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Imidacloprid

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Imidacloprid (fin fish) - Addendum

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Addendum to the monograph prepared by the 94th Meeting of the Committee and FAO JECFA Monograph 28.

Background

At its twenty-fifth meeting, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) requested an evaluation of imidacloprid for use in all fin fish and for the Joint FAO/WHO Expert Committee on Food Additives (JECFA) to recommend maximum residue limits (MRLs) for muscle and fillet (muscle with skin in natural proportions).

Imidacloprid (CAS no. 138261-41-3) was previously reviewed by the Committee at its 94th meeting (FAO and WHO, 2023). The Committee derived a toxicological acceptable daily intake (tADI) of 0–0.05 mg/kg bw per day and a toxicological acute reference dose (tARfD) of 0.09 mg/kg bw.

Due to the absence of a study to assess the impact of imidacloprid on representative human intestinal microbiota, it was not possible to determine a microbiological acute reference dose (mARfD) or a microbiological acceptable daily intake (mADI), thus the Committee was unable to establish an acute reference dose (ARfD) or an acceptable daily intake (ADI) for imidacloprid. As the Committee could not establish an ADI or an ARfD, MRLs could not be recommended.

Current evaluation

Imidacloprid was on the agenda for the current meeting to complete the assessment.

The previously derived tADI of 0–0.05 mg/kg bw/d and the tARfD of 0.09 mg/kg bw were confirmed at the current meeting as the overall health-based guidance values (HBGVs), as the microbiological data provided indicated that mADI and mARfD were not required for imidacloprid.

No additional residue data were submitted for the current meeting.

The Committee reviewed the data contained in the monograph prepared by the 94th Meeting of the Committee, which contained the residue data used to generate upper tolerance limits and estimate dietary exposure (FAO and WHO, 2023). For ease of reference, the key information is represented below.

Residues in food and their evaluation

Conditions of use

Imidacloprid is registered as the veterinary medicinal product Ectosan Vet 1 000 mg/g powder for treatment solution for fish (hereafter referred to as Ectosan), which contains 100 percent imidacloprid. This product is currently authorized for use in Norway (MTnr. 20-13358) and is indicated for the treatment of pre-adult and adult salmon lice *Lepeophtheirus salmonis* infestation in Atlantic salmon *Salmo salar* and rainbow trout *Oncorhynchus mykiss*. It is a bath treatment for use in closed containment vessels (well-boats) only, due to environmental concerns. The product has an approved withdrawal period of 98 degree-days for both Atlantic salmon and rainbow trout.

Dosage

The authorized dosing regimen is 20 mg imidacloprid per litre of sea water for a period of 60 minutes in a well-boat.

It has been noted that the duration of immersion in the treatment baths might be extended to up to 6 hours because of the method used to administer the product.

Appraisal

At the current meeting, JECFA established an ADI of 0–0.05 mg/kg bw/d and an ARfD of 0.09 mg/kg bw, based on the toxicological effects of the drug.

Pharmacokinetics

The pharmacokinetics in fish appears to be similar in all species for which data are available. Imidacloprid is distributed to all tissues in various proportions and hardly metabolized. The only metabolite seen is 5-hydroxy imidacloprid.

The Committee identified imidacloprid as the sole marker residue in Atlantic salmon and rainbow trout fillet and determined that a value of 0.7 was appropriate for the marker residue to total radioactive residue ratio (MR:TRR).

Residue Depletion

The authorized dosing regimen is 20 mg/L administered in a treatment bath for 60 minutes. However, in field conditions it has been noted that it is not always possible to remove the fish from the treatment baths within a reasonable time, which is why data from studies using increased durations of immersion (up to 360 minutes) were provided.

The Committee considered the residue depletion study by Longshaw (2020) to be the pivotal study, as this gave the worst-case results in terms of extent and persistence of imidacloprid residues in Atlantic salmon fillet (Table 1). It was noted that this was because the salmon had been exposed to the treatment solution for longer than the approved duration (6-fold longer). However, it was also noted that this was a practical consideration since the salmon had to be treated in well-boats to prevent exposure of the environment to imidacloprid. As a result, in some cases it can take longer than the approved treatment time to remove the salmon from the treatment bath. It was also noted that this was the study used to set the withdrawal period for the one approved product in a Member State.

Table 1. Mean concentration (± SD) of imidacloprid (µg/kg) in Atlantic salmon fillet 1, 7, 14, 21, 28 and 33 days post exposure

Days post treatment (Degree-days)	60 min Mean ± SD	196 min Mean ± SD	360 min Mean ± SD
1 (15.6)	359 ± 63	740 ± 83	1 372 ± 114
7 (108.8)	71 ± 15	160 ± 24	296 ± 56
14 (206.8)	12.73 ± 3.81	27.45 ± 9.87	54.73 ± 15.90
21 (313.2)	<LLOQ	6.29 ± 2.28[a]	9.57 ± 3.70
28 (422.1)	<LLOQ	<LLOQ	2.68 ± 1.64[a]
33 (508.6)	<LLOQ	<LLOQ	<LLOQ

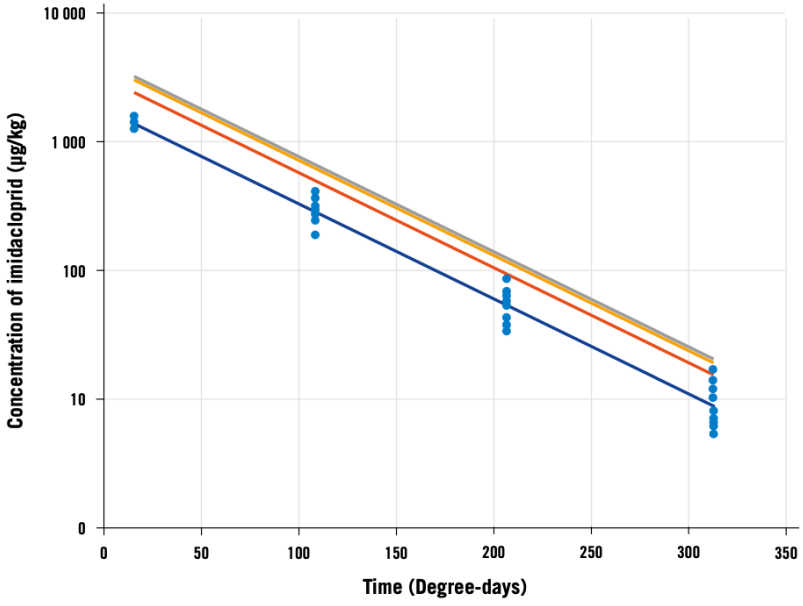
Notes: LLOQ: lower limit of quantification (4 µg/kg); [a]where one or more samples were <LLOQ, the value was taken as 2 µg/kg (1/2 LLOQ) in order to calculate the mean; SD: standard deviation

Source: based on Longshaw, M. 2020. *Extended ECTOSAN® bath exposure and sampling of Atlantic salmon (Salmo salar) for residue analysis*. Report ARD-0014. Ardtoe Marine Laboratory, Ardtoe, Argyll, UK. Sponsor submitted.

It should be noted that there are no data available for repeated treatments, but imidacloprid would be expected to accumulate in fish tissues upon repeated treatments that occur too close together.

The MRLs recommended for salmon fillet are based on the upper limit of the one-sided 95 percent confidence interval over the 95th percentile of residue concentrations (95/95 upper tolerance limit, or UTL) for the 98 degree-day post-treatment data from the non-radiolabeled residue depletion study in Atlantic salmon. The tolerance limits for imidacloprid in Atlantic salmon fillet are shown in Figure 1.

Figure 1. Tolerance limit considerations for imidacloprid in Atlantic salmon fillet



Notes: blue: regression line; orange: 95/95 UTL regression line; yellow: 95/99 UTL regression line; grey: 99/99 UTL regression line

Source: based on Longshaw, M. 2020. *Extended ECTOSAN® bath exposure and sampling of Atlantic salmon (Salmo salar) for residue analysis*. Report ARD-0014. Ardtoe Marine Laboratory, Ardtoe, Argyll, UK. Sponsor submitted.

Dietary exposure assessment

Dietary exposure from pesticide residues

The Committee noted at the 94th meeting of JECFA that dietary exposure to imidacloprid may also occur through its multiple registered uses as a pesticide. A review of previous assessments of pesticide residues showed that dietary exposure from this source is low and most likely not a substantial contributor to overall dietary exposure.

Chronic dietary exposure estimates

At the 94th JECFA, the global estimate of chronic dietary exposure (GECDE) to imidacloprid residues was estimated based on the potential occurrence of imidacloprid residues in Atlantic salmon muscle and all fin fish meat. However, no ADI was recommended at that meeting.

The ADI established at the current meeting is 0–0.05 mg/kg bw.

Based on incurred residues in Atlantic salmon (fillet) and a withdrawal period of 98 degree-days, the estimate of chronic dietary exposure for adults and the elderly (1.0 µg/kg bw per day) is 2 percent of the upper limit of the ADI. For children and adolescents estimated exposure (2.7 µg/kg bw per day) is 5 percent of the upper limit of the ADI, and for infants and toddlers, estimated exposure (0.9 µg/kg bw per day) is 2 percent of the upper limit of the ADI.

Based on consumption of total fin fish meat, the exposure for adults and the elderly (1.8 µg/kg bw per day) is 4 percent of the upper limit of the ADI. For children and adolescents, exposure (3.8 µg/kg bw per day) is 8 percent of the upper limit of the ADI, and for infants and toddlers, exposure (1.2 µg/kg bw per day) is 2 percent of the upper limit of the ADI.

Acute dietary exposure estimates

At the 94th JECFA, the global estimate of acute dietary exposure (GEADE) to imidacloprid residues was estimated based on the occurrence of residues in Atlantic salmon muscle and all fin fish meat. However, no ARfD was recommended at that meeting.

At the current meeting, the ARfD was established as 0.09 mg/kg bw (90 µg/kg bw).

The acute dietary exposure for adults and children (6.2 and 6.6 µg/kg bw, respectively) based on consumption of Atlantic salmon was 7 percent of the ARfD. Acute exposure based on consumption of fin fish (34.1 and 23.8 µg/kg bw) was 38 and 26 percent of the ARfD for adults and children, respectively.

Maximum residue limits

In recommending MRLs for imidacloprid in fin fish fillet (muscle with skin in natural proportions) and muscle, the Committee considered the following:

- The ADI for imidacloprid is 0–0.05 mg/kg bw.
- The ARfD for imidacloprid is 0.09 mg/kg bw.
- Imidacloprid is used as a pesticide and as a veterinary drug.

- Imidacloprid is authorized for use in Atlantic salmon and rainbow trout. The maximum recommended dose is 20 mg/L once, by immersion in a seawater treatment bath for 60 min. The withdrawal period is 98 degree-days for both species.
- Under field conditions, it may not be possible to remove all the fish from the treatment bath immediately after 60 min. Therefore, extended exposure up to 360 min was considered.
- Imidacloprid is the marker residue in Atlantic salmon and rainbow trout muscle and fillet.
- The ratio of the concentration of marker residue to that of total residue was calculated to be 0.7.
- Data on residues in Atlantic salmon and rainbow trout were provided which were derived with a validated analytical method for quantifying imidacloprid in muscle and fillet.
- A validated analytical method for determining imidacloprid in Atlantic salmon and rainbow trout muscle and fillet is available and may be used for monitoring purposes.
- The MRL recommended for salmon and trout muscle, or fillet, is based on the 95/95 UTL at 98 degree-days from an unlabelled residue depletion study in Atlantic salmon.
- The Committee recommended an MRL for Atlantic salmon and rainbow trout fillet (muscle with skin in natural proportions), or muscle, of 600 µg/kg.

The Committee recommended that the MRL be extrapolated to all fin fish.

When considering the possibility of recommending the extrapolation of MRLs, the Committee referred to the discussion at the CCRVDF on the "Proposed approach for the extrapolation of maximum residue limits of veterinary drugs to one or more species" (FAO and WHO, 2021).

Although there are no pharmacokinetic or residue depletion data currently available for species other than Atlantic salmon and rainbow trout, experience shows in general that fish do not metabolize pharmaceutical compounds to a great extent. As such, it is considered to be unlikely that the MR:TRR in non-salmonid fin fish species would be much different from that seen in Atlantic salmon.

It should be noted, however, that water temperature influences the extent of absorption, extent of metabolism, and the rate of elimination in fish. The data available do not address rate or extent of metabolism at higher water temperatures. Many other farmed fin fish species are kept at higher temperatures than salmonid species, and so might have different metabolic profiles, including an increased metabolism which would lead to a lower MR:TRR being calculated, leading to an underestimate of human dietary exposure.

Nonetheless, the Committee considered that, as the worst-case scenario had been used for estimating the likely dietary exposure, there would be a margin of safety for the proposed MRL that could take into account slight differences in metabolism between salmonids and non-salmonids.

References

FAO & WHO (Food and Agriculture Organization of the United Nations & World Health Organization). 2021. *Report of the 25th Session of the Codex Committee on Residues of Veterinary Drugs in Foods.* https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-25%252FREPORT%252FFinals%252FREP21_RVDFe.pdf

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