Pre-Application Assistance – APVMA Written Assistance - Request Tier 2 as part of the '2021-22 Priority Setting Forum of the Assistance Grants – Access to Industry Priority Uses of Agvet Chemicals program' (Grant Program).

Applicant name: FISHERIES RESEARCH AND DEVELOPMENT CORPORATION
Assistance tier: 2
PAA number: 132617
PAA name: Baycox® (68946) / Freshwater and marine finfish / Susceptible parasites / DAWE2021

Summary of proposed application:

This PAA lodged by **Fisheries Research and Development Corporation** is to seek assistance to confirm data requirements for an off label permit submission of a toltrazuril oral solution/suspension registered product Baycox Coccidiocide for Piglets and Cattle (#68946) for the treatment and prevention of susceptible protozoa parasites in marine and freshwater finfish. Specifically, advice on data requirements on the areas of Efficacy and Target animal safety, Environment, Human health/worker safety and Residues and Trade is sought for the proposed application.

APVMA advice:

The APVMA has reviewed your pre-application assistance application and provides the following advice under each of the relevant risk areas.

Human health (Toxicology and Worker Health and Safety):

As the product is registered, a toxicology module is not required, however the use in aquaculture is quite different than the existing uses in pigs and cattle. In order to understand the likely situations where occupational exposure may occur, a detailed description of the fish feed manufacturing process is required, including the quantities of product handled on a daily basis, and the frequency with which any of the treated feed is produced. In addition, exposure may occur while handling treated feed, hence a detailed description of the administration of treated feed and the quantities handled on a daily basis, including the frequency of administration of treated feed to the farmed fish. This will be done under a module 6.3 assessment.

Residues and Trade:

You are proposing to conduct a residues study (no additional details provided) in support of registration of the use of toltrazuril on freshwater and marine finfish.

For registration, metabolism and residues decline data will be required as this will be the first registration of toltrazuril on a new target animal species.

Metabolism:
As use of toltrazuril has not previously been considered, the appropriate marker residue will need to be determined for fish. For registration, a metabolism study in accordance with VICH 46

guidelines should be provided. For an initial minor use permit, a strong scientific argument demonstrating the appropriate marker residue may be adequate.

Residues studies:
For registration, residues studies compliant with current APVMA and VICH guidelines will be required for assessment (https://apvma.gov.au/node/719; https://www.ema.europa.eu/en/vich-gl57-studies-evaluate-metabolism-residue-kinetics-veterinary-drugs-food-producing-species). Residues trials should address the appropriate marker for fish and be reflective of the proposed use with regard to dose rate, route of administration, target species and WHP. You are encouraged to seek guidance regarding trial design through the tier 3 PAA process.

For registration, a residues module 5.2 assessment will be required (module 5.3 for permit assessment) based on current APVMA module descriptors.

Environment:

There are no suitable reference products to address the environmental risks of the proposed use of Baycox Coccidiocide for Piglets and Cattle on freshwater and marine finfish. Therefore, an environmental assessment is required.

For veterinary medicinal products (VMPs), the APVMA has adopted VICH guidelines on data requirements for environmental safety. For an antiparasitic chemical such as toltrazuril, a Phase II assessment[1] is required for which a module 7.2 assessment applies.

The application package must include supporting data to inform the assessment. As per VICH guidelines, this includes data on degradation in aquatic systems (OECD 308). If initial chemical studies indicate a potential for the toltrazuril to photolyse or hydrolyse, then photolysis or hydrolysis studies may be conducted.

In terms of environmental effects studies, data should be supplied on the toxicity to freshwater fish (OECD 203), Daphnia (OECD 202), and algae (OECD 201), and toxicity to marine fish (OECD 203), crustaceans (e.g. mysid shrimp as per OCSPP 850.1035), and algae (i.e. *Skeletonema costatum* as per OCSPP 850.4500). Chronic/ reproduction and sediment toxicity testing is conditional based on the outcomes of the acute assessment.

Because the log Kow of toltrazuril is >4, then evidence from metabolism/residues/excretion, biodegradation studies and molecular mass should be considered to see whether there is the potential for bioaccumulation to occur. If so, then a bioconcentration in fish study should be supplied (OECD 305).

Please note that the APVMA has limited environmental data relevant to toltrazuril in its holdings that can be used to support the proposed product for use in finfish:

- Aqueous photolysis
- Adsorption/desorption to soils
- Acute toxicity to fish
- Acute toxicity to *Daphnia magna.*

[1] https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl38-environmental-impact-assessments-veterinary-medicinal-products-vmps-phase-ii_en.pdf

Efficacy and target animal safety:

Generally, the APVMA cannot assess data as part of PAA request. If you would like to have available data assessed before submitting an application you can submit an item 25 application which allows for the assessment of technical data.

The literature provided with this PAA appears to be providing evidence of efficacy of toltrazuril against various protozoan parasites of fish. It also appears that there were Australian trials conducted with Baycox® (68946) in yellowtail kingfish fingerlings. These will be very important in the consideration of efficacy and safety under the Australian use situation. However as the submitted report is a summary and not a detailed scientific study report, it is difficult to indicate whether the data from these trials would adequately support efficacy and target animal safety.

Generally, in instances where the APMVA holds safety data in the target or related animal species, field study data demonstrating satisfactory tolerance in the target species following administration of the test product at the recommended treatment dose for the recommended duration of therapy may be considered adequate in lieu of a specific target animal safety study depending on the validity and robustness of the field trials. However, in this instance, the APVMA currently does not hold any safety data on toltrazuril in fish, thus a basic controlled study demonstrating the safety of the product in the target species should be provided. You have indicated a dose rate of 10-50 mg active toltrazuril /kg fish bodyweight. It is noted, from your summary report, that the efficacy studies were conducted at only two doses- 25mg/kg and 50mg/kg. In order to be satisfied of product safety, the APVMA requires demonstration of a margin of safety in the target species, where the product is tested at doses in excess of the recommended treatment dose (for example, 3X and 5X the proposed maximum dose rate). Safety of repeated use will also need to be demonstrated. A safety study should also be conducted using the recommended dose rate over a period that is a multiple of the proposed duration of treatment.

Scientific publications, in which safety in fish was demonstrated at toltrazuril doses in excess of the recommended treatment dose and over a period that is a multiple the proposed duration of treatment may be submitted in-lieu of studies.

Further guidance on demonstrating efficacy and target animal safety of veterinary products for use in farmed finfish can be found at https://apvma.gov.au/node/405 . An 8.3 efficacy and safety assessment module is applicable.

International assessments:

The APVMA will consider relevant international assessments, provided the data supporting the assessment are also provided. Guidance for the submission of international data can be found on the APVMA website (https://apvma.gov.au/node/14186).

Resulting application:

The likely item number for this application is item **21**. The likely modules, timeframes and fees applicable, based on the current fee structure, for the proposed application are:

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Module level	**Module type**	**Timeframe***	**Fee**
1	Preliminary assessment	(1 month)	
5.3	Residues	8 months	
6.3	Work Health and Safety	4 months	
7.2	Environment	7 months	
8.3	Efficacy and crop safety	3 months	
11.1	Finalisation	3 months	
Total		**11 months**	**$350**

**The timeframe for the application commences when the application passes preliminary assessment and all fees are paid. The total timeframe is the timeframe of the longest assessment module plus the timeframe of the finalisation module. The APVMA has up to 1 month to undertake preliminary assessment once the application has been lodged.*

Please note that applications may still be subject to recategorisation under section 70B of the Agricultural and Veterinary Chemicals Code. If recategorisation is required, you will be given the reasons why the modules are to be changed and the opportunity to respond.

If additional information is requested under section 159 of the Agricultural and Veterinary Chemicals Code during the assessment of the application, an extended timeframe as outlined in Schedule 6 of the Agricultural and Veterinary Chemicals Code Regulations will apply.

The assistance provided by the APVMA is based on the information provided in your Pre-application Assistance request. If the information you have provided is not complete or correct, that could limit the effectiveness of the assistance provided by the APVMA.

The APVMA gives no undertaking that any application lodged after receiving Pre–application Assistance will be approved.

Outcome:

If you require clarification of any issues addressed in this PAA, please contact the case management team at the APVMA (casemanagement@apvma.gov.au). If you are seeking advice on additional/new questions you will need to apply for further pre-application assistance under a new application (https://apvma.gov.au/node/108).

When submitting this record in support of an application please ensure that you include it in your information list.