

18 June 2021

Supporting document 2

Microbiology Risk Assessment – M1018

Maximum Residue Limits (2020)

Executive summary

This Supporting Document provides information relating to antimicrobial resistance (AMR) implications undertaken for relevant agricultural pesticides and veterinary (agvet) chemicals and food commodities requested through the Maximum Residue Limits (MRL) (2020) Harmonisation Proposal, M1018.

As stated in the Guide to submitting requests for maximum residue limit (MRL) harmonisation proposals, FSANZ has specific regard to requests for veterinary chemicals, including antimicrobials, which are considered on a case by case basis in consultation with the APVMA.

FSANZ concludes that residues of flumequine and the eight triazole fungicides arising from the variations requested do not represent an unacceptable risk to public health and safety from antimicrobial resistance / cross-resistance to important antimicrobials used in human medicine. However, this assessment does not take into account the broader 'One Health' issues associated with antimicrobial resistance. This is particularly of relevance to flumequine, a member of the class of quinolone antibiotics. Quinolones are considered to be of high importance for use in human health in Australia, and of highest priority in the WHO list of critically important antimicrobials for human medicine.

Table of contents

EXECUTIVE SUMMARY	1
1. RISK ASSESSMENT.....	2

1. Risk assessment

Consideration of antimicrobial resistance (AMR) implications for variations requested for antifungal and an antibacterial chemical was undertaken on a case-by-case basis, taking into account any similarities of structure or function with compounds included in either Australia's¹ or the WHO's² prioritisations of the importance of antimicrobials used in human medicine.

Two classes of compounds were flagged for further consideration: the veterinary drug flumequine, and a number of triazole fungicides: difenoconazole, fenbuconazole, flusilazole, flutriafol, mefentrifluconazole, metconazole, propiconazole and tebuconazole.

Flumequine is a second-generation fluoroquinolone antibacterial³ which is active against both Gram-negative and Gram-positive organisms. It inhibits DNA gyrase and topoisomerase enzymes necessary for bacterial cell division. It is no longer in use for treatment of humans, but continues to be used around the world in various food-producing animals. Quinolones are included in both the Australian and WHO lists of important antimicrobials used in human medicine^{1,2}.

The APVMA considers AMR risks for uses of antimicrobials which are proposed for use on-farm in Australia, and includes fluoroquinolones in its list of substances not permitted for use on food-producing animals in Australia⁴. Flumequine is, therefore, not approved by the APVMA for use as a veterinary medicine in any animal species in Australia. However, the APVMA has advised FSANZ that since the use of flumequine in Australia is not proposed, and as there are Codex MRLs for residues of flumequine in fish species other than those requested in this Proposal, the APVMA does not have any concerns associated with this harmonisation request and does not object to the proposed MRLs for import purposes.

Triazole fungicides are considered essential chemicals for fungal disease management in a number of crops, and are widely used in agriculture around the world. Triazoles are also used in the treatment of human mycoses. There is evidence of the emergence of fungicide-resistant isolates of human pathogens—such as *Fusarium* and *Aspergillus* species—which has been related to exposure to fungicides used in agriculture⁵. However, triazoles are not included in either the Australian or WHO lists of important antimicrobials used in human medicine.

FSANZ concludes that residues of flumequine and the eight triazole fungicides arising from the variations requested do not represent an unacceptable risk to public health and safety from antimicrobial resistance / cross-resistance to important antimicrobials used in human medicine. However, this assessment does not take into account the broader 'One Health' issues associated with antimicrobial resistance. This is particularly of relevance to flumequine, a member of the class of quinolone antibiotics. Quinolones are considered to be

¹ *Importance ratings and summary of antibacterial uses in human and animal health in Australia*, June 2018, Office of Health Protection, Australian Government Department of Health, Canberra. www.amr.gov.au/resources/importance-ratings-and-summary-antibacterial-uses-human-and-animal-health-australia. Accessed 17 December 2020.

² *Critically important antimicrobials for human medicine*, 6th revision 2018, World Health Organization, Geneva; www.who.int/foodsafety/publications/antimicrobials-sixth/en/. Accessed 17 December 2020.

³ www.ema.europa.eu/en/documents/mrl-report/flumequine-summary-report-2-committee-veterinary-medicinal-products_en.pdf

⁴ <https://apvma.gov.au/node/11626>

⁵ Ribas E Ribas AD, Spolti P, Del Ponte EM, Donato KZ, Schrekker H, Fuentefria AM. Is the emergence of fungal resistance to medical triazoles related to their use in the agroecosystems? A mini review. *Braz J Microbiol.* 2016;47(4):793-799. doi:10.1016/j.bjm.2016.06.006. www.ncbi.nlm.nih.gov/pmc/articles/PMC5052333/. Accessed 17 December 2020.

of high importance for use in human health in Australia, and of the highest priority in the WHO list of critically important antimicrobials for human medicine.