Further Public Submissions on the Proposed Amendments to the Poisons Standard

Notice under subsection 42ZCZQ of the Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary to the Department of Health publishes herein all valid public submissions made in response to the invitation for further submissions on the interim decisions regarding the proposed amendments to the Poisons Standard. These submissions were considered by the chemicals scheduling and/or medicines scheduling delegates.

In accordance with the requirements of subsection 42ZCZQ of the Regulations these submissions have had confidential information removed.

Material claimed to be commercial-in-confidence was considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015), issued by the Australian Health Ministers Advisory Council (AHMAC). The SPF is accessible at: https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.

[redacted]

The Secretary
Chemical Scheduling Secretariat
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Dear Sir/Madam

Public Comment Submission to the Delegate's Interim Decision under subsection 42ZCZP of the Therapeutic Goods Regulations 1990

We refer to the notice published on 1 October 2015 of the Delegate's interim decision under subsection 42ZCZP of the *Therapeutic Goods Regulations 1990*, inviting public submissions, with respect to certain substances, addressing a matter raised in section 52E of the *Therapeutic Goods Act 1989*.

[redacted] provided comments on the following ACCS agenda items for the August 2015 meeting:

- 1.1 3-hexenoic acid, cyclopropylmethyl ester;
- 1.3 *Clitoria ternatea* extract;
- 1.7 Carcinogenic amines;
- 1.9 Phenol 4-amino-3-methyl; and
- 1.10 Phenol 5-amino-2-methyl;
- 1.11 Phenol 2-amino-6-chloro-4-nitro;

[redacted] also provided comments on the following ACCS/ACMS agenda items for the August 2015 joint meeting:

- Methylisothiazolinone (MIT); and
- Methylchloroisothiazolinone (MCI);

We now provide additional comments on **carcinogenic amines, methylisothiazolinone** (MIT); and **methylchloroisothiazolinone** (MCI); in this submission. Please find our comments attached.

[redacted] supports the Delegate's decision on **3-hexenoic acid, cyclopropylmethyl ester**; **phenol 4-amino-3-methyl**; **phenol 5-amino-2-methyl**; and **phenol 2-amino-6-chloro-4-nitro**; and has no objections to the Delegate's decision on ***Clitoria ternatea* extract.**

With regard to the implementation dates as drafted, it appears that the transition period is deemed to have started on the date the interim decision was released, though the decision has not yet been finalised. Given that the interim decision does not have any legislative standing, it would make more sense that the transition period and implementation date be taken from the date of the final decision.

[redacted]

[redacted]

We look forward to further advice from the Delegate. Should the Delegate require any additional information from [redacted] at this stage please do not hesitate to contact me on [redacted]

Yours sincerely

[unsigned for electronic submission]

[redacted]

15 October 2015

[redacted]

3-isothiazolone, 2-methyl- (methylisothiazolinone)

[redacted] has previously provided comments on MIT for the July 2014 meeting of the ACCS and the August 2015 joint meeting of the ACCS/ACMS. Our submissions to those meetings are provided as Attachment 1.

With regard to the Delegates' Interim Decision for;

- **Leave-on cosmetic preparations or therapeutic goods**

We have no objections to the Schedule 6 entry as proposed with a 24 month transition period to allow for reformulation of any affected products.

- **Rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application**

[redacted] has several concerns with the proposed 0.0015% (15 ppm) exemption cut-off.

Effective concentration of MIT as a preservative

At a concentration of 0.0015% or 15 ppm, MIT is not an effective preservative and will not fulfil its intended function of protecting finished product formulations from microbial contamination under normal conditions of manufacture and use. Based on reports from our members, we understand that a concentration of 0.005% (50 ppm) of MIT is the absolute minimum effective concentration in a formulation produced in pristine manufacturing settings (i.e. much better than the usual good manufacturing hygiene levels). It is usually included in formulations at 0.01% (100 ppm) as this is the dose at which it is effective against bacteria.

Anecdotally, we are aware that some manufacturers have trialed the use of MIT as a preservative at a concentration of 0.0015% pre-empting the EU regulations, which notably have yet to be finalised and adopted into the Cosmetic Regulation (EC 1223/2009). The results of the trial showed that products were not adequately preserved. This is a concern as some smaller companies in Australia may believe that they can just reduce the preservative level used in their products and not replace it with another preservative.

Availability and choice of preservatives – need for a broad overview

As noted in our previous submissions, preservatives are chemicals intended to kill microorganisms and will therefore show some level of toxicity. However, without preservatives, products cannot be protected from microorganisms which then raises other health concerns.

Removing any preservative from the currently available set of preservatives will require companies to consider whether there are other preservatives available that are as effective for all of their formulations – there is no absolute guarantee that the replacement preservative will be any better in terms of health outcomes i.e. preservative efficacy and/or significantly improved preservative toxicity profile. Research into new types of preservatives necessarily takes time, and again, there is no guarantee that there will be a better health outcome.

For example, we understand that MIT is an effective replacement for parabens to preserve personal care products. Due to the focus on potential yet unproven health concerns around parabens, we understand that some companies have removed parabens from their formulations and replaced them with MIT. This leaves an interesting question for these companies if MIT cannot be used as a preservative – whether to go back to using parabens, or find some other preservative (if possible).

[redacted]

We believe that there is a need to maintain as broad a choice of preservatives as possible for formulators of products to choose from, as narrowing the choice of preservatives available can potentially lead to increased risk from greater exposure to a narrower range of preservatives i.e. increased exposure to a single type of a preservative.

International Status & Ongoing Assessment

Globally, MIT is currently used in readily available leave-on and rinse off cosmetics and topical therapeutic goods (such as medicated washes and sunscreens) at concentrations up to 0.01% (100 ppm).

We reiterate that the EU SCCS opinion is currently in draft and has not yet been finalised, with the public comment period having closed on 8 September 2015. **There is no EU regulatory proposal to restrict the use of MIT in rinse-off products at this time.**

The US CIR Panel reviewed the June 2015 SCCS opinion on Methylisothiazolinone (MI) and noted that they looked at the same information as the SCCS but came out with a different conclusion[1]. In September 2014, *"the CIR Expert Panel concluded that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be non-sensitizing, which may be determined based on a QRA."* Although the Panel voted not to open the report on MI, they indicated that they will be monitoring reports of sensitization rates to this preservative.

Industry stakeholders in Europe provided considerable information to inform the SCCS opinion during the comment period, including a Quantitative Risk Assessment (QRA) of MIT when used at a concentration of 0.01% (100ppm) in a rinse-off cosmetic. A presentation of the methodology and results of this QRA prepared by the ASEAN Cosmetics Associations based on data from Cosmetics Europe is included as Attachment 2.

A full results table indicating the QRA outcome for all of the different product categories when MIT is used at a concentration of 100 ppm is included in the attachment.

The QRA was used to assess the risk of induction of skin allergy in consumers for a wide range of cosmetic products and to identify the safe levels ensuring prevention of induction of new sensitisation. Exposure data for most of the commonly used products has been taken from various credible sources including SCCS notes of guidance and the QRA guidance document for fragrance allergens[2]. Where data have not been available internal data from member companies has been used or suitable surrogates identified. A representative product portfolio was assessed which included the major product/exposure scenarios for cosmetics and safety assessment factors were applied in consistency with the QRA technical guidance document for fragrance allergens.

Our industry colleagues in Europe believe that the QRA methodology provides an assessment of the potential of induction of skin allergy and that there is a negligible risk inducing skin sensitization when MIT used in rinse-off products up to 100ppm. A proposal was put to the EU Commission that the final SCCS opinion on MIT should be deferred until there is further expert to expert dialog with the SCCS on the QRA and cosmetovigilance methodologies that have been presented.

We have also been informed by our colleagues in the ASEAN Cosmetics Associations that further work is being carried out in Europe by industry (IFRA) in partnership with the Joint Research Centre[3] (JRC) - the European Commission's in-house science service which employs scientists to carry out

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[1] http://www.cir-safety.org/supplementaldoc/september-2015-post-meeting-announcement

[2] QRA Technical Dossier http://www.ifraorg.org/view_document.aspx?docId=22180

[3] Joint Research Centre https://ec.europa.eu/jrc/

[redacted]

research in order to provide independent scientific advice and support to EU policy. The focus of this work is to further improve on the QRA methodology under the IDEA project[4] (International Dialogue for the Evaluation of Allergens), which will facilitate a more robust safety assessment for the use of MIT in rinse-off products. An outcome is expected in 2016. Please refer to the correspondence from ACA included as Attachment 3.

Way forward
As no regulatory action has yet been finalised in the EU, an option could be to further defer the final decision on MIT until the SCCS draft opinion is finalised or until the refined QRA is available.

If the Delegates are committed to making a final decision on the scheduling of MIT now, [redacted] respectfully requests that an exemption cut-off of 0.01% (100 ppm) for use of MIT in rinse-off products is considered, based on the September 2014 CIR Expert Panel conclusions, with a transition period of 24 months. This would bring Australia into alignment with other overseas jurisdictions, and allow for the continued use of safely preserved products already available in Australia.

Over the course of the 24 month transition period, we would expect to see the finalised SCCS opinion, the outcome from the new QRA and any resulting regulatory changes in Europe. If required, this further information could then be used to support a review of the cut-off concentration.

- **For non-cosmetic products**

We support the exemption cut-off of 1000ppm as detailed in the interim decision for *"other preparations that are not for human use"*. We do however question whether the proposed wording of the exemption will, in practice, capture the range of products that it was intended to.

In the interim decision, this exemption is to allow for the use of MIT at concentrations up to 0.1% (1000 ppm) in *"products not intended for direct application to the skin*". This intent does not seem to have been captured fully in the wording of the schedule entry referring to *"other preparations that are not for human use"*.

As detailed in previous submissions, MIT is used in a wide range of products including floor polishes, shoe polishes, ironing sprays, stain removers, carpet cleaners, air-fresheners etc. The term *"not for human use"* may prove problematic in that these products are certainly used by humans, but are not intended for application to one's person.

To clarify the intent of the exemption, [redacted] suggests amending the wording of the schedule entry as follows;

METHYLISOTHIAZOLINONE except:

a) …
b) other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.

[4] IDEA Project http://www.ideaproject.info/

[redacted]

Methylchloroisothiazolinone (MCI)

[redacted] has no objections to the proposed Schedule 6 entry for methylchloroisothiazolinone (MCI) or the exemption cut-off of 0.0015% (15 ppm) total of methylchloroisothiazolinone and methylisothiazolinone for rinse off cosmetic preparations or therapeutic goods intended for topical rinse-off application.

We do however question the exemption cut-off in the schedule entry for "other preparations not for human use" which is also 0.0015% (15 ppm). We believe that this may be an editorial error, as the reasoning in the interim decision suggests that this exemption should be the same as that proposed for MIT, which is 0.1% (1000ppm).

If the proposed cut-off is indeed 0.1% (1000ppm) not 0.0015% (15ppm) as drafted in the interim decision document, [redacted] have no objections to this exemption.

As included in our comments for MIT above, use of the term *"not for human use"* in the schedule entry exemption may prove problematic. To clarify the intent of the exemption, [redacted] suggests amending the wording of the schedule entry as follows;

METHYLCHLOROISOTHIAZOLINONE except:

a) in rinse off cosmetic preparations or therapeutic goods intended for topical rinse off application containing 0.0015 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total; or
b) other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylchloroisothiazolinone and methylisothiazolinone in total.

We also question the new Appendix F entry – perhaps another editorial error? As drafted in the interim decision, it refers to methylisothiazolinone (MIT) not methylchloroisothiazolinone (MCI).

[redacted]

Carcinogenic Amines

As communicated in our previous submission, [redacted] remains concerned with the large number of amines being considered together, particularly as the proposal is to ban the substances.

We are disappointed to note that our request that the decision on the scheduling of azo dyes be deferred at this stage to allow industry more time to review their current formulations has not been granted. As already identified, our members have raised concerns that the large number of substances being considered has made it difficult to check all the chemicals on the list. This means that the true impact of this proposed scheduling entry may not yet be clear.

The proposed entry is very broad and based on feedback from our members, already has conflicts in terms of different SUSMP entries with different requirements for the same ingredient. An example provided to us was for 4-Amino-m-cresol, a derivative ingredient that when used in an oxidative hair dye product could fall under this proposed schedule entry. This chemical was also considered individually, with the Delegate's interim decision stating that this substance should be a new Schedule 6 entry.

It would be very difficult for users of the SUSMP to link their search of an ingredient to the carcinogenic amines entry and all the possibilities of diazotisation reactions. This raises questions as to the level of regulatory effectiveness that could be expected from such a complex entry. It is our understanding that most of these listed substances as currently supplied in hair dye products are not likely to form an azo dye[5].

The Interim Decision makes no provisions for the two substances identified as having been assessed and subsequently allowed to be used as cosmetic colourants in the EU (CAS numbers 85-85-9 and 68391-30-0 respectively). The scheduling entry as proposed could mean that products assessed as safe and freely available to consumers in Europe would no longer be permitted for sale in Australia.

We do not believe that there is sufficient evidence to support inclusion of these two substances in Schedule 7. The proposed Schedule 7 entry should be amended to include a statement to the effect that the schedule entry does not apply if there is another specific schedule entry, and add the two substances in a separate schedule entries (in Schedule 6 or 7 as appropriate) with exclusions for cosmetic dye use.

The proposed Schedule 7 entry, without the inclusion of allowable cut-off limits, also has the potential to be problematic. When considering the status of unscheduled ingredients where derivatives of these seven entries may be present as an impurity, substances could be inadvertently captured as an impurity at any concentration is covered by the Schedule 7 entry.

The proposed implementation date of February 2016 does not allow sufficient time for manufacturers to identify any products which may be affected by the proposed scheduling entry, and if necessary, reformulate their products. The process of substituting a colorant in a cosmetic product and performing the relevant stability and quality testing of the new product takes at least 12 months. These considerations should be allowed for in the implementation date.

[5] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_162.pdf

[redacted]

REPORT TITLE: **Bicyclopyrone: Comments on the Interim Scheduling Decision**

DATE: 15 October 2015

AUTHOR: [redacted]

CONTACT PERSON [redacted]

Bicyclopyrone: Comments on the Interim Scheduling Decision

OCS has concluded that data from the developmental toxicity studies in the rat and in the New Zealand White rabbit confirm that bicyclopyrone is not a developmental toxicant in these species/strains.

Two developmental toxicity studies were conducted in the Himalayan rabbit and in these studies there were findings, on both visceral and skeletal examination of the foetuses, which OCS concluded were sufficient to raise concerns that bicyclopyrone was a developmental toxicant in the Himalayan rabbit.

[redacted] has already comment on the urogenital and skeletal findings in the Himalayan rabbit and would like to take this opportunity to provide some comments on the cardiac findings and post implantation loss in this rabbit strain.

Cardiovascular findings

Increases in cardiovascular changes were observed in both studies in Himalayan rabbits but not in the New Zealand White. The majority of these changes were diagnosed as interventricular septal wall effects which can be separated into two specific categories:

(1) interventricular septal defects affecting the muscular portion of the wall between the ventricles or large defects of the membraneous portion, which are classed as malformations

(2) a category of interventricular wall changes described as either small interventricular septal defects, diverticula, or abnormal surface appearance of the perimembranous portion of the septal wall, which are considered transient effects and are classed variations

Interventricular septal defects classed as malformations

Septal defects involving the interventricular muscular wall are considered a permanent change that could affect potential survival. The incidence across both studies in Himalayan rabbits is shown in **Table 1**.

Table 1: Incidence of Interventricular Muscle Wall Defects in Himalayan Rabbits

Dose (mg/kg/day)	0	1	10	50	250
No. Fetuses (No. Litters Examined)					
Study I	123(21)	-	129(21)	106(19)	115(21)
Study II	148(22)	106(20)	114(20)	-	85(18)
% Fetuses (% Litters) Affected					
Study I	0	-	0	0	3(14)
Study II	1(5)	2(10)	1(5)	-	7(28)
No. Fetuses (No. Litters) Affected					
Study I	0	-	0	0	3(3)
Study II	1(1)	2(10)	1(1)	-	6*(5)

Statistically significantly different from controls, *p < 0.05

As a class, cardiovascular malformations are the most common defect seen in laboratory animals and humans and a review of the literature reveals a background incidence of specific cardiovascular defects in control populations. (American Heart Association, 2005; Hoffman and Kaplan, 2002; Holson et al, 2006). However, the incidence of interventricular muscle wall defects in Himalayan rabbits at 250 mg/kg/day was outside the historical control range and is considered a treatment-related effect.

There is no dose relationship to this finding, an increase above background data being seen only at 250 mg/kg. Maternal toxicity, as evidenced by a lower cumulative bodyweight gain and stomach irritation was noted in both studies at 250 mg/kg, the stomach irritation being sufficient to cause the early removal of two dams from Study 2.

Interventricular changes affecting the perimembranous portion of the septal wall

Observations of minor changes in the perimembranous portion of the interventricular septum were categorized as small septal defects, diverticula (pockets in the surface that did not communicate between the ventricles), or abnormal appearance of the septal wall.

An examination of the incidences of these changes across the two studies revealed a large variability within the population (**Table 2**).

Table 2: Incidence of Ventricular Septal Variations in Himalayan Rabbits

Dose (mg/kg/day)	**0**	**1**	**10**	**50**	**250**
No. Fetuses (No. Litters Examined)					
Study I	123 (21)	-	129(21)	106(19)	115(21)
Study II	148(22)	106(20)	114(20)	-	85(18)
% Fetuses (% Litters) Affected					
Study I	5(24)	-	13*(38)	20*(53)	37*(90)*
Study II	16(68)	8*(30)*[a]	11(50)	-	31*(72)
# Fetuses (# Litters) Affected					
Study I	6(5)	-	17*(8)	21*(10)	42**(19)**
Study II	23(15)	8*(6)* [a]	12(10)	-	26*(13)

Statistically significantly different from controls, *p < 0.05, **p<0.01.
([a]) The incidence of interventricular septal variations was significantly decreased at 1 mg/kg/day compared to the controls.

There is an increased incidence of septal variations at 250 mg/kg but at lower dose levels the number of fetuses and litters affected at any dose group is below that of the control value in Study 2. The control incidence in the second study illustrates how common this finding is in the Himalayan rabbit and the difference in incidence between control animals in the first and second study illustrates the variability.

In short gestation animals, such as rats and rabbits, a significant amount of development occurs in the lactation period. Closing of the interventricular septum happens late in gestation in all animals and in short gestation animals it follows that ‘shunts’ in the shared ventricular walls may close in lactation. Solomon (1997) showed that in rats a low percentage of septal defects seen at birth in the Sprague-Dawley rat were not evident at the end of lactation indicating that such findings are transient and have no consequence post-natally.

There was no evidence of interventricular septal variations in the New Zealand White rabbit but it is worthy of note that in these studies foetal evaluation took place on day 29 of gestation, one day later than the evaluations in the Himalayan rabbit. Given that the septa would be expected to be closing at this time, a one day difference could make a significant difference to the appearance of the interventricular septum. Indeed, the high percentage of control animals showing septal variations and the significant variability in these findings in the Himalayan rabbit suggests that foetal examination took place at a time of active closure of the cardiac septa.

Summary of the cardiovascular findings

In the Himalayan rabbit there are 2 distinct findings associated with the interventricular septum.

a. Defects affecting the muscular wall are considered malformations. The incidence of these findings is increased in the top dose group (250 mg/kg) only in association with evident maternal toxicity.

b. Findings in the perimembraneous region of the septum are considered variations. The incidence of these findings is increased at the top dose group only in association with evident maternal toxicity. At lower dose levels (50 mg/kg and below) the incidence is within the control data from the second study and at these dose levels the findings are considered incidental to treatment.

Post-implantation loss

In the first study in the Himalayan rabbit there was statistically significant increase in the incidence of post-implantation loss at any dose level whilst in the second study an increase was noted at the top dose level. (Table 3)

Table 3: Post implantation Loss in Himalayan Rabbits

	0 mg/kg	1 mg/kg	10 mg/kg	50 mg/kg	250 mg/kg
Study 1					
Post-implantation loss	19		20	27	32
% of implant sites	13.4		13.4	20.3	21.8
Mean	0.9		1.0	1.4	1.5
Standard Deviation	1.0		1.1	1.5	1.7
Number of dams affected	12		11	10	12
Study 2					
Post-implantation loss	12	16	17		40
% of implant sites	7.5	13.1	17.0		32.0
Mean	0.5	0.8	0.9		2.2**
Standard Deviation	0.7	1.0	1.2		1.6
Number of dams affected	10	10	9		15

Statistically significantly different from controls, *p < 0.05, **p<0.01.

In the first study the absolute number of post- implantation losses and the percentage of implantation sites affected was slightly higher than the concurrent control at 50 and 250 mg/kg. However the number of dams affected was not increased above the concurrent control number.

Inspection of the individual animal data (Appendix 9 in each report) confirms that the total number of resorptions at 50 mg/kg was heavily influenced by 2 dams – Number 47 which lost 4 of the original 7 implants and number 48 which lost 4 of the original 10 implants. Other dams had a similar profile to the control group. At 250 mg/kg the total number of resorptions was again heavily influenced by 2 dams – Number 62 which lost 6 of the original 7 implants and number 63 which lost 4 of the original 9 implants. Other dams had a similar profile to the control group. Had the slightly higher post-implantation loss in the 50 and 250 mg/kg groups in this study been attributable to dosing with bicyclopyrone a higher overall number of dams would have been expected to be affected. The fact that just 2 dams in each group seem to be influencing the overall number of loses is supported by the higher standard deviation of the mean in these groups and the fact that the incidences are not statistically significant.

In the second study a statistically significant number of post-implantation losses was noted at the 250mg/kg dose level. At this dose level there was evident maternal toxicity as shown by a lower cumulative bodyweight gain and stomach irritation which was sufficient to cause the early removal of 2 dams from study 2. The post implantation losses in this group are predominantly early which supports an effect secondary to maternal toxicity.

Summary of the post-implantation loses

The statistically significant increase in post-implantation loss at 250 mg/kg in Study 2 is considered to be treatment related and to be secondary to the evident maternal toxicity at this dose level.

The slightly increased incidence of post-implantation loss at 50 and 250 mg/kg in Study 1 is not statistically significant. There is no increase in the number of dams involved and the increase is considered attributable to a higher incidence of resorptions in only 2 animals per dose group. The incidence of post-implantation loss in Study 1 at 50 and 250 mg/kg is considered incidental to treatment.

Conclusions

In the Himalayan rabbit there is a treatment related increase in the incidence of cardiac septal malformations and variations and post-implantation loss at 250 mg/kg in the presence of evident maternal toxicity. At doses of 50 mg/kg and below there is no increased incidence of septal malformations and the incidence of septal variations is highly variable but within the incidence seen in control animals in the second study.

The incidence of early post-implantation loss is statistically significantly increased in the second study at 250 mg/kg, the pattern reflecting the maternal toxicity at this dose level. In the first study although there is a slight (non-significant) increase in the number of post-implanatation losses at 50 and 250mg/kg there is no increase in the number of dams affected and, at both dose levels, the increase in mean incidence is attributable to 2 dams showing a higher number of early resorptions. There is no treatment related effect on post-implantation loss in study 2.

Overall treatment related effects on the cardiac septum and on post-implanation loss in the Himalayan rabbit are restricted to the top dose level, 250 mg/kg. At lower dose levels the small differences from concurrent control are considered to be incidental to treatment.

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