9 November 2023
EMA/CVMP/88291/2011-corr.[1]
Committee for Veterinary Medicinal Products

European public MRL assessment report (EPMAR)

Azamethiphos (extension to fin fish)

On 23 May 2012 the European Commission adopted a Regulation[2] establishing maximum residue limits for azamethiphos in fin fish, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Azamethiphos is intended for use in fish farming to control external parasites with an application rate of 0.1 to 0.2 mg/litre as a bath treatment.

Fish Vet Group Ltd submitted the application for the extension of maximum residue limits to the European Medicines Agency, on 26 January 2011.

Based on the available data, the Committee for Medicinal Products for Veterinary Use recommended on 15 September 2012 the establishment of maximum residue limits for azamethiphos in fin fish.

Subsequently the Commission recommended on 14 March 2012 that maximum residue limits in fin fish are established. This recommendation was confirmed on 4 April 2012 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 23 May 2012.

[1] *The EPMAR was updated in November 2023 to correct the unit of the ADI in section 3.5.*
[2] Commission Implementing Regulation (EU) No 436/2012,O.J. L 134, of 24.05.2012

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Azamethiphos
Therapeutic class:	Antiparasitic agents/Agents against ectoparasites/Organophosphates
Procedure number:	EU/11/185/FVG
Applicant:	Fish Vet Group Limited
Target species:	Fin fish
Intended therapeutic indication:	To control external parasites
Route(s) of administration:	Waterborne use

1. Introduction

Azamethiphos is an organophosphorus insecticide which acts by inhibition of cholinesterase activity.

In Atlantic salmon azamethiphos is used in fish farming to control external parasites with an application rate of 0.1 to 0.2 mg/litre as a bath treatment.

Azamethiphos was previously used as a pesticidal spray for control of flies and cockroaches in warehouses and other buildings, but the authorisation was withdrawn by Commission Regulation (EC) No. 2076/2002 of 20 November 2002.

Azamethiphos was previously assessed by the CVMP and a pharmacological ADI of 0.025 mg/kg bw, i.e. 1.5 mg/person was established.

Currently, azamethiphos is included in table I (Allowed substances) of the Annex to Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Azamethiphos	Not applicable	*Salmonidae*	No MRL required	Not applicable	No entry	No entry

Fish Vet Group Limited submitted the application for the extension of maximum residue limits for azamethiphos from *Salmonidae* to fin fish to the European Medicines Agency on 21 February 2011.

Azamethiphos is intended for use in fin fish (e.g. sea bass, sea bream, coy and tilapia) for the treatment of external parasites with an intended application rate for this use of 0.1 to 0.2 mg/litre as a bath treatment.

2. Scientific risk assessment

2.1. Safety assessment

Azamethiphos was previously assessed by the CVMP and a pharmacological ADI of 0.025 mg/kg bw, i.e. 1.5 mg/person was established based on the NOEL of 2.5 mg/kg bw/day from a dog study (brain cholinesterase activity) and applying a safety factor of 100. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

No residue data were submitted. For the previous assessment with regard to establishment of maximum residue limits in salmon the data summarised in the paragraphs below were considered:

2.2.1. Pharmacokinetics in target species

The absorption of azamethiphos following the topical treatment of salmon was low and there was no bioaccumulation. Depletion of total azamethiphos-related residues in salmon was rapid.

Because of the low residue concentrations, the nature of the residues in salmon muscle was not investigated. Dissected portions of tissues such as skin and liver were homogenised and extracted but the large amounts of co-extracted fish materials and the low amount of radioactivity present precluded characterisation of metabolites. Because significant concentrations of radioactivity were present in bile, the characterisation of metabolites in bile was attempted. The major metabolite, accounting for more than 50% of the radioactivity in bile fluid, was the glucuronic acid conjugate of 2-amino-3-hydroxy-5-chloropyridine. This metabolite had been identified as one of the major metabolites of azamethiphos in rat and goat urine.

2.2.2. Residue depletion studies

Residue depletion was faster in muscle than in other tissues such as liver and skin. Immediately after treatment of salmon with ^{14}C-azamethiphos, formulated as the 50% wettable powder, at a nominal concentration of 0.2 mg/litre in the water, for one hour, mean total residues in muscle were 20 µg equivalents/kg and depleted to 4 µg equivalents/kg, 12 hours after the end of treatment. Over the same time period, mean total residues in salmon skin depleted from 117 µg equivalents/kg to 16 µg equivalents/kg.

The water temperature during the experiment was in the range 11.1 to 13.2°C. Fish were caught at intervals of 1 and 12 hours, and 1, 2, 3 and 7 days after the end of treatment. Although it was intended to sample 10 fish per time point, only 8 fish and 9 fish were taken on days 2 and 3 respectively because some of the fish escaped. Residues in muscle and skin were analysed for azamethiphos using an analytical method based on HPLC with UV detection. Residues of azamethiphos in all samples were below the limit of detection (20 µg/kg), at all time points.

No specific residue depletion data in other fin fish species were provided considering that in accordance with the CVMP *Note for guidance on the establishment of maximum residue limits for Salmonidae and other fin fish (EMEA/CVMP/153b/97-FINAL)* and the *Notice to applicants and Guideline - Veterinary medicinal products - Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin* (Volume 8) the conclusions regarding the residues in meat and skin of *Salmonidae* can be applied to other fin fish.

2.2.3. Monitoring or exposure data

Not available.

2.2.4. Analytical method for monitoring of residues

An analytical method for the determination of residues of azamethiphos in salmon tissues based on HPLC with UV detection and described in the ISO 78/2 format was available. The method was of appropriate specificity and it had been shown that residues of dichlorvos, trichlofon, and the azamethiphos metabolite 2-amino-3-hydroxy-5-chloropyridine did not interfere in the assay. The limit

of quantification was 42 µg/kg for salmon muscle and for salmon skin. Validation data for muscle with skin in natural proportions were not provided and data for accuracy and precision were provided at only 2 concentrations.

The substance is included in table 1 of the Annex of Regulation 37/2010 for *Salmonidae* as "No MRL required" therefore an analytical method for monitoring purposes is not required.

No analytical method for the determination of residues of azamethiphos in other fin fish was provided. Considering that in the previous evaluation it was concluded that no MRL was required for *Salmonidae* no analytical method was required for other fin fish.

2.2.5. Findings of EU or international scientific bodies

No information available.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

In view of the nature of the substance such data are not considered necessary.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

None.

3.3. Elaboration of MRLs

When assessing the data submitted for the establishment of maximum residue limits for salmon it was concluded that immediately after the end of treatment, the amount of total residues likely to be ingested by consumers represents less than 20% of the ADI. Residues of azamethiphos in salmon muscle and skin were always below the limit of detection, even in fish caught within one and 12 hours of treatment. Therefore the Committee considered that there was no need to establish an MRL for azamethiphos in *Salmonidae*.[3]

In order to conclude on the possibility of extending the previous conclusions on the establishment of maximum residue limits for azamethiphos in *Salmonidae* to other fin fish the Committee took into consideration the *CVMP Note for guidance on the establishment of maximum residue limits for Salmonidae and other fin fish* and the *Notice to applicants and Guideline - Veterinary medicinal products - Establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin* (Volume 8).

In line with the principles detailed in these guidance documents, considering the knowledge on the variation in residue depletion within classes of animals, and therefore on the exposure assessment, risk characterisation should not differ substantially within an animal class, in this case between different fish species. The Committee therefore considered that, also in this case, the risk characterisation did not differ between fish species. The Committee also considered that, even though available data comparing the metabolism of veterinary drugs in *Salmonidae* and other fish species are limited,

[3] See http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500010778.pdf and http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500010779.pdf

significant differences between the metabolic profile of substances used in fish species are not apparent. The main difference in metabolism of veterinary medicines in fish appears to be the rate at which the metabolism occurs, which depends on the temperature of the water.

Based on these considerations the conclusions of the assessment for salmon can be applied equally to other fin fish, i.e. no MRL for azamethiphos in fin fish is necessary for the protection of the human health.

3.4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits recommended for azamethiphos based on data in *Salmonidae* to other food producing species and food commodities. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (YES/NO)	Justification
Ruminants	No	Metabolism in fish is significantly different from ruminants and therefore there are no scientific grounds on which to base an extrapolation of MRLs from fish to ruminants. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in ruminant-derived food commodities.
Pigs	No	Metabolism in fish is significantly different from pigs and therefore there are no scientific grounds on which to base an extrapolation of MRLs from fish to pigs. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in pig tissues.
Poultry	No	Metabolism in fish is significantly different from poultry and therefore there are no scientific grounds on which to base an extrapolation of MRLs from fish to poultry. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in poultry-derived food commodities.
Horses	No	Metabolism in fish is significantly different from horses and therefore there are no scientific grounds on which to base an extrapolation of MRLs from fish to horses. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in horse tissues.
Rabbits	No	Metabolism in fish is significantly different from rabbits and therefore there are no scientific grounds on which to base an extrapolation of MRLs from fish to rabbits. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in rabbit tissues.
Honey	No	Residue depletion in honey does not occur through metabolism and consequently conclusions drawn from data

		on residues in other food products cannot be extrapolated to honey. The available data are not sufficient to allow adequate evaluation of the risk to consumer safety posed by residues in honey.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the pharmacological ADI of 0.025 mg/kg bw (i.e. 1.5 mg/person) was previously established as the overall ADI for azamethiphos,
- immediately after the end of treatment of salmon when the water temperature was about 11°C, the amount of total residues likely to be ingested by consumers represent less than 20% of the ADI,
- residues of azamethiphos in salmon muscle and skin were always below the limit of detection, even in fish caught within one and 12 hours of treatment,
- the safety of azamethiphos was previously evaluated for the establishment of MRLs in Salmonidae at which point it was concluded that no MRLs were required for the protection of consumer safety; in view of the known similarities in residue depletion between fish species the same conclusions can be considered to apply to other fin fish species;

the CVMP recommends the extension of the maximum residue limits for azamethiphos and the modification of the entry in Commission Regulation (EU) 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Azamethiphos	Not applicable	Fin fish	No MRL required	Not applicable	No entry	Antiparasitic agents/ Agents against ectoparasites

4. Background information on the procedure

Submission of the dossier	26 January 2011
Steps taken for assessment of the substance	
Application validated:	21 February 2011
Clock started:	22 February 2011
CVMP opinion adopted:	7 April 2011
Request from Commission for reconsideration	12 September 2011
CVMP revised opinion adopted	15 September 2011