23 July 2019

chemicals.scheduling@health.gov.au

Dear Sir/Madam

Interim decision on rescheduling proposal for MCPB

I refer you to your published interim decision on the rescheduling of MCPB stemming from the March 2019 ACMS/ACCS meeting[1].

Nufarm made this application under our general stewardship obligations due to new information generated since an MCPB product was last sold in Australia many years ago.

We respectfully request that the interim decision be reviewed as all of the facts contained in our submission do not appear to have been taken into consideration.

The interim decision taken by the TGA is to not amend the poison schedule of MCPB from Schedule 5 to Schedule 6. The rationale for this decision (as published on the TGA website) is solely based on the eye irritancy of two MCPB formulations, not taking into consideration the second criteria for which a threshold was crossed according to your Scheduling Policy Framework (oral toxicity).

The rationale is correct in that only the formulations presented demonstrated severe eye irritancy, whilst the active constituent of MCPB Acid was only slightly irritating. However, as noted on pages 9, 10, 12, 13, 14, 15, 16 and 18 of our application (and in submitted oral toxicity study reports), both the MCPB Acid and MCPB Sodium formulations demonstrated moderate levels of oral toxicity which meet the criteria for a Schedule 6 chemical.

An Appendix to this submission includes select pages from our application which have been reproduced highlighting key passages to re-emphasise this previously submitted information.

On a weight of evidence basis, it is clear that (in accordance with the Scheduling Policy framework) MCPB as an Acid, or when incorporated in formulated products, meets the criteria of a Schedule 6 Poison. This is on the grounds of both moderate oral toxicity and severe eye irritancy; only the eye irritancy can be attributed to a potential formulation effect as the oral toxicity threshold has been crossed by both the acid and one of the formulations.

Nufarm is aware of the need to develop guidance material for private applicant submissions on AgVet Chemicals, including aligning your application form with the changes in the legislative framework in 2017 that allows private applicant submissions to be made for these chemicals. In the guidance material being prepared, we suggest the TGA specifically address instances where it would request full formulation details of AgVet Chemicals so dealings with the TGA can be predictable and transparent. Whilst in this instance these details are irrelevant given the MCPA Acid meets the criteria of a Schedule 6 Poison before being formulated with other ingredients, we want to ensure future applications contain all the information you require.

Note that this is an updated version of our original submission in which we requested a copy of the briefing paper that accompanied our application when it was presented for the Committee's consideration to assist us in understanding the process that has led to this interim decision. The Secretariat kindly provided a copy of this briefing paper and provided us with an opportunity to update our submission. Based on this paper, we wish to raise the following comments and questions in the interests of process improvement:

- Given the introduction to the paper identifies the grounds of our application are on the basis of both the acute oral toxicity and eye damage thresholds, why did the briefing paper only raise specific issues and questions to be considered by the ACCS in regard to the eye damage threshold? That is, why weren't these issues and questions also asked given that two thresholds for rescheduling we equally met (note that the issues and questions below are reworded from the actual briefing paper which only referred to the eye damage threshold):

[1] https://www.tga.gov.au/book-page/23-interim-decision-relation-mcpb

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[redacted]

- Does the ACCS support the proposal to reschedule MCPB from Schedule 5 to Schedule 6 in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) – the Poisons Standard, owing to the potential of the acid and one of the salts to be moderately acutely toxic via oral exposure?
- Is the ACCS satisfied that there is sufficient evidence of moderate acute oral toxicity clearly indicating that MCPB requires upscheduling to S6 from S5?

- Given the committees rationale only included references to eye damage, we are concerned that this is what may have led to a considerable amount of additional work for all parties in reviewing information and preparing additional submissions to ensure that the entirety of our application is appropriately considered in this process. Can the Secretariat suggest how we can improve future applications to ensure we better demonstrate situations where more than one threshold is crossed so both are treated equally throughout the rest of the process?
- We were not previously aware that ACCS are asked in the briefing paper to recommend an implementation date as part of their recommendation (as this does not appear on the Application Form). If our submission on the interim decision is accepted by the Delegate and up-scheduling does occur, please be advised that our preference is for a 1 Oct 2019 implementation date. Nufarm hold the only registrations for MCPB in Australia with the APVMA, so there is no need to consider a delayed implementation. Along with meeting our stewardship obligations to ensure the appropriate Schedule is assigned as soon as possible, our reason for requesting this date is to align with the launch of a new product containing MCPB. In the future, is an applicant's preference for this date something that would be useful to be included in the application form?

The briefing paper also included references from overseas regulators where a similar chemical, MCPA, was used as a surrogate for similar decisions around hazard classifications in those countries. Nufarm note that in The Poison Standard, MCPA is classified as a Schedule 6 Poison (with some exceptions based on the concentration in certain presentations) which further supports this application.

We also note that this paper also indicates that MCPB was Scheduled under S6 prior to 1990, but the paper noted no information was available to the Secretariat to indicate when or why it was rescheduled to S5. Given the data Nufarm have submitted in support of this application was generated after 1990, it is likely that this is irrelevant, but it does indicate that this data adds to the weight of evidence that Schedule 6 is the appropriate classification for MCPB based products.

In conclusion, given the clear alignment our submission has with the Scheduling Policy Framework, Nufarm do not believe any further information is required to reconsider the interim decision of the Committee and align the final decision of the Delegate with our proposal as below:

Schedule 5 – Proposed Amendment	{listing removed}
Schedule 6 – Proposed Amendment	MCPB

Yours sincerely

[redacted]

David Rumbold
ANZ Lead Regulatory

Note: I am authorised to make this application on behalf of Nufarm as a senior manager and the original applicant for this proposal.

[redacted]

APPENDIX – EXCERPTS FROM APPLICATION

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1. OVERVIEW

1. A new herbicidal product containing a combination of MCPB DMA (MCPB acid present at 300 g/L), MCPA DMA (MCPA acid present at 20 g/L) and Flumetsulam (10 g/L) is to be introduced to the Australian market for the control of broadleaf weeds in new and established pastures. This product is to be supplied as a concentrate for dilution and application to pastures using tractor-mounted/trailed boom sprayer or similar.

   MCPB (and its esters and salts) are currently included in Schedule 5 of the Poison Standard.

   Currently the salts of MCPA are included in Schedule 6 of the Poison Standard except when present in product at less than 50%, in which case they are listed in Schedule 5. The MCPA concentration of the new herbicidal product described above (20 g/L) would attract a Schedule 5 classification.

   Flumetsulam is included in Appendix B, Part 3 of the Poison Standard.

   The toxicological profile of the MCPA DMA salt and Flumetsulam are well understood at higher levels of concentration in agricultural chemical products, so are not relevant to this application.

   This application concerns the potential of the salts of MCPB to cause irreversible eye (corneal) damage and the moderate toxicity via the oral route of MCPB acid and MCPB Na salt.

   Severe eye damage and moderate oral toxicity are hazards that are outside of the criteria for Schedule 5.

   Eye irritation studies in animals (refer to Table 1) show the progression of the eye damage from day 2 following installation of the neat product in the test eye. This damage was not reversed by day 21.

   Acute oral toxicity studies in animals (refer to Table 1) show oral toxicity in the range of 500 to 2,000 mg/kg b.w.

   These hazard classifications meet the criteria for Schedule 6.

Page 13 (Table 1)

Parameter	Species	MCPB Acid	Formulation A: MCPB DMA salt 300 g/L	Formulation B: MCPB Na salt 400 g/L	S5 criteria	S6 criteria
Acute Oral LD50	Rat	680 mg/kg bw	> 2000 mg/kg bw	500 – 2000 mg/kg bw	2000 – 5000 mg/kg bw	50 – 2000 mg/kg bw
Acute Dermal LD50	Rat	> 2000 mg/kg bw	> 2000 mg/kg bw	> 2000 mg/kg bw	> 2000 mg/kg bw	200 – 2000 mg/kg bw
Acute Dermal Irritation	Rabbit	Non-irritating	Non-irritating	Slight - Moderate	Slight - moderate	Severe
Acute Eye Irritation	Rabbit	Slightly irritating	Severe	Severe	Slight - moderate	Severe
Acute Inhalation LC50	Rat	>1,400 mg/m^3 (4 hours)[#]	>5000 mg/m^3 (4 hours)	>5000 mg/m^3 (4 hours)	> 3000 mg/m^3 (4 hours)	500 – 3000 mg/m^3 (4 hours)
Skin Sensitisation (LLNA)	Mice / Guinea pig	Non-sensitiser (Guinea pig)	Non-sensitiser (Mice)	Non-sensitiser (Guinea pig)	Weak - nil	Moderate - severe

[#]: Maximum practicable concentration.

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Acute oral LD50 (rat) for MCPB acid is 680 mg/kg b.w. which would trigger an S6 classification. It is greater than 2000 mg/kg b.w. for formulation A and is between 500 to 2000 mg/kg b.w. for formulation B (which would also trigger an S6 classification). Refer to the following studies for further information:

- MCPB acid - Brunt, P. (2003a)
- MCPB DMA - Aswalkar, D. A. (2018)
- MCPB Na - McRae, I. (1995)

CONCLUSION

2. MCPB (including its salts and esters) is listed in Schedule 5. Currently the closely related salts of MCPA are Schedule 6 except when present in product at less than 50%, in which case they are listed in Schedule 5.

   This application concerns the potential of salts of MCPB in an herbicide product to cause irreversible eye (corneal) damage and that MCPB acid, and one form of MCPB salt, has been shown to be moderately acutely toxic via the oral route. Therefore, is it suggested that the entries be altered to the following;

1.1 Schedule 5 – Proposed Amendment

{listing removed}

1.2 Schedule 6 – Proposed Amendment

MCPB

[redacted]