treated in a day); 3-150 m circumference pens treated by a well boat per day;
[d] Dermal absorption value of 42%;
[e] Daily exposure (mg a.i./kg bw/day) = PHED unit exposures ((dermal × absorption) + inhalation) × amount handled per day (kg a.i.) × 0.001 mg/µg / body weight (80 kg);
[f] MOE = Oral NOAEL of 0.24 mg/kg bw/day ÷ Exposure (mg /kg bw/day). Target MOE is 300; (rounded, 3 sig. digits)
[g] Pre-mixing with a 1 L of water in closed container followed by further dilution into a 500 L dosing tank (continuous agitation) and pump application to cages or treatment wells;
[h] The expected scenario is the placement of WSP into pre-dilution water followed by open mixing with further dilution water, and open pouring or mechanical pumping into cages.

While the treatment scenario can be variable (number of workers, type of treatment, application rate, number and size of cages, etc.), operator exposures while wearing the required personal protective equipment (PPE) are not considered to be of concern when the WSP packs are pre-diluted and directly added to the dosing tanks of the well boat, or mixed with larger dilution water volumes before open or closed transfer into tarpaulin-enclosed or skirted cages. Furthermore, the risks of treating multiple small cages, using pumping equipment or open-pouring is considered to be over-estimated by the skirted treatment of two large cages, and therefore, are not of concern.

#### 3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Aquaculture Sites

There is potential for exposure to workers entering treated aquaculture sites. The duration of exposure is considered to be short-term, and the primary route of exposure would be through the dermal route. Given the nature of the activities performed, dermal contact with treated water should not be of concern. Inhalation is not considered as there is no mist or vapour associated with the turnover of treatment and rinse water, and azamethiphos is not considered to be volatile.

### 3.4.3 Residential Exposure and Risk Assessment

#### 3.4.3.1 Bystander Exposure and Risk

Sea cages being treated are isolated, and in open water, which does not allow direct contact with the general public or recreational areas during application. In addition, a label statement "do not use treated seawater for recreational activities until post-treatment tidal flushing occurs" is present on the label to mitigate post-application exposures. Bystander exposure is not considered to be a concern based on the dilution effect of a large volume of seawater, flushing from tidal movement, and currents.

## 3.5 Exposure from Drinking Water

### 3.5.1 Concentrations in Drinking Water

As the proposed use for the end-use product Salmosan Vet is for direct application to ocean water, human exposure of azamethiphos from drinking water is not anticipated.

## 3.6 Food Residues Exposure Assessment

### 3.6.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in salmon tissues is azamethiphos. The data gathering/enforcement analytical method is valid for the quantification of azamethiphos residues in salmon matrices. Based on a weight-of-evidence approach, it was concluded that residues were stable in frozen salmon matrices for the short frozen storage interval of less than 2 months. The salmon residue trials using Salmosan 50WP end-use product containing azamethiphos conducted in a closed system treatment tank under approved and exaggerated conditions (for example, treatment rate and withholding period) are sufficient to support the proposed maximum residue limit.

### 3.6.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™).

#### 3.6.2.1 Chronic Dietary Exposure Results and Characterization

The following criterion was applied to the basic chronic analysis for azamethiphos: residues in fish at the MRL level which cover salmon. The basic dietary exposure for food use (alone) for the total population, including infants and children, and all representative population subgroups is less than 2% of the ADI. Aggregate exposure from food and drinking water was not conducted since there is no expectation of azamethiphos in drinking water as the current use is for treatment of sea lice in farmed salmon.

#### 3.6.2.2 Acute Dietary Exposure Results and Characterization

The following assumption was applied to the basic acute analysis for azamethiphos: residues in fish at the MRL level which cover salmon. The basic acute dietary exposure (food alone) for the supported use of azamethiphos on farmed salmon is less than 8% of the ARfD for all population subgroups ($95^{th}$ percentile, deterministic).

### 3.6.3 Aggregate Exposure and Risk

There is no expectation of azamethiphos in drinking water from the use on farmed salmon for the control of sea lice. As such, no aggregation of dietary exposure from food and drinking water is required. As there are no recreational uses, aggregation of dermal and dietary exposure is also not required.

### 3.6.4 Maximum Residue Limits

**Table 3.6.4-1 Proposed Maximum Residue Limits**

| Commodity | Recommended MRL (ppm) |
|---|---|
| Fish | 0.05 |

For additional information on this MRL in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in fish matrices, analytical methodology, fish residue trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

## 4.0 Impact on the Environment

### 4.1 Fate and Behaviour in the Environment

In the aquatic environment, oceanic dispersion is the primary and most important route of dissipation for azamethiphos. Azamethiphos can be transformed by aerobic and anaerobic microorganisms as well as photolysis and hydrolysis. Azamethiphos is not considered to be persistent in the marine environment. Azamethiphos is not expected to partition or bind to sediment or bioaccumulate in aquatic or terrestrial organisms. Azamethiphos is not expected to volatilize from water. Under field conditions, aquatic oceanic dispersion studies demonstrated that azamethiphos disperses very quickly and demonstrated little vertical movement downward in the water column when the tarped net pen and horizontal discharge well boat methods were used and moderate vertical movement downward in the water column when the skirted net pen and angled or vertical discharge well boat methods were used.

Four major transformation products were detected in laboratory studies: monomethyl ester CGA-18809, CGA-55016, CGA-51236 and GS-36533. All four major transformation products are expected to disperse faster than they are formed. All four major transformation products are also anticipated to not meet TSMP track 1 criteria.

Environmental fate data for azamethiphos are summarized in Appendix I, Table 7. The chemical names and structures of azamethiphos transformation products formed in the environment, as well as a summary of their occurrence in environmental fate studies, are presented in Appendix I, Table 8.

### 4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using models which take into consideration the application rate(s), chemical properties and

environmental fate properties of the pesticide. Ecotoxicology information includes short-term and long-term toxicity data for various organisms or groups of organisms from aquatic habitats including invertebrates, vertebrates, and algae. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum total application rate) and sensitive toxicity endpoints. In the case of azamethiphos, the screening level risk assessment was conducted by assuming that non-target organisms would be exposed to the target application rate of 0.15 mg/L azamethiphos for a period of time ranging from 1 hour to 10 days depending on the ecotoxicological end-point. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as oceanic dispersion) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

### 4.2.1 Risks to Terrestrial Organisms

The use pattern for azamethiphos is either by direct application to a tarped or skirted aquaculture net pen or by application of the product into a well boat where the treatment water is then discharged directly into the ocean by flushing jets. Azamethiphos is not anticipated to volatilize from water, nor is it anticipated to persist in the aquatic environment. Azamethiphos is also not anticipated to bioaccumulate, bioconcentrate or biomagnify. Exposure to terrestrial organisms is therefore anticipated to be negligible. The use of azamethiphos will pose a negligible risk to non-target terrestrial organisms due to a lack of potential exposure.

### 4.2.2 Risks to Aquatic Organisms

A risk assessment for azamethiphos and its transformation products was conducted for marine aquatic organisms. A summary of aquatic toxicity data for azamethiphos is presented in Appendix I, Table 9.

It was determined that the transformation products will undergo extremely rapid dilution rates in a period of less than 3 hours. These dilution rates far exceed the rates at which the transformation products will be produced. As such, it was determined that there would be negligible exposure to non-target organisms from any of the transformation products of azamethiphos. The structures of the transformation products were ran though the U.S. Environmental Protection Agency's EPI

suite model in order to determine their log $K_{ow}$ values. It was determined that: the log $K_{ow}$ of the four transformation products ranged from 0.69 to 3.79. Due to the calculated $K_{ow}$ values, the transformation products are therefore not anticipated to bind or partition to sediment. In addition based on the half-life of 8.9 days for azamethiphos and dispersion rates of approximately 100 over the first few hours post release, it is anticipated that the dilution of the transformation products will exceed their rates of formation by several orders of magnitude. The transformation products therefore pose a negligible risk to non-target marine organisms.

For acute toxicity studies, uncertainty factors of 1/2 and 1/10 the $EC_{50}$ ($LC_{50}$) are typically used for aquatic plants and invertebrates, and fish species, respectively, when calculating RQs. No uncertainty factors are applied to chronic NOEC endpoints. For groups where the LOC is exceeded (i.e. RQ $\geq$1), a refined Tier 1 assessment was conducted to determine risk resulting from oceanic mixing from skirted and tarped net pens, and well boats for both pelagic and benthic non-target organisms separately. Screening level RQs for azamethiphos were calculated based on the highest maximum skirted application rate of 15 mg a.i./L. The refined risk assessment was conducted using toxicity end-points for which the exposure period is closer in line with the length of exposure anticipated upon release from a skirted net pen, a tarped net pen or a well boat. Notably, 5 × 1-hour pulse doses for pelagic invertebrates and 9 × 30-minute pulse doses for benthic invertebrates.

The 5 × 1-hour pulse dose exposure scenario was designed to simulate a pelagic non-target organism being exposed to multiple treatment plumes over the course of several days for one hour in duration per plume. The study was conducted in a way that resulted in a total exposure time of 5 hours spread out over the course of 5 days. This type of exposure scenario seeks to mimic the exposure conditions that may happen during the course of a farm site treating multiple net pens over the course of 5 days or the scenario of an organism traveling from one farm site conducting treatments to an adjacent farm site also conducting treatments over the course of several days. Pelagic non-target organisms tend to be relatively mobile compared to their benthic counterparts and can either actively travel great distances from swimming, such as in the case of fish and marine mammals, or travel passively by moving with the prevailing current. Pelagic organisms therefore have the potential to travel from one farm site to an adjacent farm site over the course of several days. The likelihood of a pelagic organism being exposed to multiple treatment plumes from the same farm site is less than their benthic counterparts; however, it was determined that the potential for a pelagic organism to remain in the vicinity of a farm site treating multiple cages over the course of several days could not be ruled out.

The 9 × 30-minute pulse dose exposure scenario was designed to simulate a benthic non-target organism being exposed to multiple treatment plumes over the course of several days for 30 minutes in duration per plume. The study was conducted in a way that resulted in a total exposure time of 4.5 hours spread out over the course of 3 days. This type of exposure scenario seeks to mimic the exposure conditions that may happen during the course of a farm site treating multiple net pens over the course of 3 days. Benthic non-target organisms tend to be less mobile than their pelagic counterparts and are not anticipated to travel significant distances towards or away from a given farm site over the course of several days. Furthermore, in the case of active lobster holding facilities, it is assumed that the benthic adult lobsters are not mobile at all as they will be in holding cages and therefore could be exposed to multiple treatment plumes from a

farm site that is up-current over the course of the farm site's net pen treatments. The 30 minute exposure time seeks to approximate the amount of time required for a given treatment plume to pass through a given area.

The refined risk assessment also took into consideration the rapid dispersion of azamethiphos over the course of the first hour post release and was conducted using the EEC of azamethiphos after 1-hour post release from tarped and skirted net pens and the 50 minute post release EEC from well boats.

It was determined through pelagic field dye dispersion studies, that azamethiphos rapidly disperses over the first hour post release, decreasing in concentration by a factors of approximately 100 within the first hour for skirted and tarped net pens and by a factor of approximately 3000 in the first hour in the case of a well boat treatment. The refined risk assessment for pelagic non-target organisms was conducted with both the 90$^{th}$ percentile 1-hour pelagic water column EEC as well as the mean 1-hour pelagic water column EEC. Using the 1-hour EEC also provided an additional advantage with respect to coinciding with the 1-hour pulse dose exposure scenario of the ecotoxicity end-points used in the pelagic risk assessment. In the case of the well boats, the 50-minute EEC was chosen as a conservative EEC over the 1-hour as the determination of the 1-hour EEC was not possible with the available well boat dispersion data.

It was also determined that azamethiphos decreases in concentration with increased water depth depending on the treatment method being used. As such, the refined risk assessment for benthic organisms took into consideration this decrease in concentration based on water depth and was conducted using the maximum estimated EEC for water depths of 10, 20 and 30 meters.

Various different EEC scenarios were developed based on the different application methods for azamethiphos, notably two skirted net pens being treated simultaneously, 2 tarped net pens being treated simultaneously, a single skirted net pen being treated at a time, a single tarped net pen being treated at a time and the various types of well boats currently being used. Scenarios with higher EEC's such as two overlapping skirted net pen plumes resulting from 2 skirted net pens being released at the exact same time were examined first as they represent the highest anticipated EEC. EEC's based on water depth for the various application methods were also calculated and separate risk assessments conducted based on the application method and the depth of the water at the time of treatment.

The calculated RQs for azamethiphos are summarized in Appendix I, Tables 10-19.

**Invertebrates**

Azamethiphos is very highly toxic to marine invertebrates on an acute and chronic exposure basis. The ecological database used for the risk assessment of azamethiphos to non-target invertebrates spanned a large number of species. Not only was there a significantly high number of species tested and reviewed but also a high number of different exposure times and exposure scenarios for certain invertebrate species, notably, those species which were identified as being the most sensitive to azamethiphos. In all, 32 different ecotoxicological end-points for invertebrates were reviewed and incorporated into the risk assessment for azamethiphos. The

RQs for marine invertebrates resulting from exposure to azamethiphos exceeded the LOC at the screening level. The use of azamethiphos, therefore, has the potential to pose a risk to marine aquatic invertebrates. The risk to marine invertebrates was further characterized by looking at exposure from oceanic dispersion as well as ecotoxicological end-points from pulse dose exposure scenarios. Separate refined risk assessments were conducted for pelagic invertebrates and benthic invertebrates.

**Pelagic invertebrates**

The refined risk assessment for pelagic invertebrates was conducted with a 5 × 1-hour pulse $LC_{50}$ toxicity end-point conducted on lobster larvae and combined with the 1-hour post release EEC of two overlapping skirted net pen treatments, a single skirted net pen treatment, two overlapping tarped net pen treatments and a well boat treatment conducted with a well boat with horizontally mounted flushing jets. Well boats with 45 degree angled flushing jets and vertical flushing jets were not considered during the risk assessment for pelagic invertebrates as the EEC's calculated with the horizontal flushing jets represent the highest anticipated EEC in the pelagic water column following a well boat treatment. Overlapping plumes from the skirted net pen treatment represent the highest overall EEC resulting from the use of azamethiphos, followed by overlapping tarped net pen plumes, a single skirted net pen plume and a single tarped net pen plume.

The LOC of 1 for pelagic marine invertebrates was slightly exceeded during the refined risk assessment of 2 overlapping skirted net pens (RQ = 1.5). The following label statement is required on the product label to mitigate the risk from two overlapping skirted net pen treatments: "DO NOT treat more than 1 skirted net pen simultaneously." will be required on the end-use product label for azamethiphos.

The RQ for pelagic marine invertebrates was equal to the LOC of 1 during the refined risk assessment of 2 overlapping tarped net pens. The following label statement is required on the product label in order to mitigate the risk from more than 2 overlapping tarped net pen treatments: "DO NOT treat more than 2 tarped net pens simultaneously".

The LOC of 1 for pelagic marine invertebrates was not exceeded during the refined risk assessment of a single skirted net pen (RQ = 0.75) treatment or the well boat application method (RQ = 0.2). A conservative buffer zone of 1 km down current from active lobster holding facilities is required on the azamethiphos end-use product label to protect lobster being held in active lobster holding facilities. The 1 km buffer zone is conservative as it is anticipated that the concentration of azamethiphos in the marine environment decreases to the 1-hour EEC used in the refined risk assessment within approximately 400 meters of the treatment site.

**Benthic invertebrates**

For benthic invertebrates the refined risk assessment was conducted with a NOEC toxicity end-point derived from 9 × 30-minute pulse dose exposures conducted on adult lobster and combined with the maximum EEC for a given water depth for skirted net pens, tarped net pens, well boats with horizontal discharge jets, well boats with 45 degree angled discharge jets and well boats with 90 degree vertical discharge jets. The NOEC was based on survival, molting, mating, behaviour, cement gland development and reproduction.

The LOC of 1 for benthic marine invertebrates was exceeded during the refined risk assessment for skirted net pens when the water depth at time of treatment was 10 meters or less. The LOC of 1 was only slightly exceeded when the water depth at time of treatment was 20 meters. The LOC of 1 was not exceeded at a water depth of 30 meters. Although a risk assessment was only conducted every 10 meters, due to the LOC of 1 being only slightly exceeded at the 20-meter depth and given the conservative nature of this risk assessment using only the maximum EECs, it is anticipated that skirted net pen treatments at water depths greater than 20 meters will pose a negligible risk to benthic invertebrates. The following label statement is required on the end-use product label in order to mitigate the risk from skirted net pen treatments conducted in water depths of 20 meters or less: "DO NOT apply to skirted net pens in water depths of 20 meters or less".

The LOC of 1 for benthic marine invertebrates was exceeded during the refined risk assessment for tarped net pens when the water depth at time of treatment was 10 meters or less. The LOC of 1 was not exceeded when the water depth at time of treatment was 20 meters or greater. Although a risk assessment was only conducted every 10 meters, based on the rapid decline of the RQs in function of water depth and due to the conservative nature of this risk assessment using only the maximum EECs, it is anticipated that tarped net pen treatments at water depths greater than 10 meters will pose a negligible risk to benthic invertebrates. The following label statement is required on the end-use product label in order to mitigate the risk from tarped net pen treatments conducted in water depths of 10 meters or less: "DO NOT apply to tarped net pens in water depths of 10 meters or less"

A risk assessment was not conducted for benthic marine invertebrates for well boats with a horizontal discharge jet as azamethiphos was not detected at water depths of 10 meters or greater when this type of horizontal flushing jet was employed. Azamethiphos therefore poses a negligible risk to benthic invertebrates when used with a well boat with a horizontal discharge pipe.

The LOC of 1 for benthic marine invertebrates was exceeded during the refined risk assessment for well boats with 45 degree and 90 degree angled discharge jets at water depths of 10 meters and only slightly exceeded at water depths of 20 and 30 meters. Although the LOC of 1 was slightly exceeded at the 20-meter and 30-meter depths, the LOC was calculated using the maximum EEC for that water depth and it is anticipated that this maximum concentration will decrease rapidly over time. Due to the conservative nature of this risk assessment using only the maximum EECs it is anticipated that well boats with 45 degree angled discharge jets that discharge their treatment water at waters depths greater than 20 meters will pose a negligible risk to benthic invertebrates.

The following label statement is required on the end-use product label in order to mitigate the risk from well boats with 45 degree angled discharge jets: "DO NOT flush treatment water from a well boat with a 45 degree or 90 degree angled flushing pipe in water depths of 20 meters or less."

**Marine Fish**
Azamethiphos is moderately toxic to highly toxic to marine fish on an short-term exposure basis. The ecological database used for the risk assessment of azamethiphos to non-target fish spanned a large number of species. Twelve different ecotoxicological end-points for freshwater and marine fish were reviewed and incorporated into the risk assessment. Even though the use pattern for azamethiphos is for saltwater aquaculture only, the fresh water species were included simply to increase the robustness of the risk assessment and to provide aditional information on interspecie sensitivity. The LOC of 1 was exceeded at the screening level for only 2 species (rainbow trout and brown trout). The risk to marine fish was further characterized by looking at exposure from oceanic dispersion. When the 1-hour post release EEC of two overlapping skirted net pens was considered, the refined RQs for marine fish were 0.2 and 0.1, and therefore, the LOC of 1 was not exceeded. The use of azamethiphos is therefore expected to pose a negligible risk to marine fish.

**Freshwater Fish and Amphibians**
The use of azamethiphos is expected to pose a negligible risk to freshwater fish and amphibians due to a lack of potential exposure.

**Marine mammals**
Due to the fact that azamethiphos is not persistent in the environment and the very low potential for azamethiphos to enter the food chain, azamethiphos is expected to pose a negligible risk to marine mammals.

**Algae**
Azamethiphos was moderately toxic to algae; however, the calculated RQs for algae did not exceed the LOC at the screening level. The use of azamethiphos is therefore expected to pose a negligible risk to algae.

### 4.2.3 Further Risk Characterization

It was determined in Section 4.2.2 that non-target pelagic invertebrates may be at risk from the use of azamethiphos during the first hour post release from a tarped net pen, a skirted net pen or a well boat treatment. This first one hour coincides with a distance of approximately 400 meters from the original point of release. As mentioned in Section 4.2, toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level). In the case of the risk assessment for azamethiphos, an adjustment to the toxicity end-point to account for potential differences in species sensitivity was not required as the PMRA had access to numerous and varied marine invertebrate species well beyond the data requirements for non-target marine invertebrates which are normally required to support a registration. For the risk assessment conducted on azamethiphos, the PMRA had access to a robust marine invertebrate

toxicity database. During the screening level risk assessment, it was determined that azamethiphos poses a negligible risk to oysters and gastropods. The screening level risk assessment identified only a slight risk to mussels. The screening level risk assessment determined that azamethiphos may pose a risk to copepods, amphipods, shrimp and lobster. Lobster was identified as the most sensitive species of all the invertebrate species tested.

Several levels of conservatism were built into both the screening level risk assessment as well as the refined risk assessment for all species tested. The first level of conservatism for many of the species tested was the fact that many of the end-points were based off of either a 24 to 96 hour exposure period. In the case of lobster larvae and adult lobster, the PMRA had access to more non-conventional exposure scenarios such as 5 × 1-hour pulse doses as well as 9 × 30-minute pulse doses. The PMRA then further took the acute toxicity $LC_{50}$ end-point from these exposure scenarios and applied an adjustment factor of 2. In other words, the PMRA chose to artificially increase the sensitivity of the risk assessment two fold by applying this adjustment factor. In general many pelagic invertebrates have a very limited range and move in the pelagic water column along with the prevailing current. Although a probabilistic analysis on the likelihood of the same invertebrate remaining in a treatment plume for 24 to 96 hours or encountering five different plumes of azamethiphos was not conducted, the PMRA concluded that the use of these exposure scenarios for a given non-target individual can be seen as highly conservative as it is unlikely that a given invertebrate would likely remain in a treatment plume for 24 to 96 hours, would encounter five different plumes of azamethiphos or find itself within any of the simulated five plumes for an entire hour for each and every plume.

As lobster larvae was determined to be the most sensitive non-target invertebrate, risk mitigation applied to mitigate the risks towards lobster larvae will inherently also mitigate the risks towards other less sensitive non-target invertebrate and vertebrate species. Based on the multiple levels of conservatism built into the risk assessment for non-target pelagic invertebrates, including the over-estimated exposure time, the application of the two-fold adjustment factor to the sensitivity of the $LC_{50}$ end-points and combined with the unlikelihood that a given individual will find itself in five different treatment plumes for a duration of 1 hour, the PMRA concludes that population level effects on invertebrate communities are not anticipated as a result from the use of azamethiphos.

During the registration of azamethiphos for emergency use, the following risk mitigation statements appeared on the end-use product label (Salmosan 50WP) in order to minimize potential risks to non-target aquatic invertebrates and lobster held in active lobster holding facilities.

> "For sea cage with full open bottom (skirted) or enclosure tarpaulin treatments, a maximum of two net pens may be treated per aquaculture farm site per day. For use with a fully enclosed treatment well boat, a maximum of three net pens may be treated per aquaculture farm site per day.
>
> To prevent toxic effects on local aquatic organisms and to prevent toxic waste of azamethiphos to be washed into the littoral zone, treatment should be performed at outgoing tide or during periods with a local outgoing current.

Product is designed for the treatment of fish; however, at levels greater than the treatment dose, the product could be harmful to fish and aquatic life."

These statements were originally placed on the registration of Salmosan 50WP for emergency use as additional conservative risk mitigation measures in the absence of a full review of the on-going studies being conducted by the Department of Fisheries and Oceans and incorporation of these studies into the risk assessment. The PMRA has now completed the full review of azamethiphos for use in aquaculture and has concluded that these statements do not represent increased risk mitigation to non-target organisms when compared to the revised risk mitigation statements being proposed for Salmosan Vet.

The first risk mitigation statement on the emergency use registration label of Salmosan 50WP focused on the maximum number of treatments allowed per farm site per day. However the current full risk assessment identified that non-target organisms will be at the greatest risk within the first hour post treatment from two overlapping net pen plumes. As such, the risk mitigation statements on the Salmosan Vet label will focus on number of treatments that are permitted simultaneously rather than maximum number of treatments permitted within a 24-hour period at a given farm site. The current full risk assessment did not identify an increase in risk based on the number of net pens that are treated per farm site per day. As such, this statement was removed as it was determined that it was not an effective statement to mitigate the risk to non-target organisms from the use of azamethiphos.

The second statement on the emergency use label encourages users to perform treatments only during outgoing tides or during periods with a local outgoing current. This was determined to be problematic for both aquaculture farms and active lobster holding facilities where the aquaculture farm is located in areas where an active lobster holding facility is in the direction of the outgoing current or the outgoing tide. As such, this statement was modified to both encourage treatments during outgoing tides and/or prevailing outgoing currents, however, only when the aquaculture farm is located at a distance greater than 1 km down current from an active lobster holding facility.

The last statement pertaining to fish toxicity has been removed as it was determined that based on the use pattern of azamethiphos, azamethiphos poses a negligible risk to fish.

These revised label statements represent risk mitigation based on a more robust dataset and review. These revised risk mitigation statements reflect the conclusions of the current full risk assessment for azamethiphos and are improvements to the overall risk mitigation measures required to mitigate the risks to non-target invertebrates from the use of azamethiphos.

### 4.2.4 Incident Reports

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

There have been no environmental incidents involving azamethiphos in the PMRA database, as of 3 April 2016. When products containing azamethiphos are registered in Canada, the PMRA will continue to monitor for incident reports.

## 5.0 Value

Atlantic salmon (*Salmo salar)* is the predominant species of salmon farmed in Canada. Atlantic salmon are farmed in British Columbia, New Brunswick, Newfoundland and Labrador, and Nova Scotia, with most farmed Atlantic salmon being produced in British Columbia and New Brunswick. Sea lice (*Lepeophtheirus salmonis*) are a significant and chronic pest in marine aquaculture. Sea lice are ectoparasites of salmonids which attach to the fish and feed off the mucus, skin, gills, and blood. Under aquaculture conditions, pest populations can increase to very high levels. Severe infestations of sea lice are seriously detrimental to fish health, are an animal welfare concern, and can lead to loss of infested fish stock. In particular, sea lice are damaging to juvenile salmon. Other available alternatives have use limitations such as life stage controlled and application water temperature. Alternative treatments for control of sea lice include emamectin benzoate, hydrogen peroxide, and teflubenzuron. Emamectin benzoate and teflubenzuron are in-feed veterinary drugs: widespread resistance to emamectin benzoate is present in Canada, and teflubenzuron is only efficacious on moulting stages of sea lice, not pre-adult or adult stages. Hydrogen peroxide cannot be used when water temperatures are above 14°C. Salmosan Vet has value as it can be used to control sea lice in situations where other products are not effective or cannot be used, and is compatible with current aquaculture sea lice management programs. Salmosan Vet may contribute to resistance management as it can be used in rotation with other sea lice control products.

Value information which was assessed included an expert review summary report on three trials conducted in Scotland and Norway to determine the efficacy of azamethiphos for control of sea lice infestations of farmed Atlantic salmon. These trials demonstrated control (>90%) of pre-adult and adult sea lice with an application rate of 0.2 ppm of product applied to completely enclosed tarped net pens for a treatment duration of 30 to 60 minutes. While no studies were submitted testing use in well boats, Salmosan Vet has been used with this method in Canada under emergency registration at an application rate of 0.2 ppm of product. Application using well boats is functionally similar to fully enclosed tarp treatments; therefore extrapolation from data submitted to support the fully enclosed tarp treatments was possible. In addition, well boat application has been reported to be the most successful treatment method, and is preferred by Canadian aquaculturists.

The trials demonstrated that treatment using the open-bottom skirted method will result in decreased efficacy, even at rates as high as 0.4 ppm of product. While the skirt treatment is not a preferred method of application due to concerns regarding efficacy, there are circumstance where other treatment methods are not possible, practical, or safe (for example, strong currents, very large net pens). Given the high levels of injury and loss which can occur from serious sea lice outbreaks and the limitations of alternatives, this application method has value when no other application method can be used. An increased application rate of 0.3 ppm of product was supported as a higher rate is required to compensate for product lost through the open bottom. In addition, the history of use of this application method in Canada under emergency registration demonstrated that the open-bottom skirted method can provide acceptable treatment.

The greatest concern with use of azamethiphos from a value perspective is the potential for the development of resistance, as sea lice have developed resistance to other active ingredients in Canada. Resistance to azamthiphos has been reported in other jurisdictions where this active ingredient has been used to control sea lice. The Salmosan Vet label has a resistance management statement to provide directions to reduce the chance of resistance development.

### 5.1 Effectiveness Against Pests

The submitted data supported use of Salmosan Vet for control of pre-adult and adult sea lice in farmed Atlantic salmon applied as a bath treatment with an application duration of 30 to 60 minutes at a rate of 0.2 ppm of product (0.1 ppm azamethiphos) in well boats and fully enclosed tarped net pens, or at a rate of 0.3 ppm of product (0.15 ppm azamethiphos) in open-bottom skirted net pens.

## 6.0 Pest Control Product Policy Considerations

### 6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, azamethiphos and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Azamethiphos does not meet TSMP Track 1 criteria, and is not considered a TSMP Track 1 substance. See Appendix I, Table 20, for comparison with Track 1 criteria.

[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

- The major transformation products of azamethiphos do not meet TSMP Track 1 criteria, and are not considered TSMP Track 1 substances.

### 6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade azamethiphos does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.
- The end-use product, Salmosan Vet, does not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

## 7.0 Summary

### 7.1 Human Health and Safety

The toxicology database submitted for azamethiphos is adequate to define the majority of toxic effects that may result from exposure. In short-term and chronic studies on laboratory animals, the primary effects were inhibition of cholinesterase activity in plasma, erythrocytes and brain, as well as decreases in body weight. There was no evidence of oncogenicity in rats or mice after longer-term dosing and, overall, azamethiphos was not considered to be genotoxic. There was no evidence of sensitivity of the young in reproduction or developmental toxicity studies; however, comparative measurements of cholinesterase activities in the young and adult animal were not available. In the absence of a CCA in young and adult animals, a database uncertainty factor was applied for the current risk assessment. Consideration was given to the fact that the end-use product is restricted for use only by licenced Pest Control Operators and, more importantly, that

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6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern*.

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New Pest Control Products Act.

8 DIR2006-02, *PMRA Formulants Policy and Implementation Guidance Document*.

exposure is anticipated to be low. It should be noted, however, that the approach taken for this submission will have to be revisited for any future submission involving either a new use or a use expansion, which includes the requirement for providing additional data, if necessary.

Mixers, loaders, and applicators handling Salmosan Vet and workers handling fish cages after water has been treated are not expected to be exposed to levels of Salmosan Vet that will result in an unacceptable risk when used according to label directions. The personal protective equipment and the post-application restricted entry interval on the product label are adequate to protect workers. Bystander exposure is not considered to be a concern.

The nature of the residue in fish is adequately understood. The residue definition for risk assessment and enforcement is azamethiphos in fish products. The proposed use of azamethiphos on farmed salmon does not constitute a health risk of concern for chronic or acute dietary exposure (food alone) to any segment of the population, including infants, children, adults and seniors. Sufficient residue data from a fish residue study have been reviewed to recommend an MRL. The PMRA recommends the following MRL be specified for residues of azamethiphos:

| Commodity | Recommended MRL (ppm) |
|---|---|
| Fish | 0.05 |

## 7.2 Environmental Risk

The use of Salmosan Vet, containing the active ingredient, azamethiphos, may pose a risk to non-target aquatic invertebrates. To minimize potential risks to non-target aquatic invertebrates and lobster held in active lobster holding facilities, use restrictions such as maximum number of tarped and skirted net pens that may be treated simultaneously, minimum water depths and no-use buffer zones of 1 kilometer down current from active lobster holding facilities as well as label statements to inform users of potential risks to the environment are required.

## 7.3 Value

Salmosan Vet provides a new active ingredient for control of pre-adult and adult sea lice when applied as a bath treatment. Sea lice are a significant and chronic problem in aquaculture. Injuries to fish caused by sea lice are an animal welfare concern. Untreated infestations of sea lice in farmed Atlantic salmon can lead to complete loss of fish stock. Other available alternatives have use limitations such as they only control certain life stages or they can only be applied at certain water temperatures. Salmosan Vet can be used to control sea lice in situations where other products are not effective or cannot be used. Salmosan Vet may contribute to resistance management as it can be used in rotation with other sea lice control products. While the reviewed trials demonstrated that open-bottom (skirt) application methods may lead to reduced control, this application method has value due to the serious injuries which can be caused by this pest and as there are circumstances when completely enclosed application methods are not possible.

The submitted data supported use of Salmosan Vet for control of pre-adult and adult sea lice in farmed Atlantic salmon applied as a bath treatment with an application duration of 30 to 60 minutes at a rate of 0.2 ppm product (0.1 ppm azamethiphos) in well boats and fully enclosed tarped net pens, or at a rate of 0.3 ppm product (0.15 ppm azamethiphos) in open-bottom skirted net pens.

## 8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Azamethiphos Technical and Salmosan Vet, containing the technical grade active ingredient azamethiphos, to control sea lice on Atlantic salmon.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

# List of Abbreviations

| | |
|---|---|
| ADI | acceptable daily intake |
| a.i. | active ingredient |
| ARfD | acute reference dose |
| ASAE | American Society of Agricultural Engineers |
| AR | applied radioactivity |
| BAF | bioaccumulation factor |
| BCF | bioconcentration factor |
| bw | body weight |
| bwg | bodyweight gain |
| BChE | brain cholinesterase |
| cm | centimeter |
| CCA | comparative cholinesterase assay |
| $CO_2$ | carbon dioxide |
| d | day(s) |
| DEEM | Dietary Exposure Evaluation Model |
| DNT | developmental neurotoxicity |
| $DT_{50}$ | dissipation time 50% (the dose required to observe a 50% decline in concentration) |
| $DT_{90}$ | dissipation time 90% (the dose required to observe a 90% decline in concentration) |
| DW | drinking water |
| EIIS | Ecological Incident Information System |
| $EC_{25}$ | effective concentration on 25% of the population |
| $EC_{50}$ | effective concentration on 50% of the population |
| EP | end-use product |
| EChE | erythrocyte cholinesterase |
| EDE | estimated daily exposure |
| EEC | estimated environmental concentration |
| EIIS | Ecological Incident Information System |
| F1 | first generation |
| fc | food consumption |
| fe | food efficiency |
| FIR | food ingestion rate |
| $K_{FD}$ | Freundlich adsorption quotient |
| $K_{FOC}$ | Freundlich adsorption quotient normalized to organic carbon |
| $K_{ow}$ | *n*-Octanol-water partition coefficient |
| FOB | Functional Observational Battery |
| GD | gestation day |
| g | gram |
| GUS | groundwater ubiquity score |
| $HC_5$ | hazardous concentration to 5% of the species |
| ha | hectare |
| HPLC-UV | high performance liquid chromatography with ultra violet detection |
| HDT | highest dose tested |
| hr | hour |
| IORE | indeterminate order rate equation |
| IRAC | Insecticide Resistance Action Committee |

| | |
|---|---|
| kg | kilogram |
| L | liter |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| $LR_{50}$ | lethal rate 50% |
| LOC | level of concern |
| LOAEL | lowest observed adverse effect level |
| S9 | mammalian metabolic activation system |
| MOE | margin of exposure |
| MAS | maximum average score for 24, 48 and 72 hours |
| MIS | maximum irritation score |
| MRL | maximum residue limit |
| m | meter |
| µg | micrograms |
| mg | milligram |
| mPa | milliPascals |
| nm | nonameter |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOEL | no observed effect level |
| N/A | not applicable |
| OC | organic carbon content |
| OM | organic matter content |
| P | parental generation |
| ppm | parts per million |
| PChE | Plasma cholinesterase |
| PHED. | Pesticide Handlers Exposure Database |
| PMRA | Pest Management Regulatory Agency |
| PPE | personal protective equipment |
| PVA | polyvinylacetate |
| rel | relative |
| $t_R$ | representative half-life |
| RQ | risk quotient |
| F2 | second generation |
| SFO | single first-order kinetic model |
| $K_{OC}$ | soil organic carbon partition coefficient |
| Kd | soil-water partition coefficient |
| SWCC | Surface Water Concentration Calculator |
| TGAI | technical grade active ingredient |
| TRR | total radioactive residue |
| TSMP | Toxic Substances Management Policy |
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |
| wk | week |
| WSP | water soluble packaging |
| wt | weight |

# Appendix I Tables and Figures

## Table 1 Residue Analysis

| Matrix | Method ID | Analyte | Method Type | LOQ | Reference (PMRA#) |
|---|---|---|---|---|---|
| Fish | REM 16/77 | Azamethiphos | HPLC-UV | 0.05 ppm meat, cheese, bread, apples, rice, wheat, flour, and milk | 1162578 |
| | Modified REM 16//77 | Azamethiphos | HPLC-UV | 0.02 ppm salmon muscle and skin | 1162651 |

## Table 2 Toxicity Profile of Salmosan Vet, Containing Azamethiphos (50%)

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

| Study Type/ Animal/Reference | Study Results |
|---|---|
| Acute Oral<br>Rat, Tif:RAIf<br><br>PMRA # 1162625 | $LD_{50}$ = 1548 mg/kg bw<br><br>Slightly toxic |
| Acute Dermal<br>Rat, Tif:RAIf<br><br>PMRA # 1162626 | $LD_{50}$ >3100 mg/kg bw<br><br>Low toxicity |
| Acute Inhalation<br>Rat, Tif:RAIf<br><br>PMRA # 1162627 | $LC_{50}$ = 1.87 mg/L<br><br>Slightly toxic |
| Eye Irritation<br>Rabbit, Himalayan<br><br>PMRA # 1162628 | MAS = 1.33<br>MIS = 4 at Day 1<br>Minimally irritating. |
| Dermal Irritation<br>Rabbit, Himalayan<br><br>PMRA # 1162629 | Mean score for 24 and 72 hrs = 0.5<br><br>Minimally irritating |
| Dermal Sensitization | Waiver submitted. Considered a sensitizer based on the results with the TGAI. |
| 21-day inhalation (nose-only)<br>CGA-18809 WP50 (Salmosan Vet)<br><br>Rat, RAI f SPF<br><br>PMRA # 1952459 | NOAEL not established<br>LOAEL = 0.031 mg/L (7.9/8.3 mg/kg bw/day)<br><br>Effects at the LOAEL included ↓BChE.<br><br>Effects at higher dose levels included clinical signs of neurotoxicity, ↓bwg, ↑lung wt, histopathological changes in the lungs.<br><br>↓BChE, ↓EChE, ↑lung wt, and residual inflammatory changes in the lungs were still observed in high dose (85/90 mg/kg bw/day) animals that were allowed a 21-day recovery period. |

## Table 3 Toxicity Profile of Technical Azamethiphos

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

Note: Depression of plasma cholinesterase activity (PChE) is not considered by PMRA to be a toxicologically adverse effect; it can be viewed as a marker of exposure. Depression of erythrocyte cholinesterase activity (EChE) can be viewed as a surrogate for adverse changes in peripheral nervous tissue in acute and some short-term studies. In studies of longer duration, depression of EChE alone is not considered by PMRA to be a toxicological adverse effect.

| Study Type/Animal/Reference | Study Results |
|---|---|
| Toxicokinetics<br><br>PMRA # 1162588, 1162600, 1162613, 1162624, 1162635 | In male and female rats, $^{14}$C-pyridine-labelled azamethiphos was well absorbed after single or repeat oral administration and was rapidly metabolized and excreted within 24 hours. The major route of elimination was urinary, with ≥90% of the administered radioactivity eliminated. The faecal and expired air routes accounted for less than 5 and 0.2% of the administered doses, respectively. Tissue retention of administered $^{14}$C-pyridine-labelled azamethiphos was low.<br><br>When the radiolabel was in the methylene group instead of the pyridine moiety, elimination via the expired air was increased to approximately 35%. Faecal elimination remained low, at approximately 6% or less. However, tissue retention of radioactivity from the methylene-labelled azamethiphos 6-7 days after oral administration was high, with detectable activities in the liver, kidneys, spleen, fat, muscle, ovary, testis, brain, and blood. The total calculated activity retained in the tissues was approximately 20% of the administered dose.<br><br>With radio-labelled azamethiphos, no unchanged parent compound was detected in the excreta. There was evidence that the major metabolic pathway involved degradation to 2-amino-3-hydroxy-5-chloropyridine followed by glucuronic and sulphuric acid conjugation. |
| Acute Oral<br>Rat, Tif:RAI<br><br>PMRA # 1162525 | $LD_{50}$ (♂/♀) = 1180 mg/kg bw<br><br>Slightly toxic |
| Acute Oral<br>Mouse, Tif:MAG<br><br>PMRA # 1162526 | $LD_{50}$ (♂/♀) = 1400 mg/kg bw<br><br>Slightly toxic<br><br>Within 2 hours of treatment animals in all dose groups exhibited dyspnea, sedation, curved position, diarrhea and ruffled fur. |
| Acute Oral<br>Rat, Sprague Dawley<br><br>PMRA # 1162527 | $LD_{50}$ (♂) = 1030 mg/kg bw<br>$LD_{50}$ (♀) = 834 mg/kg bw<br>Combined = 901 mg/kg bw<br><br>Moderately toxic |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Acute Dermal<br>Rat, Wistar<br><br>PMRA # 2411494 | LD50 (♂/♀) > 2000 mg/kg bw<br><br>Low toxicity<br><br>Chromodacryorrhea, hunched posture observed. |
| Acute Dermal<br>Rat, Tif:RAI<br><br>PMRA # 1162528 | $LD_{50}$ (♂/♀) >2150 mg/kg bw<br><br>Low toxicity |
| Acute Dermal<br>Rabbit, Chinchilla<br><br>PMRA # 1162529 | $LD_{50}$ (♂/♀) > 6000 mg/kg bw<br><br>Low toxicity |
| Acute Dermal<br>Rabbit, New Zealand White<br><br>PMRA # 1162530 | $LD_{50}$ (♂/♀) > 2020 mg/kg bw<br><br>Low toxicity<br><br>↓Defecation, diarrhea, small feces observed. |
| Acute Inhalation<br>Rat, Sprague Dawley<br><br>PMRA # 1162531 | $LC_{50}$ (♂/♀) >0.56 mg/L<br><br>Slightly toxic<br><br>Clinical signs included ↓activity, constricted pupils, lacrimation, nasal discharge, piloerection, ptosis, and salivation. |
| Eye Irritation<br>Rabbit, English Silver<br><br>PMRA # 1162533 | MAS = 13.45<br>MIS = 19, on Day 1<br>All scores in remaining animals 0 by Day 7.<br><br>Mildly irritating<br><br>One ♂ died on observation day 6. Tachypnea, salivation, trismus and slight tonic-clonic muscle spasms observed approximately 30 minutes after application. |
| Eye Irritation<br>Rabbit, New Zealand White<br><br>PMRA # 1162534 | MAS = 8.2<br>MIS = 11.8 at 24 hrs<br>All scores 0 by Day 10<br><br>Mildly irritating |
| Dermal Irritation<br>Rabbit, English Silver<br><br>PMRA # 1162535 | MAS = 0<br>MIS = 0<br><br>Not irritating<br><br>Approximately 30 minutes after application the animals exhibited tachypnea, salivation, trismus and slight tonic-clonic muscle spasms. |
| Dermal Irritation<br>Rabbit, New Zealand White<br><br>PMRA # 1162536 | MAS = 0<br>MIS = 1.5 at 1 hr<br><br>Not irritating |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Dermal Sensitization<br>(Optimization test)<br><br>Guinea pig, Pirbright White<br><br>PMRA # 1162538 | Positive<br><br>Dermal Sensitizer |
| Dermal Sensitization<br>(Optimization test)<br><br>Guinea pig, Pirbright White<br><br>PMRA # 1162539 | Positive<br><br>Dermal Sensitizer |
| Dermal Sensitization<br>(Modified Buehler)<br><br>Guinea pig, Hartley<br><br>PMRA # 1162540 | Negative |
| 28-day (diet)<br>(range-finding)<br><br>Rat, Sprague Dawley<br><br>PMRA # 1162544 | NOAEL and LOAEL not established as study considered supplemental<br><br>Effects noted at 162/171 mg/kg bw/day included: ↓bwg (wk 1 and overall), ↓terminal bw, ↓fc.<br><br>*EChE activity was measured; however, BChE activity was not.* |
| 90-day (diet)<br><br>Rat, Sprague Dawley<br><br>PMRA # 1162542 | NOAEL not established as effects were noted down to the lowest dose level<br>LOAEL = 1.8/2.0 mg/kg bw/day<br><br>Effects at the LOAEL included: ↓PChE, ↓EChE (at ≥wk 5).<br><br>At the highest dose (218/264 mg/kg bw/day), ↓bw and ↓EChE were still observed in animals that were allowed a 28-day recovery period.<br><br>*BChE activity was not measured in the study. EChE activity not measured at <wk 5.* |
| 90-day (diet)<br><br>Dog, Beagle<br><br>PMRA # 1162545 | NOAEL not established as effects were noted down to the lowest dose level<br>LOAEL = 1.1/1.2 mg/kg bw/day<br><br>Effects at the LOAEL included: ↓PChE, ↓EChE (at ≥wk 4.<br><br>*No effects on BChE activity observed.* |

| Study Type/Animal/Reference | Study Results |
|---|---|
| 90-day (diet)<br><br>Dog, Beagle<br><br>Repeat study in order to establish a NOAEL<br><br>PMRA # 1162546 | NOAEL and LOAEL not established since study considered supplemental (only one dose level plus controls)<br><br>No treatment-related effects were noted at a dose level of 0.26/0.33 mg/kg bw/day.<br><br>*BChE values not suitable for analysis due to fixation error.* |
| 52-week (diet)<br><br>Dog, Beagle<br><br>PMRA # 1162556 | NOAEL = 0.26/0.24 mg/kg bw/day<br>LOAEL= 2.7/2.9 mg/kg bw/day<br><br>Effects at the LOAEL included: ↓PChE, ↓EChE (at ≤wk 4).<br><br>*No effects on BChE activity observed.* |
| 21-day (dermal)<br><br>Rabbit, Himalayan<br><br>PMRA # 1162547 | NOAEL and LOAEL not established as study considered supplemental due to small number of animals/group<br><br>Effects at ≥20 mg/kg bw/day included: ↓PChE, ↓EChE, ↓BChE; ↓bw, fc (♀).<br><br>Effects were reversible following a 21-day recovery period.<br><br>*BChE activity was measured in only 2 animals/sex/dose at termination, and 1/sex during recovery.* |
| 2-year Chronic Toxicity/Oncogenicity (diet)<br><br>Rat, Sprague Dawley<br><br>PMRA # 1162551, 1162552 | NOAEL (♀) = 1.1 mg/kg bw/day<br>LOAEL (♀) = 11 mg/kg bw/day<br><br>Effects at the LOAEL included: ↑incidence of uterine distension and uterine hydrometra.<br><br>NOAEL (♂) = 8.1 mg/kg bw/day<br>LOAEL (♂) = 63 mg/kg bw/day<br><br>Effects at the LOAEL included: ↓bwg, ↓fc, ↓fe, ↓BChE.<br><br>At the highest dose (63/89 mg/kg bw/day), no depression of BChE was observed in animals that were allowed a 28-day recovery period.<br><br>No evidence of oncogenicity |

| Study Type/Animal/Reference | Study Results |
|---|---|
| 2-year Oncogenicity<br>(diet)<br><br>Mouse, (ICR) BR<br><br>PMRA # 1162553, 1162554 | NOAEL = 6.2/7.7 mg/kg bw/day<br>LOAEL = 60/76 mg/kg bw/day<br><br>Effects at the LOAEL included: ↑incidence of chronic mucosal lesions in the proximal gastrointestinal tract (especially small intestine).<br><br>No evidence of oncogenicity<br><br>*Cholinesterase activity was not measured.*<br>*Excessive food spillage occurred in the high dose group.* |
| 2-year Oncogenicity<br>(diet)<br><br>Mouse, (ICR) BR<br><br>Supplemental study conducted to obtain meaningful food consumption figures for the high dose group.<br><br>PMRA # 1162555 | NOAEL and LOAEL not established as study considered supplemental (only one dose level tested)<br><br>Effects at 517/610 mg/kg bw/day included reduced survival, pallor, ↓bwg, ↓fc, ↑rel liver wt; ↑rel kidney wt (♀).<br><br>*No histopathological examination conducted* |
| Multigeneration Reproduction (diet)<br><br>Rat, Sprague Dawley<br><br>PMRA # 1162557 | **<u>Parental toxicity</u>**<br>NOAEL = 2.7/3.0 mg/kg bw/day<br>LOAEL = 13/15 mg/kg bw/day<br><br>Effects at the parental LOAEL included: ↓bw (P and F1), ↓bwg (P), ↓fc (P) during premating.<br><br>**<u>Offspring toxicity</u>**<br>NOAEL = 3.0 mg/kg bw/day<br>LOAEL = 15 mg/kg bw/day<br><br>Effects at the offspring LOAEL included: ↓bw (F2).<br><br>**<u>Reproductive toxicity</u>**<br>NOAEL = 65/71 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>*Cholinesterase activity was not measured*<br><br>**No evidence of sensitivity of the young** |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Multigeneration Reproduction (repeat study) (diet)<br><br>Rat, Crl:CDBR<br><br>1162558, 1162559 | **<u>Parental toxicity</u>**<br>NOAEL(♂) = 2.1 mg/kg bw/day<br>LOAEL (♂) = 11 mg/kg bw/day<br><br>Effects at the parental ♂ LOAEL included: ↓bwg during premating in P animals.<br><br>NOAEL (♀) = 11 mg/kg bw/day<br>LOAEL (♀) = 53 mg/kg bw/day<br><br>Effects at the parental ♀ LOAEL included: ↓fc, ↓bw/bwg during premating, gestation and lactation (P and F1).<br><br>*No effect on BChE activity at any level*<br><br>**<u>Offspring toxicity</u>**<br>NOAEL = 11 mg/kg bw/day<br>LOAEL = 53 mg/kg bw/day<br><br>Effects at the offspring LOAEL included**:** ↓bw during lactation (F1 and F2).<br><br>**<u>Reproductive toxicity</u>**<br>NOAEL = 53 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**No evidence of sensitivity of the young** |
| Developmental toxicity (gavage)<br><br>Rat, Sprague Dawley<br><br>PMRA # 1162569 | **<u>Maternal toxicity</u>**<br>NOAEL = 75 mg/kg bw/day<br>LOAEL = 200 mg/kg bw/day<br><br>Effects at the maternal LOAEL included: salivation, lethargy, soft stools, diarrhea, chromodacryorrhea and abdominal stains, bw loss during GD 6-8, ↓bw, ↓bwg, ↓fc.<br><br>**<u>Developmental toxicity</u>**<br>NOAEL = 200 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**No evidence of sensitivity of the young.**<br><br>*Cholinesterase activity was not measured.* |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Developmental toxicity (gavage)<br><br>Rat, Sprague Dawley<br><br>PMRA # 2297164 | **Maternal toxicity**<br>NOAEL not determined as study considered supplemental.<br><br>150 mg/kg bw/day**:** ↓fc<br><br>**Developmental toxicity**<br>NOAEL not established as study considered supplemental.<br><br>150 mg/kg bw/day: ↑incidence of delayed ossification.<br><br>**Supplemental** |
| Developmental toxicity (gavage)<br><br>Rabbit, New Zealand White<br><br>PMRA # 1162570 | **Maternal toxicity**<br>NOAEL = 12 mg/kg bw/day<br>LOAEL = 36/18 mg/kg bw/day*<br><br>Effects at the maternal LOAEL included: ↑mortality (GD 10-18), bw loss (GD 7-10), ↓bwg, ataxia, salivation, miosis, dyspnea, tremors, ↓or soft/mucus stools, ↓fc.<br><br>**Developmental toxicity**<br>NOAEL = 18 mg/kg bw/day (HDT)<br>LOAEL not established<br><br>**No evidence of sensitivity of the young**<br><br>*Cholinesterase activity was not measured*<br><br>**Due to severe maternal toxicity (↓fc, ↓bwg and mortality) the high dose was reduced from 36 mg/kg bw/day to 18 mg/kg bw/day after one week of treatment (GD 14).* |
| Developmental toxicity (gavage)<br><br>Rabbit, Chinchilla<br><br>PMRA # 2297164 | **Maternal toxicity**<br>NOAEL not determined as study considered supplemental<br><br>**≥2.5 mg/kg bw/day:** mortality (2 at low dose and 3 at high dose; cause not determined)<br><br>**7.5 mg/kg bw/day:** ↓bwg<br><br>**15 mg/kg bw/day:** ↓fc<br><br>**Developmental toxicity**<br>NOAEL not determined as study considered supplemental<br><br>**15 mg/kg bw/day:** ↓bw, ↑incidence of delayed ossification<br><br>**Supplemental** |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Cell transformation in vitro<br><br>Mouse fibroblasts (BALB/3T3 cells)<br><br>PMRA # 1162560 | Results suggested that azamethiphos may have slight transformative properties. |
| Gene mutation in vitro<br>Mouse lymphoma cells (L5178Y/TK/+/-)<br><br>PMRA # 1162561 | Negative |
| Dominant lethal assay<br><br>Mouse, NMRI<br><br>PMRA # 1162562 | Negative |
| Nucleus anomaly test in somatic interphase nuclei, in vivo<br><br>Chinese Hamster bone marrow cells<br><br>PMRA # 1162563 | Negative |
| Sister Chromatid Exchange, in vivo<br><br>Chinese Hamster bone marrow cells<br><br>PMRA # 1162564 | Negative |
| DNA repair, in vitro<br><br>Rat hepatocytes<br><br>PMRA # 1162565 | Positive |
| DNA repair, in vitro<br><br>Human fibroblasts<br><br>PMRA # 1162566 | Positive |
| Bacterial mutation<br><br>*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537<br><br>PMRA # 1162571 | Negative |
| Bacterial mutation<br><br>*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537<br><br>PMRA # 1162573 | Positive for TA 100 at 1280 and 5120 µg/0.1 ml (+/-S9) |

| Study Type/Animal/Reference | Study Results |
|---|---|
| Bacterial mutation<br><br>*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537<br><br>PMRA # 1162574 | Initial test<br>Positive in TA 100 at 5120 µg/0.1 ml (+/-S9)<br><br>Confirmatory test:<br>Positive in TA 100 at all concentrations (number of revertants dependent on the quantity of S9 fraction used). |
| Gene mutation<br><br>Saccharomyces cerevisiae<br><br>PMRA # 1162576 | Positive (+/-S9) |
| Intrasanguine host-mediated gene mutation, in vivo<br>(point mutations in bacteria)<br><br>*Salmonella typhimurium* TA 98, TA 100, TA 1535<br><br>Mice, ♂ albino<br><br>PMRA # 1162575 | Negative<br><br>Supplemental (non-guideline) |
| Intrasanguine host-mediated gene mutation, in vivo<br>(point mutations in bacteria)<br><br>*Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537<br><br>Mice, ♂ albino<br><br>PMRA # 1162572 | Positive for TA 98 at highest dose only<br><br>Supplemental (non-guideline) |
| Delayed Neurotoxicity<br><br>Hen, domestic<br><br>PMRA # 1162567 | NOAEL and LOAEL not established as study considered supplemental.<br><br>At 94 mg/kg bw effects included clinical signs of toxicity (subdued appearance, unsteadiness and inability to stand) and/or mortality in all birds soon after dosing, ↓fc, bw loss during the week following dosing.<br><br>No signs of delayed neurotoxicity observed. No treatment-related histopathological findings in the spinal cord and peripheral nerves.<br><br>*Neurotoxic esterase was not measured*. |
| 90-Day Neurotoxicity<br><br>Rat, Sprague Dawley<br><br>PMRA # 2411495 | NOAEL not established as study considered supplemental due to limitations in FOB and reporting.<br><br>Effects at 5 mg/kg bw/day included: ↓EChE (at ≥wk 8)<br><br>*No effect on BChE activity* |

**Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Azamethiphos**

| Exposure Scenario | Study | Point of Departure and Endpoint | CAF[1] or Target MOE |
|---|---|---|---|
| Acute dietary | 52-week dietary study in dogs | NOAEL = 0.24 mg/kg bw/day; based on depression of erythrocyte cholinesterase activity. | 300 |
| | **ARfD = 0.0008 mg/kg bw** | | |
| Repeated dietary | 52-week dietary study in dogs | NOAEL = 0.24 mg/kg bw/day; based on depression of erythrocyte cholinesterase activity. | 300 |
| | **ADI = 0.0008 mg/kg bw/day** | | |
| Short-and intermediate-term dermal[2] | 52-week dietary study in dogs | NOAEL = 0.24 mg/kg bw/day; based on depression of erythrocyte cholinesterase activity. | 300 |
| Short- and intermediate-term inhalation[3] | 52-week dietary study in dogs | NOAEL = 0.24 mg/kg bw/day; based on depression of erythrocyte cholinesterase activity. | 300 |

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor of 42% was used in a route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

**Table 5 Integrated Food Residue Chemistry Summary**

| **Nature of the Residue in Salmon** | | **PMRA # 1807367** |
|---|---|---|
| **Radiolabel Position** | **[2-$^{14}$C]pyridyl azamethiphos** | |
| **Test Site** | Closed system treatment tank containing seawater. | |
| **Treatment** | Immersion of salmon in treatment tank containing 0.112 ppm $^{14}$C-azamethiphos | |
| **End-use product** | WP 50 Formulation | |
| **Treatment interval** | 1 hr in treatment tank followed by 168 hr in withholding tank with periodic sampling | |
| **Matrix** | **Witholding Interval (hr)** | **[2-$^{14}$C]pyridyl azamethiphos TRR (ppm)** |
| Muscle | 0 | 0.020 |
| | 48 | <0.0007 |
| Skin | 0 | 0.117 |
| | 48 | 0.012 |
| Offal | 0 | 0.047 |
| | 48 | 0.006 |
| Gills | 0 | 0.080 |
| | 48 | 0.004 |
| Liver | 0 | 0.129 |
| | 48 | 0.008 |
| Kidney | 0 | 0.089 |
| | 48 | 0.005 |
| Bile | 0 | 0.282 |
| | 3-24 (pooled)* | ~4 |
| | 48 | 0.419 |

| Metabolites Identified | Major Metabolites (>10% TRR) | Minor Metabolites (<10% TRR) |
|---|---|---|
| **Radiolabel Position** | **[2-$^{14}$C]pyridyl azamethiphos** | |
| Bile | glucuronic acid conjugate of 2-amino-3-hydroxy-5-chloro-pyridine (CGA-51236) | - |

All samples (except bile pooled from 3-24 hr withholding periods) had insufficient TRRs for further identification purposes. However, the bile sample that contained TRR of 4 ppm showed over 50 % of the TRR as the glucuronic acid conjugate of CGA-51236, which was one of the metabolites isolated from rat urine. From this, it is concluded that the metabolism of azamethiphos in salmon is similar to that which occurs in the rat, and is adequately understood.

| **Livestock Residue Study – Salmon** | **PMRA # 1162651** |
|---|---|

Azamethiphos (as Salmosan 50WP) was administered to salmon (*Salmo salar*) by immersion of the fish for one hour in a bath containing 0.2 ppm azamethiphos in seawater. Following exposure, salmon were returned to a withholding tank containing untreated seawater. Salmon were sacrificed for analysis immediately following treatment, and at 12 hours, 1 day, 3 days, and 7 days after treatment.

| Matrix | Exposure Level in seawater (ppm) | Withholding period (hr) | Azamethiphos (ppm) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Min | Max | Median | Mean | Standard Deviation |
| Muscle and skin | 0.24-0.27 | 0 | 10 | <0.02 | <0.02 | <0.02 | <0.02 | - |
| | | 12 | 10 | <0.02 | <0.02 | <0.02 | <0.02 | - |
| | | 24 | 10 | <0.02 | <0.02 | <0.02 | <0.02 | - |

Based on salmon residue study, there is no expectation of residues in salmon muscle and skin.

**Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment**

| Animal Studies | | |
|---|---|---|
| **Fish** | | |
| **Residue Definition For Enforcement** | | Azamethiphos |
| **Residue Definition For Risk Assessment** | | Azamethiphos |
| **Metabolic Profile In Animals (salmon and rat)** | | The metabolic profile of azamethiphos in salmon is adequately documented and is similar to that of the rat |
| **Fat Soluble Residue** | | No |
| **Dietary Risk From Food And Water** | | |
| **Basic chronic non-cancer dietary risk**<br><br>**ADI = 0.0008 mg/kg bw/day general population**<br><br>**No exposure from drinking water** | **Population** | **Estimated Risk % of Acceptable Daily Intake (ADI)** |
| | | **Food Alone** |
| | **All infants < 1 year** | 0.1 |
| | **Children 1–2 years** | 1.2 |
| | **Children 3 to 5 years** | 0.7 |
| | **Children 6–12 years** | 0.7 |
| | **Youth 13–19 years** | 0.4 |
| | **Adults 20–49 years** | 0.8 |
| | **Females 13–49 years** | 0.7 |
| | **Adults 50+ years** | 0.9 |
| | **Total population** | 0.8 |

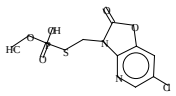
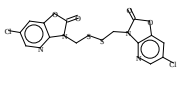
| | Population | ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD) |
|---|---|---|
| | | Food Alone |
| **Basic acute dietary exposure analysis, 95th percentile**<br><br>**No exposure from drinking water**<br>**ARfD = 0.0008 mg/kg bw general population** | **All infants < 1 year** | 0 |
| | **Children 1–2 years** | 0.1 |
| | **Children 3–5 years** | 0.1 |
| | **Children 6–12 year** | 1.6 |
| | **Youth 13–19 years** | 0 |
| | **Adults 20–49 years** | 5.4 |
| | **Females 13–49 year** | 4.7 |
| | **Adults 50+ years** | 7.1 |
| | **Total population** | 5.3 |

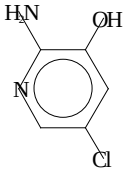
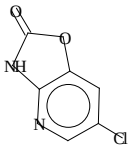
## Table 7 Fate and Behaviour of Azamethiphos in the Environment

| Study type | Test material/test system | Value | Transformation products | Comments | Reference (PMRA#) |
|---|---|---|---|---|---|
| **Abiotic transformation** | | | | | |
| Hydrolysis | Azamethiphos ($^{14}$C ring labelled – CGA-18809)<br><br>pH 5, 7 and 9; 25ºC | Half-lives:<br><br>pH 5: 33.4 days<br>pH 7: 9.8 days<br>pH 9: 4.5 hours | Major: Monomethyl ester (CGA-18809), CGA-55016, CGA-51236, Trihydroxy amino pyridines<br><br>Minor: GS-36533 | Hydrolysis is an important route of dissipation for azamethiphos. | 1162581 |
| Phototrans-formation in water | Azamethiphos [$^{14}$C ring labelled CGA-18809]<br><br>pH 7; 25 ºC | Half-life (continuous irradiation under laboratory conditions) = 1.5 minutes | Major: S-(6-hydroxy-oxazole (4,5-B), pyridin-2-(3H)-on3-yl-methyl)-0,0 dimethylthiophosphate, 6-hydroxy-oxazole (4,5-b) pyridin-2(3H)-on. | Phototransfor-mation is an important route of dissipation for azamethiphos. | 1162582 |
| | Azamethiphos (CGA-18809) unknown radio-label.<br><br>pH 8.5; 8 ºC | Half-life (continuous irradiation under semi-field conditions) = 45 hours | Transformation products were not reported. | Phototransfor-mation is an important route of dissipation for azamethiphos. | 1162639 |
| **Biotransformation** | | | | | |
| Biotrans-formation in aerobic water system with fish | Azamethiphos [$^{14}$C ring] labelled Pyridyl CGA<br><br>Salinity: 34.1 ppt,<br>DO: 78%<br>pH: 8.0<br>7.5 – 9.5 ºC | First Order Kinetic Half-life = 8.9 days. | Major: 6-chloro-oxazolo (4,5-b) pyridin-2(3H)-on<br><br>Minor: None | Azamethiphos is non-persistent in aquatic systems. | 1162604 |
| Biotrans-formation in anaerobic water systems | An anaerobic biotransformation study was not reviewed nor required during this review. | NA | NA | NA | NA |
| Soil Half-life (For TSMP | Azamethiphos [Pyridine ring-$^{14}$C] | First Order Kinetic Half-life = 6 hours. | The review of soil transformation products | Azamethiphos is non-persistent | 1162587 |

| Study type | Test material/test system | Value | Transformation products | Comments | Reference (PMRA#) |
|---|---|---|---|---|---|
| Criteria Only) | labelled and [$^{14}CH_2$] labbelled. | | was not required nor considered for this review. | in aerobic soil. | |
| **Field studies** | | | | | |
| Oceanic Dye Dispersion | New Brunswick Bay of Fundy<br><br>Single Application of Salmosan Vet formulation to skirted net pens and tarped net pens. | $DT_{50}$ = ~5 minutes<br>$DT_{90}$ = ~15 minutes<br>$DT_{99}$ = ~60 minutes | Not measured. | Azamethiphos disperses very rapidly under field conditions. | 2617429 |
| Oceanic Dye Dispersion | New Brunswick Bay of Fundy<br><br>Two simultaneous Applications of Salmosan Vet formulation to skirted net pens and tarped net pens with overlapping plumes | $DT_{50}$ = ~10 minutes<br>$DT_{90}$ = ~20 minutes<br>$DT_{99}$ = ~80 minutes | Not measured. | Azamethiphos disperses very rapidly under field conditions. | 2617429 |
| Oceanic Dye Dispersion | New Brunswick Bay of Fundy<br><br>Single Application of Salmosan Vet formulation to well boats with horizontal, angled and vertical discharge jets | $DT_{50}$ = ~5 minutes<br>$DT_{90}$ = ~20 minutes<br>$DT_{99}$ = ~40 minutes | Not measured. | Azamethiphos disperses very rapidly under field conditions. | 2617429 |

**Table 8 Transformation Products of Azamethiphos Formed in the Environment**

| Code name and synonyms | Chemical structure | Study[1] | Max %AR (day) | %AR at study end (study length)[2] | Log $K_{ow}$[3] |
|---|---|---|---|---|---|
| Monomethyl Ester of CGA-18809 |  | Hydrolysis | pH 7: 19% (33)<br>pH 9: (nd) | pH 7: 19%(33)<br>pH 9: na | 0.94 |
| CGA-55016 (disulfide of CGA-18809) |  | Hydrolysis | pH 7: 15.7% (21)<br>pH 9: (nd) | pH7: 13.8 (33)<br>pH 9: na | 3.79 |

| Code name and synonyms | Chemical structure | Study[1] | Max %AR (day) | %AR at study end (study length)[2] | Log $K_{ow}$[3] |
|---|---|---|---|---|---|
| CGA-51236 |  | Hydrolysis | pH 7: 43.2 (33)<br>pH 9: 68.6 (1) | pH 7: 43.2 (33)<br>pH 9: (26.2 (33) | 0.69 |
| GS-36533 |  | Hydrolysis | pH 7: 5.9 (22)<br>pH 9: 31.4 (1) | pH 7: 5.6 (33)<br>pH 9: (29.8 (33) | 1.04 |

[1] Refer to Tables 1 and 2 for study references
[2] In DAT (days after treatment)
[3] Modeled using Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11
AR = applied radioactivity
na = not analysed (either no reference standard used or minor non-volatile compounds which were not identified)
nd = not detected
**Bolded when appearing at >10% (major transformation product)**

## Table 9 Toxicity of Azamethiphos to Non-Target Aquatic Species

| Organism | Test substance | Exposure | Endpoint | Value (mg a.i./L) | Degree of toxicity[1] | Reference (PMRA#) |
|---|---|---|---|---|---|---|
| **Invertebrates** | | | | | | |
| Copepod *Temora longicornis* | Azamethiphos Technical | 24 hours | $LC_{50}$ | > 0.01 | Very highly toxic | 1162610 |
| Amphipod *Hyale nilssoni* | Azamethiphos Technical | 96 hours | $LC_{50}$ | > 0.0062 | Very highly toxic | 1162611 |
| Mysid Shrimp (*Mysidopsis bahia*) | Azamethiphos Technical | 96 hours | $LC_{50}$ | 0.0021 | Very highly toxic | 1162607 |
| Mussel *(Mytilus edulis L.)* | Azamethiphos Technical | 24 hours | $LC_{50}$ | > 10 | Slightly toxic | 1162608 |
| Mussel *(Mytilus edulis L.)* | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | > 100 | Practically nontoxic | 1162612 |
| Mussel *(Mytilus edulis L.)* | Azamethiphos Technical | 5 × 1-hour pulses | $LC_{50}$ | > 0.1 | Highly toxic | 1162614 |
| Oyster embryos (*Crassostrea gigas)* | Azamethiphos wettable powder | 24 hours | $EC_{50}$ (embryo development) | > 1 | Moderately toxic | 1162615 |
| Gastropod (*Patella vulgate)* | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | > 0.1 | Highly toxic | 1162616 |
| Gastropod (*Littorina littorea)* | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | > 0.1 | Highly toxic | 1162617 |
| Stage 4 and 5 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 0.0005 | Very highly toxic | 1162609 |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 48 hours | $LC_{50}$ | 0.0036 | Very highly toxic | 2618172 |
| Stage 2 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 48 hours | $LC_{50}$ | 0.0010 | Very highly toxic | 2618172 |
| Stage 3 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 48 hours | $LC_{50}$ | 0.0023 | Very highly toxic | 2618172 |

| Organism | Test substance | Exposure | Endpoint | Value (mg a.i./L) | Degree of toxicity[1] | Reference (PMRA#) |
|---|---|---|---|---|---|---|
| Stage 4 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 48 hours | $LC_{50}$ | 0.0021 | Very highly toxic | 2618172 |
| Adult Lobster *(Homarus gammarus L.)* | Azamethiphos wettable powder | 48 hours | $LC_{50}$ | 0.0014 | Very highly toxic | 2618172 |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | 1 hour | $LC_{50}$ | > 0.086 | Very highly toxic | 2618172 |
| Adult Lobster *(Homarus gammarus L.)* | Azamethiphos wettable powder | 1 hour | $LC_{50}$ | 0.025 | Very highly toxic | 2618172 |
| *Sand Shrimp (Crangon septemspinosa)* | Azamethiphos wettable powder | 1 hour | $LC_{50}$ | > 0.086 | Very highly toxic | 2618172 |
| Sand Shrimp (*Mysid sp.*) | Azamethiphos wettable powder | 1 hour | $LC_{50}$ | > 0.086 | Very highly toxic | 2618172 |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Adult Lobster *(Homarus gammarus L.)* | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | 0.75 hours | NA | 2618172 |
| *Sand Shrimp (Crangon septemspinosa)* | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Sand Shrimp (*Mysid sp.*) | Azamethiphos wettable powder | NA | 0.086 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | Azamethiphos wettable powder | NA | 0.028 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Adult Lobster *(Homarus gammarus L.)* | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | 2.5 hours | NA | 2618172 |
| *Sand Shrimp (Crangon septemspinosa)* | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Sand Shrimp (*Mysid sp.*) | Azamethiphos wettable powder | NA | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | 2618172 |
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | Azamethiphos wettable powder | 5 × 1-hour pulses with 5 day recovery between exposures | $LC_{50}$ | 0.0032 | Very highly toxic | 1162618 |
| | | | NOEC (survival) | 0.001 | Very highly toxic | 1162618 |
| Adult Lobster (*Homarus gammarus* L.) | Salmosan 50WP | 9 × 30-minute exposures over the course of 3 days | NOEC (survival, molting, mating behaviour, cement gland development, reproduction) | 0.001 | Very highly toxic | 2618172 |
| Adult Lobster (*Homarus gammarus* L.) | Salmosan 50WP | 10 days | $LOEC_{(mortality}$ following post exposure stress in the form of simulated shipping) | 0.000078 | - | 2618172 |
| Adult Lobster | Salmosan 50WP | 10 days | NOEC | 0.00012 | - | 2618172 |
| Starfish (*Asterias rubens)* | Azamethiphos Technical | 96 hours | $LC_{50}$ | > 0.1 | Highly toxic | 1162619 |
| **Fish** | | | | | | |
| (Rainbow trout, *Oncorhynchus mykiss*) | Azamethiphos Technical | 96 hours | $LC_{50}$ | 0.2 | Highly toxic | 1162595 |
| Crucian carp (*Carassius crassius*) | Azamethiphos Technical | 96 hours | $LC_{50}$ | 6 | Moderately toxic | 1162595 |
| channel catfish | Azamethiphos | 96 hours | $LC_{50}$ | 3 | Moderately | 1162595 |

| Organism | Test substance | Exposure | Endpoint | Value (mg a.i./L) | Degree of toxicity[1] | Reference (PMRA#) |
|---|---|---|---|---|---|---|
| (*Ictalurus ameiurus*) | Technical | | | | toxic | |
| Bluegill sunfish (*Lepomis macrochirus*) | Azamethiphos Technical | 96 hours | $LC_{50}$ | 8 | Moderately toxic | 1162595 |
| Guppy (*Lebistes reticulatus*) | Azamethiphos Technical | 96 hours | $LC_{50}$ | 8 | Moderately toxic | 1162595 |
| Brown trout (*Salmo trutta fario*) | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 0.29 | Highly toxic | 1162596 |
| Carp (*Cyprinus carpio*) | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 7.1 | Moderately toxic | 1162596 |
| Channel catfish (*Ictalurus ameiurus*) | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 9.2 | Moderately toxic | 1162596 |
| Bluegill sunfish (*Lepomis macrochirus*) | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 11 | Slightly toxic | 1162596 |
| Golden orfe *(Leuciscus idus melanotus)* | Azamethiphos wettable powder | 96 hours | $LC_{50}$ | 4.2 | Moderately toxic | 1162596 |
| Sheepshead Minnow *(Cyrindon variegatus)* | Azamethiphos Technical | 96 hours | $LC_{50}$ | 2.2 | Moderately toxic | 1162597 |
| Goldsinny wrasse (*Ctenolabrus rupestris*) | Azamethiphos Technical | 1 hour | $LC_{50}$ | 4.18 | Moderately toxic | 1162601 |
| **Algae** | | | | | | |
| Phytoplankton (*Phaeodactylum tricornutum)* | Azamethiphos wettable powder | 72 hours | $LC_{50}$ | > 1 | Moderately toxic | 1162621 |
| Phytoplankton (*Tetraselmus chuii)* | Azamethiphos wettable powder | 72 hours | $LC_{50}$ | > 1 | Moderately toxic | 1162621 |

[1] USEPA classification, where applicable
NA = not applicable

## Table 10 Screening level risk assessment of azamethiphos to marine organisms (Skirted Net pen application rate of 0.15 mg/L)

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Invertebrates | | | | | |
| Copepod (*Temora longicornis)* | 24-hour $LC_{50}$ | > 0.01 | 0.15 | < 30 | Exceeded |
| Amphipod (*Hyale nilssoni)* | 96-hour $LC_{50}$ | > 0.0062 | 0.15 | < 48 | Exceeded |
| Mysid Shrimp (*Mysidopsis bahia*) | 24-hour $LC_{50}$ | 0.0021 | 0.15 | 143 | Exceeded |
| Mussel *(Mytilus edulis L.)* | 24-hour $LC_{50}$ | > 10 | 0.15 | < 0.03 | Not Exceeded |
| Mussel *(Mytilus edulis L.)* | 96-hour $LC_{50}$ | > 100 | 0.15 | < 0.003 | Not Exceeded |
| Mussel *(Mytilus edulis L.)* | 5 × 1-hour pulse $LC_{50}$ | > 0.1 | 0.15 | < 3 | Exceeded |
| Oyster embryos (*Crassostrea gigas)* | 24-hour $EC_{50\ (embryo\ development)}$ | > 1 | 0.15 | < 0.3 | Not Exceeded |
| Gastropod (*Patella vulgate)* | 96-hour $LC_{50}$ | > 1 | 0.15 | < 0.3 | Not Exceeded |
| Gastropod (*Littorina littorea)* | 96-hour $LC_{50}$ | > 1 | 0.15 | < 0.3 | Not Exceeded |
| Stage 4 and 5 Lobser larvae *(Homarus gammarus L.)* | 96-hour $LC_{50}$ | 0.0005 | 0.15 | 600 | Exceeded |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | 48-hour $LC_{50}$ | 0.0036 | 0.15 | 83 | Exceeded |
| Stage 2 Lobser larvae *(Homarus gammarus L.)* | 48-hour $LC_{50}$ | 0.0010 | 0.15 | 300 | Exceeded |

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Stage 3 Lobser larvae *(Homarus gammarus L.)* | 48-hour $LC_{50}$ | 0.0023 | 0.15 | 130 | Exceeded |
| Stage 4 Lobser larvae *(Homarus gammarus L.)* | 48-hour $LC_{50}$ | 0.0021 | 0.15 | 143 | Exceeded |
| Adult Lobster *(Homarus gammarus L.)* | 48-hour $LC_{50}$ | 0.0014 | 0.15 | 214 | Exceeded |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | 1-hour $LC_{50}$ | > 0.086 | 0.15 | < 3.5 | Exceeded |
| Adult Lobster *(Homarus gammarus L.)* | 1-hour $LC_{50}$ | 0.025 | 0.15 | 12 | Exceeded |
| *Sand Shrimp (Crangon septemspinosa)* | 1-hour $LC_{50}$ | > 0.086 | 0.15 | < 3.5 | Exceeded |
| Sand Shrimp (*Mysid sp.*) | 1-hour $LC_{50}$ | > 0.086 | 0.15 | < 3.5 | Exceeded |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Adult Lobster *(Homarus gammarus L.)* | 0.085 mg/L $LT_{50}$ | 0.75 hours | NA | NA | NA |
| Sand Shrimp *(Crangon septemspinosa)* | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Sand Shrimp (*Mysid sp.*) | 0.086 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | 0.028 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Adult Lobster *(Homarus gammarus L.)* | 0.085 mg/L $LT_{50}$ | 2.5 hours | NA | NA | NA |
| Sand Shrimp *(Crangon septemspinosa)* | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Sand Shrimp (*Mysid sp.*) | 0.085 mg/L $LT_{50}$ | > 95 hours | NA | NA | NA |
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | 5 × 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.15 | 94 | Exceeded |
| | 5 × 1-hour pulses with 5 day recovery between exposures $NOEC_{(survival)}$ | 0.001 | 0.15 | 150 | Exceeded |
| Adult Lobster (*Homarus gammarus* L.) | 9 × 30-minute exposures over the course of 3 days $NOEC_{(survival, molting, mating behaviour, cement gland development, reproduction)}$ | 0.001 | 0.15 | 150 | Exceeded |
| Adult Lobster (*Homarus gammarus* L.) | 10-day $LOEC_{(mortality following post exposure stress in the form of simulated shipping)}$ | 0.000078 | 0.15 | 1,923 | Exceeded |
| Adult Lobster (*Homarus gammarus* L.) | 10-day NOEC | 0.00012 | 0.15 | 1,250 | Exceeded |
| Starfish (*Asterias rubens)* | 96-hour $LC_{50}$ | > 0.1 | 0.15 | < 3 | Exceeded |
| **Fish** | | | | | |
| Rainbow trout (*Oncorhynchus mykiss*) | 96-hour $LC_{50}$ | 0.2 | 0.15 | 8 | Exceeded |
| Crucian carp (*Carassius crassius*) | 96-hour $LC_{50}$ | 6 | 0.15 | 0.3 | Not Exceeded |
| Channel catfish (*Ictalurus ameiurus*) | 96-hour $LC_{50}$ | 3 | 0.15 | 0.5 | Not Exceeded |
| Bluegill sunfish (*Lepomis macrochirus*) | 96-hour $LC_{50}$ | 8 | 0.15 | 0.2 | Not Exceeded |
| Guppy ( *Lebistes reticulatus*) | 96-hour $LC_{50}$ | 8 | 0.15 | 0.2 | Not Exceeded |
| Brown trout | 96-hour $LC_{50}$ | 0.29 | 0.15 | 5 | Exceeded |

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| (*Salmo trutta fario*) | | | | | |
| Carp (*Cyprinus carpio*) | 96-hour $LC_{50}$ | 7.1 | 0.15 | 0.2 | Not Exceeded |
| Channel catfish (*Ictalurus ameiurus*) | 96-hour $LC_{50}$ | 9.2 | 0.15 | 0.2 | Not Exceeded |
| Bluegill sunfish (*Lepomis macrochirus*) | 96-hour $LC_{50}$ | 11 | 0.15 | 0.1 | Not Exceeded |
| Golden orfe *(Leuciscus idus melanotus)* | 96-hour $LC_{50}$ | 4.2 | 0.15 | 0.4 | Not Exceeded |
| Sheepshead Minnow *(Cyrindon variegatus)* | 96-hour $LC_{50}$ | 2.2 | 0.15 | 0.7 | Not Exceeded |
| Goldsinny wrasse (*Ctenolabrus rupestris*) | 1-hour $LC_{50}$ | 4.18 | 0.15 | 0.4 | Not Exceeded |
| **Algae** | | | | | |
| Phytoplankton *(Phaeodactylum tricornutum)* | 72-hour $LC_{50}$ | > 1 | 0.15 | < 0.3 | Not Exceeded |
| Phytoplankton *(Tetraselmus chuii)* | 72-hour $LC_{50}$ | > 1 | 0.15 | < 0.3 | Not Exceeded |

NA = not applicable

**Table 11 Assessment of potential risk from oceanic dispersion of azamethiphos to pelagic marine organisms from 2 overlapping skirted net pen plumes using the 90th percentile 1-hour EEC.**

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| **Invertebrates** | | | | | |
| Copepod *(Temora longicornis)* | 24-hour $LC_{50}$ | > 0.01 | 0.0032 | < 0.6 | NOT Exceeded |
| Amphipod (*Hyale nilssoni)* | 96-hour $LC_{50}$ | > 0.0062 | 0.0032 | < 1.03 | Slightly Exceeded |
| Mussel *(Mytilus edulis L.)* | 5 × 1-hour pulses $LC_{50}$ | > 0.1 | 0.0032 | 0.1 | NOT Exceeded |
| Stage 1 Lobser larvae *(Homarus gammarus L.)* | 1-hour $LC_{50}$ | > 0.086 | 0.0032 | < 0.1 | NOT Exceeded |
| Sand Shrimp *(Crangon septemspinosa)* | 1-hour $LC_{50}$ | > 0.086 | 0.0032 | < 0.1 | NOT Exceeded |
| Sand Shrimp (*Mysid sp.*) | 1-hour $LC_{50}$ | > 0.086 | 0.0032 | < 0.1 | NOT Exceeded |
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | 5 × 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.0032 | 2 | Slightly Exceeded |
| **Fish** | | | | | |
| Rainbow trout (*Oncorhynchus mykiss*) | 96-hour $LC_{50}$ | 0.2 | 0.0032 | 0.2 | NOT Exceeded |
| Brown trout (*Salmo trutta fario*) | 96-hour $LC_{50}$ | 0.29 | 0.0032 | 0.1 | NOT Exceeded |

**Table 12 Assessment of potential risk from oceanic dispersion of azamethiphos to pelagic marine organisms from 2 overlapping skirted net pen plumes using the 1-hour mean EEC.**

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Amphipod (*Hyale nilssoni)* | 96-hour $LC_{50}$ | > 0.0062 | 0.0024 | < 0.77 | NOT Exceeded |
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | Five 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.0024 | 1.5 | Slightly Exceeded |

**Table 13 Assessment of potential risk from oceanic dispersion of azamethiphos to pelagic marine organisms from 2 overlapping tarped net pen plumes using the mean 1-hour EEC.**

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | Five 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.0016 | 1 | Equal |

**Table 14 Assessment of potential risk from oceanic dispersion of azamethiphos to pelagic marine organisms from a single skirted net pen plume using the mean 1-hour EEC**

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | Five 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.0012 | 0.75 | NOT Exceeded |

**Table 15 Assessment of potential risk from the use of azamethiphos to pelagic marine organisms from a well boat using the 50-minute well boat EEC.**

| Organism | Exposure Endpoint | Value (mg/L) | EEC (mg/L) | RQ | LOC |
|---|---|---|---|---|---|
| Lobster Larvae of unknown larval stage (*Homarus gammarus* L.) | Five 1-hour pulses with 5 day recovery between exposures $LC_{50}$ | 0.0032 | 0.0003 | 0.2 | NOT Exceeded |

**Table 16 Assessment of potential risk from the use of azamethiphos to benthic marine organisms from a skirted net pen treatment in function of depth and using the NOEC for survival, molting, mating, behaviour, cement gland development and reproduction following nine 30-minute pulse exposures over the course of 3 days.**

| Depth | EEC (mg/L) | End-point Value (mg/L) | RQ | LOC |
|---|---|---|---|---|
| 0 | 0.15 | 0.001 | 150 | Exceeded |
| 10 | 0.15 | 0.001 | 150 | Exceeded |
| 20 | 0.0015 | 0.001 | 1.5 | Exceeded |
| 30 | ND | 0.001 | <1 | Not Exceeded |

**Table 17 Assessment of potential risk from the use of azamethiphos to benthic marine organisms from a tarped net pen treatment in function of depth and using the NOEC for survival, molting, mating, behaviour, cement gland development and reproduction following nine 30-minute pulse exposures over the course of 3 days.**

| Depth | EEC (mg/L) | End-point Value (mg/L) | RQ | LOC |
|---|---|---|---|---|
| 0 | 0.1 | 0.001 | 100 | Exceeded |
| 10 | 0.01 | 0.001 | 10 | Exceeded |
| 20 | 0.0001 | 0.001 | 0.1 | Not Exceeded |
| 30 | Not detected (less than 0.0001) | 0.001 | <0.1 | Not Exceeded |

**Table 18 Assessment of potential risk from the use of azamethiphos to benthic marine organisms from a 90 degree well boat flushing pipe treatment in function of depth and using the NOEC for survival, molting, mating, behaviour, cement gland development and reproduction following nine 30-minute pulse exposures over the course of 3 days.**

| Depth | EEC | End-point Value (mg/L) | RQ | LOC |
|---|---|---|---|---|
| 0 | 0.125 | 0.001 | 125 | Exceeded |
| 10 | 0.0125 | 0.001 | 12.5 | Exceeded |
| 20 | 0.002 | 0.001 | 2 | Slightly Exceeded |

**Table 19 Assessment of potential risk from the use of azamethiphos to benthic marine organisms from a 45 degree well boat flushing pipe treatment in function of depth and using the NOEC for survival, molting, mating, behaviour, cement gland development and reproduction following nine 30-minute pulse exposures over the course of 3 days.**

| Depth | EEC | End-point Value (mg/L) | RQ | LOC |
|---|---|---|---|---|
| 0 | 0.125 | 0.001 | 125 | Exceeded |
| 10 | 0.003 | 0.001 | 3 | Exceeded |
| 20 | 0.0014 | 0.001 | 1.4 | Slightly Exceeded |

**Table 20 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria**

| TSMP Track 1 Criteria | TSMP Track 1 Criterion value | | Active Ingredient Endpoints |
|---|---|---|---|
| CEPA toxic or CEPA toxic equivalent[1] | Yes | | Yes |
| Predominantly anthropogenic[2] | Yes | | Yes |
| Persistence[3]: | Soil | Half-life ≥ 182 days | Aerobic Soil Half-life = 6 hours. |
| | Water | Half-life ≥ 182 days | Longest reported Aquatic Half-life = 9.8 days. |
| | Sediment | Half-life ≥ 365 days | A sediment half-life was not available. However based on a high solubility of 1582 mg /L at 25ºC |

| | | | |
|---|---|---|---|
| | | | and a low log $K_{ow}$ of 1, azamethiphos is not expected to partition to sediment. |
| | Air | Half-life ≥ 2 days or evidence of long range transport | A half-life in air was not available. However, volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure ($<1.39 \times 10^{-6}$ Pa) and Henry's Law Constant ($2.85 \times 10^{-7}$ atm·m$^3$/mol). |
| Bioaccumulation[4] | Log $K_{ow} \geq 5$ | | 1 |
| | BCF ≥ 5000 | | A BCF value was not available however based on a high solubility of 1582 mg /L at 25ºC and a low log $K_{ow}$ of 1, azamethiphos is not expected to bioaccumulate. |
| | BAF ≥ 5000 | | A BAF value was not available however based on a high solubility of 1582 mg /L at 25ºC and a low log $K_{ow}$ of 1, azamethiphos is not expected to bioaccumulate. |
| Is the chemical a TSMP Track 1 substance (all four criteria must be met)? | | | No, does not meet TSMP Track 1 criteria. |

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e. all other TSMP criteria are met).
[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, log $K_{ow}$).

# Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

There are no American Tolerances or Codex MRLs for azamethiphos.

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry

| PMRA Document Number | Reference |
|---|---|
| 2292434 | Application for Use of Salmosan in Canada-TGAI, DACO: 2.0 CBI |
| 2292435 | Azamethiphos Manufacturing process, DACO: 2.11 CBI |
| 2296384 | Certificate of Analysis - Last 20 batches, DACO: 2.13.3 CBI |
| 2604869 | 2016, Detailed production process description, DACO: 2.11 CBI |
| 2604870 | 2016, Impurity Discussion, DACO: 2.11.4 CBI |
| 2292446 | J18428 Aza M709 Validation, DACO: 2.13.1 CBI |
| 2606343 | 2016, Method of Analysis LC164, DACO: 2.13.1 |
| 2606344 | 2016, Validation LC164, DACO: 2.13.1 |
| 2604871 | 2016, LC 175, DACO: 2.13.1 |
| 2604872 | 2016, VP252, DACO: 2.13.1 |
| 2604873 | 2016, VP272, DACO: 2.13.1 |
| 2604874 | 2016, VR107, DACO: 2.13.1 |
| 2604875 | 2016, VR119, DACO: 2.13.1 |
| 2604876 | 2016, Certificate of Analysis [CBI Removed], DACO: 2.13.2I CBI |
| 2604877 | 2016, Certificate of Analysis [CBI Removed], DACO: 2.13.2 CBI |
| 2605260 | 2016, Azamethiphos [CBI Removed] Spectra, DACO: 2.13.2 CBI |
| 2605261 | 2016, Azamethiphos[CBI Removed] Spectra, DACO: 2.13.2 CBI |
| 2292441 | J18391 Final Report, DACO: 2.13.1 CBI |
| 2604878 | 2016, 5 Batch Analysis, DACO: 2.13.3 CBI |
| 2604879 | 2016, Summary Table five batch analysis, DACO: 2.13.3 CBI |
| 2297167 | Specification for Azamethiphos, DACO: 2.11.2 CBI |
| 2297168 | Certificate of Analysis, DACO: 2.11.2 CBI |
| 2297165 | Formula and Manufacture.pdf, DACO: 2.11.1 CBI |
| 2555753 | 2015, Determination of azamethiphos for assay and related substances by HPLC-UV, DACO: 3.4.1 |
| 2555752 | 2014, Validation of LM-065, DACO: 3.4.1 |
| 2297180 | Animax Specification for 20g Salmosan Soluble Sachet Film, DACO: 2.11.2 CBI |
| 2297181 | Animax Specification for 100g Salmosan Soluble Sachet Film, DACO: 2.11.2 CBI |
| 2297183 | Animax Specification for Salmosan 100g Paper Pouch, DACO: 2.11.2 CBI |
| 2297184 | Animax Specification for salmosan 20g Paper Pouch, DACO: 2.11.2 CBI |
| 2297185 | Animax specification for salmosan 100g inner carton, DACO: 2.11.2 CBI |
| 2297186 | Animax Specification for salmosan 20g inner carton, DACO: 2.11.2 CBI |
| 2555748 | 2015, Day 0 stability Study, DACO: 3.5.10 |
| 2555749 | 2015, Day 14 Stability Study, DACO: 3.5.10 |
| 2604880 | 2016, Stability Testing Time 0, DACO: 2.13.3 |
| 2604881 | 2016, Stability Testing Time 3Months, DACO: 2.13.3 |

| PMRA Document Number | Reference |
|---|---|
| 2604882 | 2016, Stability Testing Time 6 Months, DACO: 2.13.3 |
| 2605262 | 2016, Stability time point 9 months, DACO: 2.13.3 |
| 2555747 | 2015, Sample Photographs, DACO: 3.5.10 |

## 2.0 Human and Animal Health

| PMRA Document Number | Reference |
|---|---|
| 1162525 | Acute Oral LD50 of Technical CGA-18809 in the Rat. 1972. DACO: 4.2.1. |
| 1162526 | Acute Oral LD50 of Technical CGA-18809 in the Mouse. 1972. DACO: 4.2.1. |
| 1162527 | Acute Oral Toxicity Study in Rats. 1990. DACO: 4.2.1. |
| 1162528 | Acute Dermal LD50 of Technical CGA-18809 in the Rat. 1972. DACO: 4.2.2. |
| 1162529 | Acute Dermal LD50 in the Rabbit of Technical CGA-18809. 1977. DACO: 4.2.2. |
| 1162530 | Acute Dermal Toxicity Study in Rabbits.1990. DACO: 4.2.2. |
| 1162531 | Acute Inhalation Toxicity Study in Rats. 1990. DACO: 4.2.3. |
| 1162533 | Irritation Of Technical CGA-18809 in the Rabbit Eye. 1972. DACO: 4.2.4. |
| 1162534 | Primary Eye Irritation Study in Rabbits. 1990. DACO: 4.2.4. |
| 1162535 | Skin Irritation in the Rabbit After Single Application. 1972. DACO: 4.2.5. |
| 1162536 | Primary Dermal Irritation Study with Rabbits. 1990. DACO: 4.2.5. |
| 1162538 | Report on Skin Sensitizing (Contact Allergenic) Effect in Guinea Pigs of CGA-18809. 1982. DACO: 4.2.6. |
| 1162539 | Report on Skin Sensitizing Effects in Guinea Pigs of CGA-18809, Alfacron. 1983. DACO: 4.2.6. |
| 1162540 | Dermal Sensitization Study in Guinea Pigs. 1990. DACO: 4.2.6. |
| 1162542 | 90 Day Dietary Toxicity Study in Rats with Compound CGA-18809. 1975. DACO: 4.3.1. |
| 1162544 | CGA-18809: 4-Week Oral (Dietary Administration) Dose Range-Finding Study in the Rat. June 1986. DACO: 4.3.1. |
| 1162545 | CGA-18809 Toxicity Study in Beagle Dogs (Final Report: Dietary Administration For 13 Weeks). 1975. DACO: 4.3.1. |
| 1162546 | CGA-18809: Toxicity Study in Beagle Dogs: Additional Group (Dietary Intake for 13 Weeks Followed by 4 Weeks Observation). 1976. DACO: 4.3.1. |
| 1162547 | CGA-188809 Technical: 21-Day Percutaneous Toxicity Study in Rabbits. 1978. DACO: 4.3.4. |
| 1162551 | CGA-18809: Lifetime Oral (Dietary Administration) Oncogenicity and Toxicity Study in the Rat with an Interim Kill After 52 Weeks and a 4 Week Treatment-Free Period. Final Report. 1991. DACO: 4.4.1, 4.4.2. |
| 1162552 | CGA-18809: Lifetime Oral (Dietary Administration) Oncogenicity and Toxicity Study in the Rat with an Interim Kill After 52 Weeks and a 4 Week Treatment-Free Period. Final Report. 1991. DACO: 4.4.1, 4.4.2. |

| PMRA Document Number | Reference |
|---|---|
| 1162553 | CGA-18809: Lifetime Oral (Dietary Administration) Oncogenicity Study in the Mouse. 1987. DACO: 4.4.1, 4.4.2. |
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## 3.0 Environment

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### 4.0 Value

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## B. Additional Information Considered

## i) Published Information

### 1.0 Human and Animal Health

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### 2.0 Environment

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