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Department of Health
Therapeutic Goods Administration

Scheduling Scoping Study (Phase 1)

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Regulation



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Executive Summary

This review of current processes and scheduling decisions in relation to cosmetic and fragrance ingredients has been conducted as part of a project seeking to consider opportunities to further amend and implement the changes arising from the review of the Scheduling Policy Framework (SPF¹) and scheduling process for medicines and chemicals. The review also directly addresses a number of concerns raised by industry relating to scheduling decisions and limitations of current scheduling arrangements. These concerns primarily relate to consistency of scheduling decisions across related substances, clarity of definition of derivatives of scheduled items, the capture of low-level impurities by schedule entries and the creation of unique Australian restrictions and labelling requirements for cosmetic products.

Thirty cosmetic ingredients that had been the subject of scheduling applications between March 2016 and June 2018 were reviewed and the scheduling decisions or recommendations were compared against the respective EU Cosmetics Directive entries to determine the degree of concordance/discordance with a major trading regulatory jurisdiction. These substances were examined for consistency across the decisions for related substances, and evaluated for proportionality with the risks arising from their use. The adequacy of the scheduling applications to support the deliberations of the scheduling committee and the delegate was also assessed for a proportion of the substances, against the various matters the legislation and SPF required to be considered.

Of the 30 cosmetic (excluding hair dye) ingredient substances considered for scheduling between March 2016 and June 2018, the recommendations were largely or entirely concordant with EU cosmetics regulations for only five. For nine substances that the EU has prohibited for use in cosmetics, the scheduling decision, while clearly intended to restrict use in cosmetics, allows their continued use as S6² entries. In the case of methylisothiazolinone for example, its use in personal skin wipes has continued with the product carrying the signal heading of POISON, leading to enquires from the public concerned at the apparent incongruity of a personal wipe carrying this heading. For twelve of the compounds, the scheduling outcome is overly restrictive, discordant with the level of risk presented by the substances and products containing the substance require unique Australian labelling, with substantial attendant costs imposed on Australian Industry. For five substances the scheduling outcome is inconsistent with similar substances already in the Poisons Standard, generally due to inconsistent management of skin sensitisation, and at least three decisions result in unintended cross regulatory capture affecting a range of non-cosmetic uses such as complementary medicines. For at least two of the substances the entries are ambiguous, either because the capture of derivatives is indeterminable (Phenol) or the entry does not unambiguously specify the actual substance intended to be captured (Fennel oil). The *hazard*-based assessments underpinning many of the scheduling applications also raise issues of public perception and confidence in the process with one substance explicitly (but from a *risk* perspective wrongly) identified as a carcinogen yet recommended for inclusion in S5³ and S6.

The legislative basis for scheduling requires a *risk-based* approach, balancing the risks presented by a substance in the form and at the levels used in consumer and other products against the benefits availability of such products provide. In general, applications for the scheduling of cosmetic ingredients were found to be primarily hazard based reflecting the regulatory environment of the applicant, and did not adequately address issues related to risk, or the regulatory (and cross regulatory) impact of the proposed scheduling. The requirement for ingredients permitted for use in complementary medicines, for example, includes that they are not included in a schedule of the Poisons Standard. The proposed scheduling of geraniol in S6 for example would result in a number of

¹ <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

² Schedule 6: **Poison** – Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

³ Schedule 5: **Caution** – Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

essential oils that are currently included in Appendix B⁴ being both S6 and unscheduled, and therefore simultaneously both eligible and ineligible for approval as an ingredient in listed medicines.

Many of the issues identified reflect the limited availability of detailed guidance documentation to support applicants in the preparation of the documentation required for robust scheduling deliberations. Appropriate technology support for the submission of scheduling applications would greatly facilitate the provision of guidance to applicants and the maintenance of readily accessible records of decisions for the secretariat, scheduling committee, delegate and other stakeholders.

Industry concerns regarding the low-level presence of impurities that are included in Schedules 7-10 were considered by examining two case studies, ethylene oxide (S7⁵) and 1,4-butanediol (S10⁶). Both these substances are used industrially as reagents in the synthesis of various cosmetic ingredients such as surfactants and polymers, and low level or trace impurities are therefore not unusual, but are not covered by exemptions which exist for impurities of schedule 1 to 6 substances. The lack of a formal tolerance for low levels of S7 – S10 impurities of synthesis is inconsistent with both the sophistication of modern analytical techniques and the general tolerance granted for impurities in agricultural and veterinary chemicals, and creates substantial unintended regulatory compliance burdens for industry. These issues are addressable through the development of appropriate impurity cut off provisions for S7 to S10 substances.

Another industry concern considered is the uncertainty of regulatory capture inherent in the current broad and ambiguous definition of derivative. Although the definition is necessarily broad to prevent deliberate circumvention of restrictive scheduling for drugs of abuse or addiction or potent toxicants, the scope of the current derivative definition collectively covers drugs of abuse, drugs of addiction, potent poisons and the wide range of consumer and domestic chemicals with much narrower spectrums of concern. Relatively simple procedural modifications combined with a more nuanced range of definitions for 'derivatives' that provide guidance to the scheduling committee⁷ and delegate in identifying derivatives of likely concern might substantially reduce the ambiguity and reduce the potential for unintended and inappropriate capture of substances.

In identifying options for scheduling process improvement, priority/preference has been given to those that do not require changes to either enabling legislation or government policy. Many of the options identified may require further analysis to determine their viability and suitability. Substantial improvements in the scheduling outcomes for cosmetic and consumer product ingredients can be achieved through largely procedural reforms and the provision of improved guidance to applicants, delegates and the committee members. Proposed areas for consideration include:

- alignment of scheduling decisions with international regulatory requirements where practicable and appropriate;
- preparation for the scheduling committee and respective delegates of improved, science based, guidance for estimating acute risk of dilute preparations to provide a sound foundation for consistent decision making;
- improvement of the scheduling application form to require broader assessment of the impact of scheduling decisions on industry and to ensure that all affected preparations (such as essential oils) are considered;
- liaison with the ACCC to ensure ingredient lists on cosmetic products must contain any substance identified in the EU cosmetics directory as requiring inclusion on the label in compliance with the various cut off values specified.

⁴ Appendix B: 'substances considered not to require control by scheduling'

⁵ Schedule 7: **Dangerous Poison** – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

⁶ Schedule 10: **Substances of such danger to health as to warrant prohibition of sale, supply and use** - Substances which are prohibited for the purpose or purposes listed for each poison.

⁷ The Advisory Committee on Chemicals Scheduling, ACCS

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- improved engagement between relevant advisory committees where a substance under consideration crosses regulatory boundaries;
 - routine, explicit, definition of derivatives that should be captured for each new entry;
 - develop standardised, contextualised definitions for derivatives appropriate for different toxicological or other end points driving the scheduling decision; and
 - develop improved options for managing 'low level presence' as impurities of substances included in Schedules 7 to 10.

Glossary

Table 1 Glossary of Abbreviations

Acronym	Expansion
ACCC	Australian Competition and Consumer Commission
ACCS	Advisory Committee on Chemical Scheduling
ACD	Allergic Contact Dermatitis
ACCM	Advisory Committee on Complementary Medicines
ACMS	Advisory Committee on Medicines Scheduling
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AICS	Australian Inventory of Chemical Substances
CMEC	Complementary Medicines Evaluation Committee
CORs	Comparable Overseas Regulators
DST	Dermal Sensitisation Threshold
ECHA	European Chemicals Agency
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
IMAP	Inventory Multi-tiered Assessment and Prioritisation process
IFRA	International Fragrance Association
Joint ACMS-ACCS	Joint Advisory Committees on Medicines and Chemicals Scheduling
JECFA	Joint WHO/FAO Expert Committee on Food Additives
LOAEL	Lowest Observed Adverse Effect Level
NESIL	No Expected Sensitisation Induction Level
NICNAS	National Industrial Chemicals Assessment Scheme
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Cooperation and Development
OTC	Over The Counter
PPE	Personal Protective Equipment
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCCS	Scientific Committee on Consumer Safety (Europe)
SCCP	Scientific Committee on Consumer Products (Europe)
SPF	Scheduling Policy Framework
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
WoE	Weight of Evidence

General Issues

Introduction

In 2016-2017, the Department of Health (Health) reviewed the Scheduling Policy Framework (SPF⁸) and scheduling process for medicines and chemicals. That review identified that improvements were required to streamline the process by which chemicals are scheduled.

As part of a project seeking to consider opportunities to further amend and implement these changes, Health requested an Expert Review of current processes and scheduling decisions in relation to cosmetic and fragrance ingredients to identify how closely Australia's decisions align with other regulators (in particular the EU). Of particular interest was an exploration of whether there are opportunities to harmonise chemical scheduling outcomes with requirements of comparable overseas regulators (CORs). In conducting this review consideration has also been given to concerns raised by industry, and their proposed improvements in processes to address those concerns.

In reviewing the scheduling process for cosmetic ingredients, a distinction is made between substances generally present in very low concentrations (such as fragrances and flavours) and other ingredients such as surfactants, which may be present at considerably higher levels. This review has focused primarily on the former in recognition of the low levels of use in cosmetic products, the low level of risk generally presented by these substances, and the consequent potential for disproportionate impacts of regulatory burdens placed on industry by scheduling decisions discordant with international practice in major markets.

Before examining the nature of the information and advice provided to the delegate (and referred to the scheduling committee) in scheduling applications for cosmetic ingredients, and the delegate's subsequent scheduling proposals/decisions, a consideration of the nature and scope of cosmetic ingredients, the regulatory environment for such ingredients in Australia and the legislative objectives of scheduling is appropriate.

Staging

This review is primarily a scoping study to identify potential areas for improvement in the current processes and attention has been addressed to two broad groups of issues;

1. **General issues** related to the operation of the Poisons Schedules
 - a. Interpretation and suitability of derivatives definition for substances in the various schedules,
 - b. Unambiguous identification of scheduled substances,
 - c. Capture of low level impurities by Schedules 7, 8, 9 & 10
 - d. Consideration of unintended regulatory impacts
2. Adequacy of Scheduling submissions
 - a. Have all the matters the committee must have regard to been adequately and robustly addressed to support the decision making of the Committee.
 - i. Section 52 (e)
 - ii. The SPF
 - iii. The Scheduling Handbook⁹

⁸ <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

⁹ <https://www.tga.gov.au/publication/scheduling-handbook-guidance-amending-poisons-standard>

Industry Concerns

Industry representatives have raised a number of concerns which broadly fall under the following categories:

- no provision to exempt trace levels (impurities) of Schedule 7, 8, 9, or 10 substances in cosmetic or fragrance materials;
- inconsistencies in regulatory recommendations between scheduling applications for related substances or substances with similar hazard profiles;
- the interim scheduling decisions (issued in May 2017) for benzyl salicylate, anise alcohol and cinnamaldehyde were not consistent with other decisions for amyl cinnamaldehyde and hexyl cinnamaldehyde; geraniol (3,7-dimethyl-2,6-octadien-1-ol); and isoeugenol, substances that are also fragrance/flavour ingredients with similar toxicity profiles;
- inconsistencies with international regulations;
- proposed scheduling for benzyl salicylate, anise alcohol and cinnamaldehyde were discordant with regulation under the EC Cosmetics regulation;
- Australian-specific labelling; and
- the EU Cosmetics Regulation does not routinely require statements such as 'Keep out of reach of children' or 'avoid exposure to skin' for hair dye products.

What is a Cosmetic or Fragrance Chemical

In Australia and Internationally the regulation of chemicals intersects with the regulation of drugs, food constituents/additives, pesticides and industrial chemicals. Surfactants used in cosmetics or pharmaceuticals are equally likely to be found in drilling muds, fracking fluids, pesticide formulations or a myriad of other industrial and domestic uses. The Schedule 4 substance deanol (also known as 2-dimethylaminoethanol) also has local and international uses in cosmetics, paints, lacquers and varnishes. Most fragrance chemicals are also found naturally in foods such as herbs and spices, complementary medicines, and OTC products, often at higher levels than may be used in a fragrance. Geraniol for example is a simple monoterpene composed of 2 isoprene sub units, and is formed early in the biosynthesis pathway of more complex terpenoids (Eslahi, Fahimi, & Sardarian, 2018). Consequently, geraniol occurs at significant levels in a range of essential oils that have been formally considered for inclusion as an approved ingredient for listed medicines by ACCM, or its predecessor CMEC, and the Complementary and OTC Medicines Branch.

There is therefore significant potential for narrowly focused, compartmentalised regulatory proposals by individual agencies or applicants through the scheduling mechanism to result in unintended consequences unless a broad consideration of the use patterns of individual and related classes of substance proposed for scheduling is undertaken and provided to the delegate.

Equally the toxicology data for an individual substance is likely to be distributed across a range of regulatory agencies with a substantial proportion of that data not visible to any individual agency or the scheduling secretariat. Isoeugenol (a component of clove oil) for example was originally proposed for scheduling as a result of an application to the Australian Pesticides and Veterinary Medicines Authority (APVMA) for use as a farmed fish anaesthetic. Subsequent review by the National Industrial Chemicals Assessment Scheme (NICNAS) under its Inventory Multi-tiered Assessment and Prioritisation (IMAP) process resulted in proposed amendments to the Poisons Standard entry. Isoeugenol is additionally used as a food, and is also used medicinally as a local anaesthetic.

In addition to the broad overlap of individual substances across regulatory jurisdictions, individual chemicals will exist as a member of broad classes or groups with related functions/properties or related structures. Chemical classes might for example include fatty acid esters of glycerol, or polyethoxylated surfactants or quaternary ammonium or phenolic disinfectants. Restrictions on one isolated member of a class may simply shift usage to closely related members with closely similar functional properties, or inadvertently and inappropriately capture 'derivatives' with less hazardous

profiles. Consequently, scheduling decisions not attached to a specific application for approval of a product should not be limited to individual substances in isolation, but rather should consider related members of each relevant class, or be considered in the context of the class of compounds as a whole.

Option for Consideration

Considerations of cosmetic ingredients within classes (that is a group of related substances) rather than individually may facilitate consistency, improve the overall quality of data (through 'read across') and reduce unintended or unforeseen regulatory impact.

The Regulatory Environment

The regulatory environment for chemicals in Australia is complex, duplicative, fragmented and prone to compartmentalisation. The poisons scheduling process is only one, relatively small, component of this regulatory environment and, at the Commonwealth level, intersects with the regulatory regimes for consumer products (ACCC), pesticides and veterinary chemicals (APVMA), human pharmaceuticals, complementary medicines and medical devices (TGA), and industrial chemicals (NICNAS and enHealth). Any individual chemical is highly likely to fall under the responsibilities of more than one of these agencies.

Cosmetics Regulation in Europe

The basis of cosmetics control in Europe is the EU cosmetics Regulation, first passed into law in 2009 (EU Cosmetics Regulation 1223/2009/EU) replacing the earlier Cosmetics Directive. The new regulations have the force of law across Europe whereas the previous directive required incorporation into the law of each individual member of the EU, leading to inconsistencies in implementation. The EU cosmetics regulation does not impose compositional standards for cosmetics and does not require pre-approval of ingredients for use in cosmetics. The onus on safety of cosmetic products rests with the manufacturer and the notified 'Responsible Person' who must take individual legal responsibility for the safety of each product for which they are the notified 'Responsible Person'. The choice of safe ingredients and use levels is the responsibility of the 'Responsible Person' (advised by his safety assessor, and subject to in-market surveillance by the national authorities).

For some substances, the EU legislator has identified the need to introduce EU-harmonised restrictions. These are laid down in the Annexes II to VI of the EU Cosmetics Regulation, providing a set of lists, limiting the use of some ingredients to guarantee the safety of the final preparation:

- Annex II lists substances which may not be used;
- Annex III lists substances which may be used subject to certain conditions and restrictions;
- Annex IV is a positive list of colouring agents (currently still excluding hair dyes);
- Annex V is a positive list of preservatives; and
- Annex VI is a positive list of UV filters.

Cosmetic ingredients are however subject to a range of other legislative requirements under various EU chemicals regulations (eg REACH).

To assist manufacturers to utilise fragrance ingredients at levels that are unlikely to be hazardous, the International Fragrance Association (IFRA) has created ingredient monographs that identify potential hazards and indicate safe levels of the individual substances in various categories of cosmetic product. The recommendations of IFRA are based on the advice of an expert toxicology assessment panel of the Research Institute of Fragrance Materials (RIFM) which publishes detailed risk assessments in peer reviewed journals (eg Food and Chemical Toxicology). RIFM was formed in 1966 to analyse, evaluate and distribute scientific data, cooperate with official agencies and encourage safety standards for the use of fragrance ingredients.

RIFM risk assessments also utilise extensive exposure data based on robust surveys of actual use of cosmetics by consumers. These surveys have identified the quantity of various cosmetic products applied, and the area and location of application and the frequency of use. These data provide the

basis for exposure assessment underpinning the RIFM evaluations and the IFRA standards (Cadby & Troy, 2002). Members of IFRA that supply fragrance ingredients to cosmetic manufacturers are required to provide a copy of the IFRA monograph for the ingredient to the purchaser to support safe use in cosmetic products, and therefore support compliance with EU regulations by the 'Responsible Person'.

The Nature of Poisons Scheduling

The Poisons Standard Schedules are legislative in nature (SPF) and are a Commonwealth Legislative Instrument (see the Scheduling Handbook.)

The Poisons Schedules are intended to set the level of controls on the availability, labelling and packaging of poisons primarily for domestic use. The scheduling decision making process is risk rather than hazard based. The introduction to the Poisons Standard indicates that:

Although toxicity is one of the factors considered, and is itself a complex of factors, the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance.)

The basis for risk categorisation of substances is detailed in the *Therapeutic Goods Act 1989* (The Act), the SPF and the Scheduling Handbook.

Legislative Requirements for Scheduling

An understanding of the legislative basis for the Poisons Standards, and in particular the matters that must be considered in determining the need to include a substance in the Poisons Standard, provides the context for identification of sources of potential procedural deficiencies that might lead to discordance with international regulations, and to identify any opportunities for improvement in the current process. The legislative basis for poisons scheduling is established in Section 52 E of the Act, which specifies the matters that the Secretary (or their delegate) must have regard to when considering the inclusion of a substance in a schedule of the Poisons Standard. In addition to the SPF and the advice of the scheduling committee, these matters consist of (where relevant);

- (a) the risks and benefits of the use of a substance;
- (b) the purposes for which a substance is to be used and the extent of use of a substance;
- (c) the toxicity of a substance;
- (d) the dosage, formulation, labelling, packaging and presentation of a substance;
- (e) the potential for abuse of a substance;
- (f) any other matters that the Secretary considers necessary to protect public health.

The Act directs that the matters to have regard to must be read in conjunction with the SPF. The SPF makes clear that 'poisons include medicines for human therapeutic use, veterinary medicines, agricultural, domestic and industrial chemicals where there is a potential risk to public health and safety' and that "Poisons are scheduled according to the risk of harm and the level of access control required to protect consumers."

The Scheduling Handbook also make clear that scheduling may need to be reconsidered where knowledge or practice changes. Thus, although the SPF provides a set of ostensibly hazard-based factors as a basis for achieving consistency of scheduling decisions and as an illustration of the level of *potential* risk each schedule is intended to manage, scheduling is a risk-based process. Submissions for scheduling can reasonably be required therefore to provide the information necessary to support a risk assessment and consideration by the delegate of the matters required by legislation and supporting documents to be taken into account.

Potential Sources of Discordance

Discordance between the risk assessments and risk management measures implemented by different agencies and between international jurisdictions can occur for a range of reasons. These differences are not necessarily unintended or inappropriate as they may represent differences in patterns of use, risk tolerance, or pragmatic recognition of consumer or industry need specific to a location or jurisdiction.

Discordance may however also occur through frank errors of scientific interpretation although this is relatively uncommon. More commonly, discordance occurs through the disconnect between hazard based classification systems such as the GHS and risk based regulatory schemes such as the scheduling process, a too narrow focus on individual chemical substances rather than classes, inadequate consideration of actual patterns of use and resultant exposures, lack of consideration of self-management of risk by susceptible consumers (skin sensitisation for example) or a too narrow consideration of the regulatory capture of an individual substance.

The Globally Harmonised System of Classification and Labelling of Chemicals (GHS), which forms the basis of industrial chemical labelling and regulation) was developed primarily to ensure that chemicals in the workplace are clearly labelled to identify potential workplace *hazards*. Industrial chemicals and industrial chemical products in the workplace may be used in a multitude of processes, each with their unique potential risks of exposure, and therefore risks of harm. Risk therefore cannot be pre-assessed out of context of the environment of use. The GHS consequently is not a risk-based scheme and the labelling and classification is dominantly hazard based. Equally, industrial users of chemicals are required to consider potential occupational risks to their employees within the context of their facilities and processes and implement appropriate engineering or Personal Protection Equipment (PPE) procedures to minimise exposure and therefore risk.

The regulation of drugs, pesticides, domestic chemicals and food ingredients by contrast is *risk* (and/or risk benefit) based. The principle difference between risk and hazard assessments is a consideration and estimation of the likelihood that a hazard in animal or *in vitro* toxicology studies will be manifest in humans under specific exposure scenarios. Consequently, a hazard-based classification for a specific chemical may be based on a toxicological finding that presents no significant risk in circumstances of normal use of that chemical.

Case Study: Isoeugenol is non-genotoxic, but produces tumours in old rats and mice at high life time doses without affecting survival. Although the chemical is correctly *hazard* classified under the GHS as 'Cat 3 – limited evidence of carcinogenic effect', a *risk categorisation* would state that the chemical is unlikely to present a carcinogenic risk to humans at the concentrations used, and the resultant exposures, in food and consumer products. The advice and interpretation required by the delegate is the latter rather than the former. Although an equivocal/possible *hazard* has been identified in animals under extreme exposure conditions a *risk* to humans under realistic exposure scenarios is implausible.

A wide range of essential oils and natural products in common herbs, spices and other foods yield positive findings in animal carcinogenicity studies (Ames & Gold, 1997) but do not present any known *risk* of carcinogenic effects in humans at the exposures resulting from their use. Risk communication is a critical aspect of consumer advice. Over stating risk through hazard-based categorisation creates the risk of warning fatigue, where consumers cease to take warnings and health advice seriously due to the frequency with which otherwise innocuous products carry excessive or alarming hazard statements.

Options For improvement

Identification of Scheduled Substances

In conducting a review of recent scheduling recommendations, a notable challenge was to identify unambiguously which chemical some of the relevant entries in the Poisons Standard specifically referred to. The Poisons Standard generally does not include an extensive range of chemical synonyms and only rarely includes a CAS number. In order to cross reference substances considered by the scheduling committee with the same substance considered by the EU SCCP/SCCS and those included in the EU regulation (EC) No. 1223/2009 it was necessary in many cases to extract the CAS number

from the scheduling decision documentation and search on that term in the EU documents and database.

Option

The routine inclusion of a CAS number or other internationally recognised unique identification number in the Poisons Standard entries is a simple low resource intensive mechanism for improving the accessibility and ease of interpretation of the Poisons Standard.

Presence at low levels / Impurities

The Poisons Standard allows the presence of impurities of substances included in Schedules 1 to 6 at a concentration not exceeding 10 mg per litre or 10 mg per kilogram (0.001%, 10 ppm), unless that substance is also included in Schedule 7 or 8 (in which case no tolerance is permitted), and any substance present as an impurity in a pesticide, at a level identified in the *Standards for Active Constituents*, as published by the APVMA. No allowance is made for any impurity from Schedules 7 to 10 regardless of how low the level, and regardless of whether that substance also has an S6 or S5 entry. Appendix G – Dilute preparations – provides additional exemptions for low level presence of a small number of otherwise scheduled substances.

The absence of a cut off level for impurities in cosmetic and domestic chemicals, to exempt low levels of chemical impurities included in schedules 7 to 10, does not reflect the advances in analytical techniques and creates substantial unintended regulatory compliance burdens for industry. The sophistication of modern analytic instruments and techniques is such that impurities can be detected and identified at levels in the parts per billion (ppb) or trillion (ppt).

Case Study: Industry cite the example of ethylene oxide which is an S7 substance with no cut-off or use exemption. Ethylene oxide is used in the manufacture of poly ethoxylated surfactants, and is consequently a low-level residue in many commonly used surfactants e.g. alkylphenol ethoxylates. A strict application of the Poisons Standard would make products using these surfactants S7 and require the stipulated controls and labelling. This is clearly not the intent of scheduling process.

Case Study: 1,4-Butanediol (in Schedule 10) is used industrially as a solvent and in the manufacture of some types of plastics, elastic fibres and polyurethanes. This compound is in Schedule 10 in non-polymerised form in preparations for domestic use, primarily because it is also a drug of abuse. Low levels of the compound however would be expected to remain in materials and products manufactured using it. Under the current threshold arrangements, no impurity level is permissible, and these products are also technically Schedule 10. This is unlikely to be the intent of the scheduling process.

Options

A number of options for managing low level presence of scheduled substances can be identified which include:

- greater use of Appendix G;
- designation of a generic concentration threshold for impurities (eg 1, 10 or 100 ppb, ie µg/kg) unless a specific entry specifies otherwise;
- explicit impurity cut offs for each substance in schedules 7 to 10; or
- some combination of these approaches.

Derivatives

The Poisons Standard includes in Part 1 – Interpretation – a ‘definition’ of derivatives that extends the scheduling of specific substances to related compounds that share significant structural, toxicological or pharmacological characteristics with the specific scheduled substance. The definition is necessarily broad in order to prevent deliberate circumvention of restrictive scheduling, especially of drugs of abuse or addiction or potent toxicants, to avoid repetitive schedule entries for the various salts of a specific substance and to ensure that structurally related substances with predictably similar

toxicological/pharmacological properties are captured with a single entry. The scope of the current derivative definition collectively covers drugs of abuse, drugs of addiction, potent poisons and the wide range of consumer and domestic chemicals with much narrower spectrums of concern. Because of the broad application of the definition it does not accommodate the very different issues that each class of scheduled substance present. The current definition is also so broad it is largely uninterpretable, creating considerable regulatory uncertainty. A small number of schedule entries explicitly define the derivatives covered by that entry which substantially reduces or eliminates potential ambiguity for those entries. Some relatively simple procedural modifications together with a more nuanced range of definitions for derivatives that provide guidance to the delegate in identifying derivatives of likely concern might substantially reduce the ambiguity and reduce the potential for unintended and inappropriate capture of substances.

Case Study: Ethylene oxide is used as a reagent in the production of a wide range of cosmetic products. The question arises as to whether these ethoxylated surfactants are 'derivatives' of ethylene oxide. Although chemically speaking ethylene oxide is a reagent, the vagueness of the definition of derivative creates uncertainty, even though the toxicological profile of the surfactant/polymer is significantly different to the scheduled compounds.

Options

Consideration should be given to stratifying the definition of derivative across the schedules of the Poisons Standard, differentiating between substances that are included due to the various types of adverse reactions driving the need for scheduling. The choice of definition would be based on:

- pharmacological properties of concern (based on the pharmacophore);
- systemic toxicological properties of concern (based on the toxico-phore); or
- topical/physicochemical properties of concern (based on the physicochemical property of concern – eg pH, solvent or surfactant strength)

Development of guidance for the scheduling committee, delegate, secretariat, applicants and other stakeholders should be considered to support consideration of which (or which range) of derivatives are appropriate to capture based on the nature of the risks/concerns determining the scheduling decisions.

Unintended consequences

The breadth of the derivatives definition leads to a range of potential inappropriate and unintended consequences which can be illustrated with a few examples, as follows.

Cross Regulatory Impact

To be eligible for use in a listed medicine, an ingredient, among other conditions¹⁰:

'must not be subject to a Schedule of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) also known as the Poisons Standard.'

All essential oils consist of a mixture of a range of terpenoids and related compounds, (Chizzola, 2013). Terpenoids are biosynthesised by the progressive addition of isoprene units. Geraniol and linalool are, in addition to nerol and lavandulol, primary products in terpene biosynthesis. Geraniol and nerol occur at some level in nearly all terpene-containing essential oils. The proposed scheduling of geraniol creates a range of potential unintended and inappropriate consequences.

Palmarosa oil, citronella oil and geranium oil are all included in Appendix B for any use for reasons of low toxicity. Geraniol (and its isomer, nerol), a major ingredient in palmarosa oil (approx. 65%), citronella oil (10-20%) and rose oil, and a minor ingredient in geranium oil, is included in Schedule 6 if in preparations at greater than 5%. Technically speaking all these essential oils are both not scheduled (Appendix B) and Schedule 6 according to the Poisons Standard. The second major ingredient in palmarosa oil is geranyl acetate (approx. 20%), a condensation product of geraniol and acetic acid and therefore possibly captured as a derivative. It is likely to be captured by the geraniol

¹⁰ <https://www.tga.gov.au/sites/default/files/australian-regulatory-guidelines-complementary-medicines-argcm-v8.0.pdf>

schedule entry as this does not exclude derivatives (and it readily converts to geraniol by hydrolysis) i.e. palmarosa oil is approx. 85% geraniol and its derivative.

The vagueness of the definition of derivative potentially means that the scheduling of a small number of terpenoids could result in all essential oils being barred from being included in listed and complementary medicines.

Recognition of International Standards – Precedence

Industry has proposed that Australia should adopt by reference, or incorporate in the Poisons Standard, the EU Cosmetics Directive. This proposal raises the question as to the practicality of that approach. There is precedence for recognising international regulatory requirements for flavours and fragrances in Australian regulatory Instruments. The Food Standards Code of Food Standards Australia New Zealand (FSANZ) for example recognises international approvals or safety assessments of flavouring agents in standard 1.3.1 (see break out box below).

Permitted flavouring substances, for the purposes of Standard 1.3.1, are

Flavouring substances which are listed in at least one of the following publications –

- Generally Recognised as Safe (GRAS) lists of flavouring substances published by the Flavour and Extract Manufacturers' Association of the United States from 1960 to 2011 (edition 25); or
- Chemically-defined flavouring substances, Council of Europe, November 2000; or
- 21 CFR § 172.515; or
- Flavouring substances obtained by physical, microbiological, enzymatic, or chemical processes from material of vegetable or animal origin either in its raw state or after processing by traditional preparation process including drying, roasting and fermentation; or
- Flavouring substances obtained by synthetic means which are identical to any of the flavouring substances described in subparagraph (b).

For prescription medicines, changes to a formulation involving a change relating to a colouring agent, flavour or fragrance are Self-Assessable Requests (SARs) - lower risk variations for which the sponsor can provide an assessment of their own data for the TGA to verify (TGA, 2017). This provision recognises the low risk associated with flavouring and fragrance materials **at the levels they are used in such products**. Additionally, the TGA utilises the monographs of recognised Pharmacopoeias, and for colourings:

- the Food and Agriculture Organisation (FAO)/World Health Organisation (WHO) Combined Compendium of Food Additive Specifications¹¹
- the European Union regulations - laying down specifications for food additives No. 231/2012¹²

Consequently, there are a number of directly analogous precedents that would support recognition of International regulations and non-government standards as a basis for exempting fragrance (and colouring, preservative and other) materials from scheduling.

¹¹ <http://www.fao.org/docrep/009/a0691e/a0691e00.htm>

¹² <https://publications.europa.eu/en/publication-detail/-/publication/a42dd9b2-b63f-438b-a790-1fa5995b7d41>

Options.

A relatively simple approach to exempting cosmetic ingredients from the application of the poisons schedules while adopting the provisions of the EU cosmetics guidelines and IFRA standards might be to include in Appendix B an entry along the following lines:

Fragrance compounds in cosmetic products when used at levels permitted by, and where the product is labelled in accordance with, the EU cosmetics directive (specify latest version explicitly) and when the levels used in the product are below the limits specified by the IFRA standard (specify latest version).

Some recognition of the US FDA cosmetics regulations may also be appropriate. Flavour compounds and other cosmetic ingredients might be similarly managed. An additional amendment to the interpretation section of the Poisons Standard to recognise the Appendix B entry may also be required.

Scheduling Application Adequacy

In order to explore any differences between the outcome of scheduling decisions and the provisions of the European Cosmetics Directive, a direct comparison of cosmetic ingredients proposed for scheduling has been undertaken focusing initially on the level of concordance between the decisions of the delegate and the EU Cosmetics Directive perfume ingredients for scheduling recommendations made between March 2016 and June 2018 (Table 2). The basis of delegate decisions and of scheduling committee advice to the delegate is the scheduling application. The adequacy of advice provided to the delegate and of the delegate's decisions is therefore dependent on the quality and adequacy of the application. Comments provided by Industry and the secretariat have identified a number of specific substances that have proved problematic and the scheduling applications and consequent decisions or proposals for these are examined in greater detail later in this document.

Basis for Scheduling Recommendations

As a generality, dermal cosmetic ingredients by intent are of low systemic toxicity via the dermal route. Frank carcinogens or reproductive toxicants (ie substances that present a genuine risk of such endpoints as opposed to simply triggering hazard statements) for example are unlikely to be knowingly used in cosmetic products by reputable manufacturers. Consequently, acute toxicity endpoints tend to be the primary drivers of most scheduling decisions.

The primary risk determinants of scheduling decisions for most cosmetic ingredients therefore, are the acute oral and dermal toxicity, skin and eye irritation and skin sensitisation. Each of these toxicological effects exhibit classical dose response relationships with a threshold for effect occurring at some dose (acute systemic toxicity) or level of dilution (irritation) or dose per unit area (sensitisation). Determination of the likely threshold for effect is a critical aspect of scheduling decisions and a key requirement for acceptable scheduling applications. Acute systemic toxicity through oral and dermal exposure is relatively straight forward to extrapolate across dilutions. For a product containing 10 % of a substance with an oral LD₅₀ of 1000 mg/kg bw, the product as a whole will have an LD₅₀ of 10,000 mg/kg bw (10 x 1000 mg/kg) provided other ingredients do not contribute significantly to the toxicity of the product. Arguably however, the dose that results in death of 50% of animals (LD₅₀), although used as a basis for SPF criteria, is not an especially appropriate dose metric for consumer risk assessments. A more appropriate metric might be the highest non-toxic or highest non-lethal dose, which give a more usable estimate of risk.

Similarly, for most direct eye and skin irritants, irritation will decline directly with increased dilution, although calculating a specific dilution with low to negligible irritancy generally requires experimental data. Nonetheless low concentrations, below say 0.5 %, are very unlikely to be severe irritants. Chlorocresol for example is a severe eye irritant at high concentrations (ECHA, 2018) but is approved for use as a preservative in eye drops at 0.2 % in the EU (Cosmetic Ingredient Review Panel, 1997).

For skin sensitisation the situation is somewhat more challenging. Allergic contact dermatitis (ACD) depends primarily on the activation of allergen-specific T cells. A clear distinction needs to be made between *elicitation* of a skin sensitisation reaction in previously sensitised persons versus *induction* of sensitisation in naïve individuals. The EU (cosmetic) directive is intended to address the former and the IFRA guidance the latter. Thus, the IFRA standard for anisyl alcohol sets limits for eleven product

use categories that range from 0.04% for category 1 (lip products) to 2.5% for category 11 (candles). Hand creams, in category 5, have a limit of 0.36% for safe use. The EU Cosmetics Regulation however sets a limit of 0.001 % in leave-on products and 0.01 % in rinse-off products, above which the product must be labelled with a statement of the presence of the ingredient. The two standards work in combination to ensure that products compliant with the IFRA standard will not induce sensitisation in naïve individuals, and that sensitive individuals will have the necessary information to be able to avoid a product that might illicit sensitisation. Although these limits are expressed as a percentage of the ingredient in products, those percentages, particularly for the IFRA standard, are based on a consideration of the amount of the various types of product applied and the area of application compared to the Weight of Evidence (WoE) No Expected Sensitisation Induction Level (NESIL) expressed as $\mu\text{g}/\text{cm}^2$. This approach reflects the principle dose metric for skin sensitisation of dose per unit area of skin. Neither total dose nor the concentration of a substance in a preparation provide a usable basis for *risk* estimation (unless combined with an application rate for the product that gives an exposure per unit area of skin). The entire process of the induction phase requires approximately ten days to several weeks, whereas an elicitation phase reaction develops within 1–2 days.

Thus, the purpose of labelling is to alert a sensitive person to the presence of the ingredient and to enable anyone having a reaction to identify the ingredient(s) that might be responsible. The purpose of the IFRA standard conversely is to ensure products do not contain sufficient of an ingredient to induce sensitisation in a naïve individual.

The dose per unit area, generally $\mu\text{g}/\text{cm}^2$, is a function of:

1. concentration of the substance in a product;
2. amount of product applied; and
3. area of skin product is applied to.

Various reliable sources of information are available to estimate these parameters. Skin sensitisation is a threshold effect. Sufficient of a substance must be applied per cm^2 of skin to initiate an effective immune response to lead to induction of sensitisation. A key concept that does not appear to have been addressed in scheduling submissions is that of the Dermal Sensitisation Threshold (DST). The DST has been derived utilising an analogous approach to that used for the derivation of Threshold of Toxicological Concern (TTC) – widely used internationally and within the TGA and APVMA for consideration of the toxicological significance of impurities in pharmaceuticals and pesticides.

Option - Guidance to Applicants

Not all originators for scheduling applications will be familiar with the risk based requirements for scheduling of a substance. In order for scheduling applications contain sufficient information for decision making, more comprehensive guidelines are required, indicating the nature of the required data, the preferred approach to risk assessment and the appropriate depth of analysis expected. The guidance to applicants might consist of a more guided and extensive application form, in combination with more comprehensive guidance documents on assessing risks associated with the principle hazards driving scheduling decisions (eye and skin irritation, acute oral, dermal, and inhalational toxicity and skin sensitisation) that incorporate current best practice. The application form might ideally provide a means for electronic capture of the data to support the scheduling process into the future and free up the limited secretariat resources for more value additive activities, such as ensuring appropriate and adequate consultation with potentially affected parties (agencies, commercial and community stakeholders), ensuring consistency of scheduling outcomes and limiting cross regulatory unintended impacts.

Concordance of the Scheduling Committee Advice with EU Cosmetic Requirement

Industry has expressed concern that the outcomes from scheduling deliberations on cosmetic ingredients is substantially divergent from the requirements of the international regulations most notably those of the EU Cosmetics directive. A comparison of recent scheduling decisions for cosmetic ingredients with the requirements of the EU Cosmetics Directive has therefore been conducted to gauge the extent and frequency of the divergence (Table 2 and Table 3).

Of the thirty cosmetic ingredient substances (excluding those solely used in hair dyes) considered for scheduling between March 2016 and June 2018, the recommendations and/or delegates' decisions (interim or final) were largely or entirely concordant with EU cosmetics regulations for five. For nine substances that the EU has prohibited for use in cosmetics the scheduling decision, while clearly intended to restrict use in cosmetics allows their continued use as S6 entries. In the case of methylisothiazolinone for example, its use in baby wipes has continued with the product carrying the signal heading of POISON. This outcome has elicited enquires from the public concerned at the apparent incongruity of a personal wipe carrying this heading.

For twelve of these compounds, the scheduling outcome is overly restrictive and discordant with the level of risk presented by the substances, and requires unique Australian labelling. For five substances the scheduling outcome is inconsistent with similar substances already in the Poisons Standard, generally due to inconsistent management of skin sensitisation. At least three decisions result in unintended cross regulatory capture affecting a range of non-cosmetic uses, such as complementary medicines. The proposed S6 entry for geraniol entry, for example, is discordant with a range of essential oils in Appendix B which contain high levels of geraniol. For at least two of the substances the entries are ambiguous, either because the capture of derivatives (phenol) is indeterminable, or the entry does not specify the actual substance intended to be captured (fennel oil). As some entries have more than one issue, the numbers above sum to more than the 30 substances considered.

Table 2. Regulatory Concordance* of Scheduling Decisions Related to Cosmetics (excluding Hair Dye Ingredients) March 2016-June 2018

* Concordance against EU cosmetics Regulation for concentration limits and labelling

(Comparison with EU/IFRA permitted levels and labelling requirements; fragrances, essential oils, surfactants, hair dyes)

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
Crystal violet & related dyes March 2016	<p>Schedule 10 – new entry METHYLOSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) AND THE FOLLOWING TRIARYLMETHANE DYES– for use in hair dyes</p> <ul style="list-style-type: none"> ○ Acid Violet 49 (CAS No. 1694-09-3) ○ Ethyl Violet (CAS No. 2390-59-2) ○ Basic Blue 7 (CAS No. 2390-60-5) ○ Basic Blue 26 (CI 44045) (CAS No. 2580-56-5) <p>Schedule 6 – New entries METHYLOSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) AND THE FOLLOWING TRIARYLMETHANE DYES</p> <ul style="list-style-type: none"> ○ Acid Violet 49 (CAS No. 1694-09-3) ○ Ethyl Violet (CAS No. 2390-59-2) ○ Basic Blue 7 (CAS No. 2390-60-5) ○ Methylum, 4-(dimethylamino)phenylbis4-(ethylamino)-3-methylphenyl-, acetate (CAS No. 72102-55-7) <ul style="list-style-type: none"> ▪ except when included in Schedules 4 or 10 <p>BASIC BLUE 26 (CAS No. 2580-56-5) except when used as a colourant in cosmetics not intended to be in contact with mucous membranes.</p> <p>Schedule 4 – Amend entry CRYSTAL VIOLET for human use except when used as a dermal marker. – replace “CRYSTAL VIOLET” with “METHYLOSANILINIUM CHLORIDE”</p> <p>Index entries: Crystal violet – see methylrosanilinium chloride Gentian violet – see methylrosanilinium chloride</p>	<p>Prohibited EU Cosmetics Regulation 1223/2009 Annex II: (CAS No. 548-62-9; CAS No. 1694-09-3; CAS No. 2390-59-2; CAS No. 2390-60-5; CAS No. 2580-56-5) CAS No. 548-62-9; CAS No. 2580-56-5) are on the candidate list of substances of very high concern for eventual inclusion in Annex XIV (ECHA, 2014).</p>	<p>Concordant for hair dyes</p> <p>Discordant for cosmetics. EU prohibits use in cosmetics. S6 likely to have the same effect but is not an explicit prohibition. Basic Blue 26 is unscheduled when in cosmetics not contacting mucous membranes</p>
Disperse Yellow 3 June 2016	<p>Schedule 10 – New Entry DISPERSE YELLOW 3 – for use in hair dyes (CAS 2832-40-8)</p> <p>Schedule 6 – New Entry DISPERSE YELLOW 3- except when in Schedule 10</p> <p>Appendix E, Part 2 – new entry DISPERSE YELLOW 3 Standard statements: A, S1</p> <p>Appendix F, Part 3 – new entry DISPERSE YELLOW 3 Warning Statement: 28 Safety direction: 4</p>	<p>EU Cosmetics Regulation 1223/2009 Annex II Prohibited</p>	<p>DISCORDANT FOR COSMETICS. EU prohibits use in cosmetics. S6 likely to have the same effect but is not an explicit prohibition.</p>
Chrysoidine base	<p>Schedule 6—New Entry CHRYSOIDINE except when in Schedule 10 (CAS 495-54-5)</p>	<ul style="list-style-type: none"> • EU Cosmetics Regulation 1223/2009 Annex II; (CAS 495-54-5) 	<p>DISCORDANT FOR COSMETICS. EU prohibits use in cosmetics. S6 may</p>

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>Schedule 10 —New Entry CHRYSOIDINE in preparations for use in hair dyes. Appendix E, Part 3 - new entry CHRYSOIDINE Standard statements: A, S1 (wash off skin), E1 (wash out of eyes)</p>		<p>discourage use but is not an explicit prohibition.</p> <p>Derivatives in EU more narrowly defined as 'salts'</p>
Methyldibromo glutaronitrile	<p>Schedule 6—Amend entry METHYLDIBROMO GLUTARONITRILE except when in Schedule 10 Schedule 10 - Amend entry METHYLDIBROMO GLUTARONITRILE in preparations intended to be in contact with the skin, including cosmetic use</p>	EU Cosmetic Directive 76/768/EEC Annex V - Not listed (not permitted as a preservative)	DISCORDANT EU prohibits (does not permit) use in cosmetics. S6 may discourage use but is not an explicit prohibition.
Bis-Isobutyl PEG/PPG Aug 2016	<p>Schedule 6—New Entry (CAS 921936-12-1) BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER except in rinse-off cosmetic products containing 1 per cent or less of bis-isobutyl PEG/PPG-20/35/amodimethicone copolymer when labelled with a warning to the following effect: IF IN EYES, WASH OUT IMMEDIATELY WITH WATER. Appendix E, Part 2 - New entry BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER Standard statements: A, E1 Appendix F, Part 3 - New entry BIS-ISOBUTYL PEG/PPG-20/35/AMODIMETHICONE COPOLYMER Safety direction: 1</p>	EU Cosmetic Directive 76/768/EEC – no restrictions	<p>DISCORDANT Public submission: substance is intended for use in dilute, rinse off cosmetic products; first aid statement E1 "If in eyes wash out immediately with water." normally applied to severe eye irritants is redundant; no restrictions on the use of this polymer internationally.</p> <p>Exceptionally unlikely to be more than a mild eye irritant at 1%</p> <p>The cut off alone (without FAI) likely to be adequate risk management. Scheduling application inadequate to support decision</p>
Direct Red 254 Oct 2016 Azo dye for agvet use (marker)	<p>Schedule 6 – New Entry DIRECT RED 254 except when included in Schedule 5. Schedule 5 – New Entry DIRECT RED 254 in preparations containing 30 per cent or less of Direct Red 254. Index – New Entry DIRECT RED 254 cross reference: 2-NAPHTHALENESULFONIC ACID, 7-AMINO-4-HYDROXY-3-[[P-[(P-SULFOPHENYL)AZO]PHENYL]AZO]-, BIS(TRIETHANOLAMINE) SALT Schedule 5 Schedule 6</p>	Not a permitted colour for cosmetics in the EU disodium salt (CAS No. 6300-50-1) and as the triethanolamine salt (CAS No. 64683-40-5)	<p>This colour was scheduled for the purpose of an Ag spray tracer product. It is not a permitted EU cosmetic colourant.</p> <p>However, S5 does not explicitly prohibit use in cosmetics BUT no indication it is used or would be desirable to use in cosmetics</p>
Quinoline# CAS 91-22-5	<p>Schedule 6 – New Entry QUINOLINE and its salts (excluding other derivatives). Index – New Entry QUINOLINE cross reference: 2,3-BENZAPYRIDINE Schedule 6 Appendix E, Part 2 Appendix F, Part 3</p>	EU regulation (EC) No 1223/2009 not a permitted colour Not restricted as a flavour	*DISCORDANT ; Quinoline is an alkaloid from various plant species including Mentha species. Also present in alcoholic beverages, cocoa, black tea and scotch whiskey. S6 entry too broad. Unintended capture not adequately considered. JECFA (2016) ADI 3 mg/kg bw/day (180

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>Appendix E and F - New Entries</p> <p>Appendix E - QUINOLINE Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water)</p> <p>Appendix F - QUINOLINE Warning statement: 79 (will irritate eyes). Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).</p>		mg/day for 60 kg person)
<p>Phenoxyethyl oxirane CAS 122-60-1</p>	<p>Schedule 6 - New Entry PHENOXYMETHYL OXIRANE. Appendix E - PHENOXYMETHYL OXIRANE Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water). Appendix F - PHENOXYMETHYL OXIRANE Warning statements: 12 (vapour is harmful to health on prolonged exposure), 28 [(Over) (Repeated) exposure may cause sensitisation], 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract). Safety directions: 1 (avoid contact with eyes), 3 (wear eye protection when mixing or using), 4 (avoid contact with skin), 5 (wear protective gloves when mixing or using), 7 (wash hands thoroughly after use), 8 (avoid breathing vapour), 9 (use only when in well-ventilated areas).</p>	<p>EU regulation (EC) No 1223/2009 Annex II prohibited As 1,2-Epoxy-3-phenoxypropane (phenylglycidyl ether)</p>	<p>PARTIALLY CONCORDANT EU Prohibited, AUS S6 NICNAS IMAP indicates use in Australia unknown, scheduling based on international use. S6 may discourage use but is not an explicit prohibition.</p>
<p>Amyl and hexyl cinnamaldehyde CAS 122-40-7, 101-86-0</p>	<p>Appendix B - New Entries AMYL CINNAMALDEHYDE HEXYL CINNAMALDEHYDE</p>	<p>EU: EU Cosmetics Regulation 1223/2009 Annex III—the presence of the chemical must be indicated in the list of ingredients when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products.</p>	<p>DISCORDANT EU requires name of ingredient to be on the label when above sensitisation cut off values.</p>
<p>Isoeugenol CAS 97-54-1/ 5932-68-3</p>	<p>Schedule 6 - Amend Entry ISOEUGENOL except: a) when included in Schedule 5; or b) in preparations not intended for skin contact containing 10 per cent or less of isoeugenol; or c) in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol. Schedule 5 - Amend Entry ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol except in preparations containing 10 per cent or less of isoeugenol. Appendix E, Part 2 - New Entry ISOEUGENOL Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).</p>	<p>European Union (EU) Cosmetics Regulation 76/768/EEC Annex III Part 1—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down—maximum authorised concentration in the finished cosmetic product: 0.02%; Based on qualitative risk assessment, the International Fragrance Association (IFRA) has indicated an acceptable concentration for isoeugenol in skin contact products should be 0.02%.</p>	<p>DISCORDANT EU requires labelling to state presence of the substance when ingredient is > 0.001% in leave on products and 0.01% in rinse of products</p> <p>Schedule entry does not require inclusion on label</p>

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>Appendix F, Part 3 – New Entry ISOEUGENOL Warning statements: 19 (WARNING – Skin contact may be dangerous. Take every precaution to avoid contact – wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes). Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).</p>		
<p>Climbazole CAS 38083-17-9</p>	<p>Schedule 6 – Amend Entry CLIMBAZOLE except: a) when included in Schedule 5; or b) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or c) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole. Schedule 5 – Amend Entry CLIMBAZOLE in preparations containing 40 per cent or less of climbazole except: a) in leave-on hair, face and foot cosmetic preparations containing 0.5 per cent or less of climbazole; or b) in other preparations (that are not leave-on cosmetic preparations) containing 2 per cent or less of climbazole.</p>	<p>EU Cosmetics Regulation 1223/2009 Annex V— List of preservatives allowed in cosmetic products. The maximum concentration allowed is 0.5% in ready for use preparations. The SCCS has concluded (SCCS 2013) that climbazole ‘may be used as a preservative (or non-preservative) ingredient up to a maximum concentration of 0.5% in leave-on hair and face cosmetics. Its non-preservative use in rinse-off hair cosmetics up to a maximum concentration of 2% was also considered to be safe. Its use in leave-on products other than those mentioned above was, however, not considered safe’. Furthermore, ‘the non-preservative use of Climbazole either in foot care cosmetics alone at a concentration of up to 0.5% or in combination with either shampoo (at a maximum concentration of 2%) or face cream (at a maximum concentration of up to 0.5%) or with hair lotion (at a maximum concentration of up to 0.5%), does not pose a risk to the health of the consumer. In the case, however, that 3 products, although each safe when used separately, are combined, the combinations of either shampoo, hair lotion and a foot care product or face cream, hair lotion and a foot care product (all containing Climbazole at the maximum requested concentration) cannot be considered safe for the consumer’.</p>	<p>DISCORDANT the EU prohibits use at above 0.5% and permits use only in ready to use preparations. The S5 and S6 entries might discourage use but do not prohibit it</p>
<p>Butyl benzyl phthalate Oct 2017</p>	<p>Schedule 10 – New Entry BUTYL BENZYL PHTHALATE for cosmetic use.</p>	<p>EC Annex II (List of substances prohibited in cosmetic products) and Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Annex XIV (List of substances subject to authorisation).</p>	<p>CONCORDANT</p>
<p>1-Deoxy-1-(methylamino)-D-glucitol N-C10-16 acyl derivatives March 2018 CAS 173145-38-5</p>	<p>Schedule 6 – Amend Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-ACYL DERIVATIVES except: a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N- acyl derivatives when labelled with a warning statement to the following effect: IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or b) in household cleaning preparations, other than those intended to be</p>	<p>No known international restrictions or regulations have been identified by the applicant or the secretariat.</p>	<p>FINAL DECISION DEFERRED The delegate has decided to set aside the final decision pending wider review on the scheduling of surfactants</p>

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	sprayed, containing 12 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N- acyl derivatives when labelled with a warning statement to the following effect: IF IN EYES WASH OUT IMMEDIATELY WITH WATER. Index - Amend Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES cross-reference: COCOYL METHYL GLUCAMIDE, LAUROYL METHYL GLUCAMIDE, MYRISTOYL METHYL GLUCAMIDE		
Symphytum spp. (Comfrey) Joint June 2016 CAS 84696-05-9	SCHEDULE 10—Amend entry SYMPHYTUM spp. (Comfrey) in preparations for human or animal use except when in Schedule 5. SCHEDULE 5—Amend entry SYMPHYTUM spp. (Comfrey) in preparations for dermal therapeutic or dermal cosmetic use. Appendix F (unchanged) SYMPHYTUM spp. (Comfrey) when included in Schedule 5. Safety directions: 31, 32	"Comfrey is allowed in cosmetics in the EU and is used as a skin conditioning agent, abrasive, soothing agent and antidandruff ingredient."	DISCORDANT Australian scheduling seems disconnected with risk
Geraniol & related compounds Oct 2016 NWS CAS 106-24-1	Schedule 6 – New Entry 3,7-DIMETHYL-2,6-OCTADIEN-1-OL and its isomers except in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers. Index – New Entry 3,7-DIMETHYL-2,6-OCTADIEN-1-OL cross reference: GERANIOL, NEROL, CITROL Schedule 6 Appendix E, Part 2 Appendix F, Part 3 Appendix E – 3,7-DIMETHYL-2,6-OCTADIEN-1-OL Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). Appendix F – 3,7-DIMETHYL-2,6-OCTADIEN-1-OL Warning statement: 5 (irritant). Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).	EU Cosmetics Regulation 1223/2009 Annex III—"The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)g when its concentration exceeds: – 0.001% in leave-on products; and – 0.01% in rinse-off products.'	DISCORDANT different cut offs in Australia, no requirement to include name on label Substantial unintended (and unnecessary) capture of multiple essential oils in common use and currently in appendix B.
Phenol	Schedule 6 – Amend Entry PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, except: a) when separately specified in these Schedules; or b) in preparations containing 1 per cent or less of phenols, and in preparations containing 3 per cent or less of cresols and xylenols and other homologues of phenol. Schedule 5 – Amend Entry PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, when in animal feed additives containing 15 per cent or less of such substances, except in preparations containing 1 per cent or less of phenol and in preparations containing 3 per cent or less of cresols and xylenols	European Union Cosmetic Directive 76/768/EEC Annex II—List of substances which must not form part of the composition of cosmetic products; (but a public submission notes xlenol and cresol and potentially other derivatives of phenol with boiling points below 220°C are used in cosmetics with no regulatory restrictions in the EU); suggested entry has an exclusion to salts and derivatives, to apply for cosmetics except in preparations containing 0.1% or less of phenol. This would align with the EU standards and allow for products that	DISCORDANT and ambiguous There are millions of 'derivatives' of phenol, cresol and xylenols – which of these are intended to be captured?

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>and other homologues of phenol.</p> <p>Schedule 2 – Amend Entry PHENOL, or any homologue boiling below 220°C for human therapeutic use, except:</p> <p>a) when included in Schedule 4; or b) in preparations for external use containing 1 per cent or less of phenol and in preparations for external use containing 3 per cent or less of cresols and xylenols and other homologues of phenol.</p> <p>Appendix E – PHENOL when included in Schedule 6. Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water). Warning statements: 3 (corrosive liquid), 51 (irritant to skin, eyes, mucous membranes and upper respiratory tract).</p> <p>Appendix F – PHENOL when included in Schedule 6. Safety Directions: 2 (attacks eyes - protect eyes when using), 4 (avoid contact with skin), 8 (avoid breathing dust (or) vapour (or) spray mist).</p>	<p>contain phenol as an impurity.</p>	
<p>1-Deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives CAS 1591783-13-9</p>	<p>Schedule 6 – New Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES except:</p> <p>a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives when labelled the following statement: IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or b) in household cleaning preparations, other than those intended to be sprayed, containing 10 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives when labelled with the following statement: IF IN EYES WASH OUT IMMEDIATELY WITH WATER.</p> <p>Appendix E, Part 2 – New Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES Standard statement: E1 (if in eyes wash out immediately with water).</p> <p>Appendix F, Part 3 – New Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES Warning statement: 79 (Will irritate eyes). Safety direction: 1 (Avoid contact with eyes)</p> <p>Index – New Entry 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES cross reference: cocoyl methyl glucamaide Schedule 6</p> <p>Appendix E, Part 2 Appendix F, Part 3</p>	<p>No restriction in CosIng as COCOYL METHYL GLUCAMIDE</p>	<p>DISCORDANT- no labelling required in EU</p> <p>Schedule entry appears disproportionate and disconnected to meaningful risk</p>
<p>o-Toluidine and o-anisidine</p>	<p>Schedule 10 – New Entries o-TOLUIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows except in preparations containing 0.001 per cent or less of o toluidine. o-ANISIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows except in</p>	<p>o-Toluidine and o-anisidine are restricted under Annex XVII to REACH Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations >0.1 %' (European Parliament and Council 1999;</p>	<p>CONCORDANT</p>

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>preparations containing 0.001 per cent or less of o anisidine.</p> <p>(The delegate notes that o-toluidine is present as an impurity in cosmetic preparations of Basic Violet 1 at 0.001 per cent. Dermal exposure to 0.001 per cent of o-toluidine is expected to be safe.)</p> <p>(From public submission: – A derivative of o-toluidine, Basic Violet 2 (currently unscheduled in Australia), is allowed as a colourant in cosmetic products in the EU (included in Annex IV of the Cosmetics Regulation) and is used in a variety of hair products in Australia – both as a hair dye and as a colourant in shampoos and conditioners. The schedule entry for o-toluidine will have unintentional consequences on products containing Basic Violet 2, which will no longer be able to remain on the Australian market. Basic Violet 2 is listed on the AICS but has not been assessed by NICNAS through their IMAP Assessment. The EU SCCS opinion for Basic Violet 2 in cosmetics recognises the presence of o-toluidine as a category 1B carcinogen but that low concentrations would be of ‘no concern in a hair dye formulation’)</p>	<p>European Parliament and Council 2006; European Parliament and Council 2008), o-Toluidine and o-anisidine are also included as part of 22 aromatic amines listed in Appendix 8 which places restrictions on their presence in leather or textile articles.</p> <p>o-Toluidine and o-anisidine are on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply or use is included on the candidate list whether on its own, in mixtures, or present in articles.</p> <p>ResAP (2008)¹ specifies requirements for the composition, labelling, uses and risk evaluation of tattoo inks in the European Union. ResAP (2008)¹ lists 27 aromatic amines (including o-toluidine and o-anisidine) that should not be present in tattoo inks or released from azo-colourants in concentrations that are technically avoidable. The non-binding ResAP are the reference for the national legislation in several European countries and New Zealand (NZ EPA, 2012).</p> <p>o-Toluidine and o-anisidine are listed on the following (Galleria Chemica):</p> <ul style="list-style-type: none"> • EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products. • New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain. <p>In addition o-toluidine is listed in the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") under the entry 'Toluidines, their isomers, salts and halogenated and sulfonated derivatives'.</p>	
Epidermal Growth Factor	<p>No change to scheduling (applicant proposed to amend the wording of the Schedule 7 entry for Epidermal Growth Factor (EGF), to exempt topical cosmetic preparations containing low concentrations of transgenic plant made epidermal growth factor from the scope of the Schedule 7 entry):</p> <p>Schedule 7 EPIDERMAL GROWTH FACTOR except in preparations for human therapeutic use.</p> <p>Appendix J</p>	<p>Cosling lists multiple epidermal growth factor preparations from various animal and plant sources that are permitted without restriction. Named as [source] SH-Oligopeptide-1. e.g. potatoe-SH-Oligopeptide-1</p> <p>Public submissions: Plant-made EGF for topical cosmetic use is currently permitted in EU, USA and Canada</p>	DISCORDANT EU no restriction for cosmetic use

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	EPIDERMAL GROWTH FACTOR, Condition 1 (Not to be available except to authorised or licensed persons).		
Epidermal Growth Factor October 2017	Appendix G – New Entry Column 1 – Poison: EPIDERMAL GROWTH FACTOR Column 2 – Concentration (quantity per litre or kilogram): 2 mg Index – Amend Entry EPIDERMAL GROWTH FACTOR cross reference: SH-OLIGOPEPTIDE-1, RH-OLIGOPEPTIDE-1 Schedule 7 Appendix G Appendix J, Part 2	See above	DISCORDANT EU no restriction for cosmetic use
Fennel Oil CAS 8006-84-6, 89997-98-8, 92347-02-9, 93685-73-5	Schedule 5 – New Entry FENNEL OIL except: a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification; b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning: KEEP OUT OF REACH OF CHILDREN; or c) in preparations containing 5 per cent or less of methyl chavicol. Appendix E, Part 2 – New Entry FENNEL OIL Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).), G3 (If swallowed, do NOT induce vomiting) Part 2, Section 2.4 Child-resistant closures – New Entry Column 1, Name of the poison: Fennel oil when included in Schedule 5. Column 2, Nominal capacity: 200 millilitres or less.	Fennel oil is unclassified in New Zealand and the USA with brief searches for drug products or medicines containing fennel oil, methyl chavicol, chavicol, or estragole on the FDA or MedSafe databases returning no information. Public submission: According to IFRA there is a significant difference in concentrations of estragole between basil and fennel oils. The submission questions the appropriateness of scheduling fennel oil with similar restrictions to those for basil oil.	DISCORDANT EU no restriction Entry unclear – which fennel oil is intended (root, seed, fruit, leaves?) which varieties? Crithmum maritimum L., Apiaceae Foeniculum Vulgare Capillaceum? Foeniculum Vulgare Piperatum ?
Sodium alpha-olefin sulfonates CAS 68439-57-6	The delegate’s final decision is that no scheduling entry be created for sodium α -olefin sulfonate and sodium alkyl sulfate.	EU no restriction. Called SODIUM C14-16 OLEFIN SULFONATE New Zealand Sodium alpha-olefin sulfonate is included in one cosmetic product in New Zealand as an excipient. Canada Sodium alpha-olefin sulfonate (as sodium C14-16 olefin sulfonate) is listed as a surfactant – cleansing agent for topical use. Further, sodium α -olefin sulfonates (of chain lengths C12-14, C14-16, C14-18 and C16-18) are considered to be safe when used in rinse-off products and safe up to 2% in leave-on products. The concentration of the gamma sultone impurity of any formulation (leave-on or rinse-off) is limited to unsubstituted alkane sultones 10 ppm;	CONCORDANT

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
		chlorosultones 1 ppm; and unsaturated sultones 0.1 ppm. Sodium alkyl sulfate (as sodium C12-15 alkyl sulfate) is listed as a non-medical ingredient.	
Ethyl hexanediol June 2017 CAS 94-96-2	Schedule 10 – Delete Entry Schedule 6 – New Entry ETHYL HEXANEDIOL except in preparations containing 5 per cent or less of ethyl hexanediol. Schedule 4 – Delete Entry Appendix E, Part 2 – New Entry ETHYL HEXANEDIOL Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.) Appendix F, Part 3 – New Entry ETHYL HEXANEDIOL Warning Statements: 79 (will irritate eyes) Safety directions: 1 (avoid contact with eyes).	International sources have determined that ethyl hexanediol is a safe cosmetic ingredient (Cosmetic Ingredient Review (CIR), 2011) EU: solvent; no restrictions in cosmetics Ethyl hexanediol was listed as a hazardous substance by the EPA in New Zealand in December 2006 (HSNO Approval Code HSR003694). Public submissions: Although the maximum concentration of 5% as stated in the interim decision is in alignment with the US CIR recommendation, there are no restrictions on the use of ethyl hexanediol in cosmetics in the EU, NZ or ASEAN;	DISCORDANT EU no restriction
Quinine CAS 130-95-0	Schedule 6 – New Entry QUININE in hair preparations except: c) in rinse-off hair preparations containing 0.5 per cent or less of quinine calculated as free base; or d) in leave-on hair preparations containing 0.2 per cent or less of quinine calculated as free base. Appendix F, Part 3 – New Entry QUININE Warning Statement: 28 (Repeated exposure may cause sensitisation). Index – Amend Entry QUININE cross reference: QUININE (CAS No. 130-95-0), QUININE SULFATE (1:1) (CAS No. 549-56-4), QUININE SULFATE (2:1) (CAS No. 804-63-7), QUININE SULFATE (2:1) DIHYDRATE (CAS No. 6119-70-6), QUININE SULFATE (1:1) HEPTAhydrate (CAS No. 6183-68-2), QUININE DIHYDROCHLORIDE (CAS No. 60-93-5), QUININE MONOHYDROCHLORIDE (CAS No. 130-89-2), QUININE HYDROCHLORIDE DIHYDRATE (CAS No. 6119-47-7), QUININE HYDROCHLORIDE (UNSPECIFIED) (CAS No. 7549-43-1) Schedule 7 Schedule 6 Schedule 5 Schedule 4 Appendix F, Part 3	EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down. Leave on products ≤ 0.2%, Rinse off products ≤ 0.5% New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down For all of the above, the maximum concentration allowed in ready-for-use hair preparations is 0.5% (as quinine base) in rinse-off products and 0.2% (as quinine base) in leave-on products.	PARTIALLY CONCORDANT S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions
Docusate sodium CAS 577-11-7	No change to current scheduling: Appendix B, Part 3: Substances considered not to require control by scheduling DOCUSATE SODIUM (DIOCTYL SODIUM SULFOSUCCINATE)	EU unrestricted use. Docusate sodium was registered under REACH as of 15 June 2012. The registration dossier was updated on 17 December 2016, following compliance checks by	CONCORDANT

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	<p>Date of entry: February 1970 Reason for Entry – a, low toxicity Area of Use – 7.1, general, any use</p>	<p>ECHA. Docusate sodium is used in the following products in the EU: washing & cleaning products, lubricants and greases, polymers, metal working fluids, textile treatment products and dyes, pH regulators and water treatment products, hydraulic fluids and leather treatment products. This substance is also used as an intermediate in the manufacture of another substance. Docusate sodium is used in the following areas: mining, agriculture, forestry and fishing, formulation of mixtures and/or re-packaging and municipal supply (e.g. electricity, steam, gas, water) and sewage treatment. It is used for the manufacture of: chemicals, textile, leather or fur, plastic products and food products. Docusate sodium (as dioctyl sodium sulfosuccinate) is available for General Sale in NZ.</p>	
<p>Methylisothiazolinone CAS 2682-20-4</p>	<p>Schedule 6 – Amend Entry METHYLISOTHIAZOLINONE except: a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.01 per cent or less of methylisothiazolinone; or b) in other preparations that are not intended for direct application to the skin containing 0.1 per cent or less of methylisothiazolinone.</p> <p>Unchanged:</p> <p>Appendix F, Part 3 METHYLISOTHIAZOLINONE Warning Statement: 28 (Over) (Repeated) exposure may cause sensitisation.</p>	<p>In December 2015, the SCCS adopted the fourth opinion. It was concluded that the information provided does not support the safe use of MI as a preservative in rinse-off cosmetic products up to a concentration limit of 100 ppm from the view of induction of contact allergy. For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the point of view of induction of contact allergy. It was not safe to use MI as a preservative in leave-on hair cosmetic products up to a concentration limit of 100 ppm (0.01%) from the point of view of induction of contact allergy. Currently in Annex V to Regulation (EC) No 1223/2009, max. 0.01% in rinse-off products, not permitted in leave-on products</p>	<p>PARTIALLY CONCORDANT S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions</p>
<p>Chloroacetamide Oct 2017 CAS 79-07-2</p>	<p>Schedule 6 – New Entry CHLOROACETAMIDE except a) in preparations for cosmetic use; or b) in preparations for topical therapeutic use; or c) in other preparations containing more than 0.3 per cent of chloroacetamide.</p> <p>Appendix E, Part 1 – New Entry CHLOROACETAMIDE Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).</p>	<p>Currently, chloroacetamide is authorised as a preservative in cosmetics products in entry 41 of Annex V to Regulation (EC) No 1223/2009, at a concentration up to 0.3% w/w in ready for use preparations. However, in 2015, there was a consultation process on a proposal to remove entry 41 from Annex V, and to add chloroacetamide to the list of substances prohibited in cosmetic products of Annex II to Regulation (EC) No 1223/2009 (European</p>	<p>DISCORDANT EU requires labelling with ingredient name. Cut off is the same. Prohibited in cosmetics at higher concentrations</p> <p>S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions</p>

Substance; Decision Date	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	Appendix F, Part 1- New Entry CHLOROACETAMIDE Warning Statement: 28 (Repeated exposure may cause sensitisation). Safety Direction: 4 (Avoid contact with the skin).	Commission, 2015). A decision had not been finalised at the time of the preparation of this assessment report.	
Polihexanide CAS 32289-58-0 [1]/27083-27-8 [2]/28757-47-3 [3]/ 133029-32-0 [4]	Schedule 6 - Amend Entry POLIHEXANIDE except: a) in cosmetic preparations containing 0.3 per cent or less of polihexanide; or b) when packed and labelled for therapeutic use, or c) in other preparations containing 5 per cent or less of polihexanide. Appendix F, Part 3 - Amend Entry POLIHEXANIDE Warning Statement: 28 (Repeated exposure may cause sensitisation). Safety Directions: 1 (Avoid contact with eyes); 4 (Avoid contact with skin); 8 (Avoid breathing dust (or) vapour (or) spray mist). Index Entry - Amend Entry POLIHEXANIDE cross reference: 1-(diaminomethylidene)-2-hexylguanidine, poly(iminocarbonimidoyliminocarbonimidoyl imino-1,6-hexanediyl), polyhexamethylene biguanide (PHMB) Schedule 6 Appendix E, Part 2 Appendix F, Part 3	POLYAMINOPROPYL BIGUANIDE Poly(hexamethylenebiguanide) hydrochloride [1];poly(iminoimidocarbonyl)iminohexamethylene hydrochloride [2]; Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl) [3];- [4] The chemicals are permitted as preservatives in cosmetic products in the EU and NZ at a maximum permitted concentration of 0.3%. The use of polihexanide in cosmetics in the European Union (EU) is subject to the EU Cosmetics Regulation 1223/2009 Annex V—List of preservatives allowed in cosmetic products. Polihexanide may be used as preservatives in cosmetic products at a maximum permitted concentration of 0.3%. According to the 2017 SCCS opinion a reduction in this concentration was recommended, but this has not yet been finalised, nor implemented in legislation.	PARTIALLY CONCORDANT for cosmetics S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions

Quinoline is an approved food colour with an ADI of 3 mg/kg bw/day. The S6 entry captures all uses with a concentration above 10 mg/kg bw/day. Use in a cosmetic at levels many times this would present no plausible health risk to a consumer as the exposure would remain below the ADI. Although the EC does not permit use of quinoline as a colour the S6 entry does not prohibit this use at levels below 10 mg/kg. The EU has no restriction on the use of quinoline as a flavour but the S6 entry effectively prohibits such use at levels above 10 mg/kg. The scheduling record does not indicate these issues were explicitly considered

Table 3. EU Cosmetics Regulation ((EC) No 1223/) Annex III Entries for fragrance materials considered in this Review

Ref No	Chemical Name	Common Name	CAS No	EC No	Other	Differences to Poisons Standard entry or Scheduling Proposal [†]
80	4-Methoxybenzyl alcohol	†Anise Alcohol	105-13-5	203-273-6	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0,001 % in leave-on products — 0,01 % in rinse-off products	Proposed scheduling is consistent in part Consistent ≤ 0.001% in leave on products & ≤ 0.01% for rinse off products (no labeling or restrictions other than inclusion in ingredient list) Inconsistent above these cutoffs (Additional requirement for a warning statement are Australian specific) #WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.
75	Benzyl Salicylate	†Benzyl Salicylate	115-58-1	204-261-9	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0,001 % in leave-on products — 0,01 % in rinse-off products	Scheduling proposal is largely consistent ≤ 0.001% in leave on products & ≤ 0.01% for rinse off products (no labeling or restrictions) Distinction between preparations intended for skin contact and cosmetic preparations is unclear
73	Phenol, 2-methoxy-4-(1-propenyl)-	Isoeugenol	97-54-1	202-590-7	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds:	DISCORDANT & inconsistent EU requires labelling to state presence of the substance when ingredient is > 0.001% in leave on products and 0.01% in rinse of products

Ref No	Chemical Name	Common Name	CAS No	EC No	Other	Differences to Poisons Standard entry or Scheduling Proposal [†]
					0,001 % in leave-on products — 0,01 % in rinse-off products	Schedule entry does not require inclusion on label No warning statement for skin sensitisation NESIL 250 µg/cm ² compared to Benzyl Salicylate 17700 µg /cm ² Anise Alcohol 1500 µg/cm ²
78	2,6-Octadien-1-ol, 3,7-dimethyl-, (2E)-	Geraniol	106-24-1	203-377-1	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0,001 % in leave-on products — 0,01 % in rinse-off products	DISCORDANT and INCONSISTENT different cut offs in Australia, no requirement to include name on label Substantial unintended (and unnecessary) capture of multiple essential oils in common use and currently in appendix B. No requirement for warning statement re sensitisation. NESIL 11800 µg/cm ²
87	2-Benzylideneoctanal	Hexyl Cinnamal [alpha hexyl cinnamaldehyde]	101-86-0	202-983-3	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0,001 % in leave-on products — 0,01 % in rinse-off products	DISCORDANT. No requirement to include name on ingredients list in Australia
76	2-Propenal, 3-phenyl-	†Cinnamal	104-55-2	203-213-9	The presence of the substance must be	DISCORDANT AND INCONSISTENT Proposed S6 cutoff is greater than the EU cut offs. In EU

Ref No	Chemical Name	Common Name	CAS No	EC No	Other	Differences to Poisons Standard entry or Scheduling Proposal [†]
		[Cinnamaldehyde]			indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0.001 % in leave-on products — 0.01 % in rinse-off products	only requirement is for inclusion in ingredient list. No exemption when labelled with warning statement re sensitisation. NESIL 590 µg/cm ²
67	2-Benzylideneheptanal	Amyl Cinnamal [alpha Amyl Cinnamaldehyde]	122-40-7	204-541-5	The presence of the substance must be indicated in the list of ingredients referred to in Article 19(1)(g) when its concentration exceeds: 0.001 % in leave-on products — 0.01 % in rinse-off products	DISCORDANT. No requirement to include name on ingredients list in Australia

* entries in square brackets [] in the table do not appear in the EC Annex III and have been added for clarity

The cut off values for which these label requirements apply are related to elicitation (ie causing a reaction in an already sensitive individual) and not to induction (sensitising a previously non sensitised person) which requires higher exposures. In this sense the wording “may cause sensitisation” is questionable & perhaps should perhaps read “may cause skin reactions in sensitised persons” or be omitted as is the case in the EU. If the compound is included in the ingredients list then previously sensitised individuals can avoid contact.

[†]Scheduling proposal only – consideration of this substance has been deferred

Table 4. Assessment of the Adequacy of Scheduling Application to Support Consideration of Regulatory Impact and S52(e) Matters that the delegate should have regard to

Relevant Matter	Cinnamaldehyde	Iso-eugenol	Anise Alcohol	Geraniol	Benzyl Salicylate	Comments
Chemical Characterisation	√	√	√	√	√	Generally adequate
Substance Identification						
Isomer and analogue consideration	χ	χ	χ	√	χ	Not or partially addressed – unclear if an isomer is a derivative
Definition of relevant derivatives	χ	χ	χ	χ	χ	Not or only partially addressed. Which derivatives are likely to share the toxicity driving the scheduling outcome
Natural occurrence and related materials	χ	χ	χ	χ	χ	Not addressed. Many fragrance chemicals occur in essential oils also scheduled. These need to be identified and considered in conjunction
Class definition	χ	χ	χ	χ	χ	Not or only partially addressed. Consideration of related molecules likely to share the pivotal toxicological end point
Hazard Identification	√	√	√	√	√	Straight forward
Acute Oral Toxicity						
Acute Dermal Toxicity	√	√	√	√	√	Straight forward
Acute inhalation toxicity	√	-	√	√	√	Straight forward
Skin irritation	√	√	√	√	√	Straight forward
Eye irritation	√	√	√	√	√	Straight forward
Skin sensitisation	√	√	√	√	√	Straight forward
Hazard Characterisation	√	√	√	√	√	
Acute Oral Toxicity						
Acute dermal toxicity	√	√	√	√	√	Straight forward
Acute inhalation		-				Not addressed or no data but generally not relevant for the cosmetic uses
Skin irritation	√	√	√	√	√	Greater consideration of concentration/effect relationship would improve assessments
Eye irritation	χ	X	χ	χ	χ	Inadequate attention to dose response
Sensitisation	χ	χ	χ	χ	χ	Incorrect dose metrics used (pivotal dose metric is µg/cm ² (not % or quantity applied)
Exposure						
Concentrations in use	χ	χ	χ	χ	χ	Cursory
Amount applied		χ	χ	χ	χ	Cursory

Where and how applied	χ	χ	χ	χ	χ	Cursory
Frequency of application	χ	χ	χ	χ	χ	No discussion
Product presentation	χ	χ	χ	χ	χ	No discussion
	χ	χ	χ	χ	χ	No discussion
Risk Characterisation	χ	χ	χ	χ	χ	Cursory
Risk / Benefit Considerations	χ	χ	χ	χ	χ	No discussion
Regulatory impact	χ	χ	χ	χ	χ	No discussion
Potential impacts on other regulatory schemes	χ	χ	χ	χ	χ	No discussion

√ Assessment adequate for delegate decision making, - No data, χ Assessment inadequate for delegate decision making

General Comments

The delegate, scheduling committee and secretariat rely on the information provided in the scheduling application to provide the basis for balanced, consistent and robust recommendations. The quality of the advice provided by the advisory committees, and the decisions of the delegate, are therefore dependent on the quality of the scheduling request and in particular whether the request adequately addresses each of the matters to which the scheduling committee and delegate must have regard to in formulating their advice and decisions respectively. A range of scheduling applicants will lack the background and/or experience to understand the needs of the scheduling committee/delegate and the requirements of the legislation in terms of the data and analysis required to support the decision making. The current scheduling application form and application handbook provide quite limited advice and guidance in this regard. Consequently, observations of deficiencies in the information supplied by applicants does not necessarily equate to a criticism of the applicant.

Deficiencies Common to most Cosmetic Ingredient Proposals Reviewed

Most of the scheduling submissions relating to cosmetic ingredients are essentially hazard based classification proposals, reflecting the hazard based regulatory regime for which the submitting agency is responsible. The proposals have not adequately explored the other critical aspects that the delegate and scheduling committee would be expected to consider for scheduling recommendations. Specifically, these proposals have not adequately considered:

- risks at the levels actually used in the types of products in or likely to be in the market;
- the packaging and presentation of the product;
- adequacy of any existing labelling to mitigate identified risks;
- where each type of product is used on the body;
- how much is applied;
- over what surface area;
- how frequently;
- the likely familiarity of the public with inherent risks of products (eg shampoo and soap hurt when in the eye);
- the impact of proposals on stakeholders;
- cross regulatory impacts of proposals;
- alternative mechanisms for achieving the regulatory intent; and
- which derivatives should be included as relevant/captured by the entry.

The scheduling submissions also do not adequately consider the dose response pattern for the hazards they are seeking to control, and have generally not used appropriate dose metrics for skin sensitisation (amount applied per surface area, $\mu\text{g}/\text{cm}^2$ rather than concentration in product). No consideration of dermal sensitisation thresholds (DST) has been included in the assessments, and the regulatory impact on industry of the collective scheduling proposals for cosmetic chemicals has not been addressed.

To avoid repetitive text these common deficiencies are not further commented on in the reviews of the individual submissions below.

Isoeugenol

The scheduling delegate's final decision, June 2017, was;

Schedule 6 - Amend Entry

ISOEUGENOL **except**:

- a. when included in Schedule 5; or
- b. in preparations not intended for contact with skin containing 10 per cent or less of isoeugenol.
- c. in preparations intended for skin contact containing 0.02 per cent or less of isoeugenol.

Schedule 5 - Amend Entry

ISOEUGENOL in preparations not intended for skin contact containing 25 per cent or less of isoeugenol **except** in preparations intended for contact with skin containing 10 per cent or less of isoeugenol.

Appendix E, Part 2 - New Entry

ISOEUGENOL

Standard statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 - New Entry

ISOEUGENOL

Warning statements: 19 (WARNING - Skin contact may be dangerous. Take every precaution to avoid contact - wash off after spillage and after use), 28 ((Over) (Repeated) exposure may cause sensitisation), 79 (Will irritate eyes).

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

Discussion

Isoeugenol is a naturally occurring terpenoid present in a wide range of plants, with a variety of uses including as a flavour component of cloves, and as a farmed fish anaesthetic. The scheduling submission notes a range of potential toxicological hazards including the observation of increased tumours in life time rodent studies. Isoeugenol is non-genotoxic but produces tumours in old rats and mice at high life time doses but without affecting survival of the animals. Although the chemical is correctly *hazard* classified under the GHS as 'Cat 3 - limited evidence of carcinogenic effect', a *risk categorisation* would state that the chemical is unlikely to present a carcinogenic risk to humans at the concentrations used, and the resultant exposures, in food and consumer products. Although the Cat 3 carcinogenicity classification was not a material consideration in the scheduling decision, the delegate information pack explicitly states that the reasons for the proposal include that "the chemical is classified as a carcinogen". Isoeugenol is Cramer Class I structure (low concern) and would be concluded to not be a carcinogen under a QSAR analysis, as has been used for related substances in scheduling applications from the same applicant agency.

The scheduling submission is in the public domain. The silence of the submission and documentation supporting the delegate's decision on the significance of the carcinogenicity classification to human health and safety has the potential to lead to public concern that the effect was not adequately addressed. If isoeugenol presents a genuine *risk* of carcinogenicity to

the public using products, or consuming food, containing this compound then the public would expect the substance to be prohibited. In reality isoeugenol presents no such *risk* at the levels and, in the way, exposure actually occurs. A great many natural food constituents produce cancer in aged rats when they are exposed at high doses for a lifetime, without predicting a human health risk, as Bruce Ames (the developer of the eponymous Ames Genotoxicity Test) has illustrated with the following table (Ames & Gold, 1997).

TABLE 2. Carcinogenicity of natural plant pesticides tested in rodents (49)^a

Carcinogens: ^b N = 35	Acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline · HCl, benzaldehyde, benzyl acetate, caffeic acid, catechol, clivorine, coumarin, crotonaldehyde, cycasin and methylazoxymethanol acetate, 3,4-dihydrocoumarin, estragole, ethyl acrylate, N ² -γ-glutamyl- <i>p</i> -hydrazinobenzoic acid, hexanal methylformylhydrazine, <i>p</i> -hydrazinobenzoic acid · HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, <i>d</i> -limonene, 8-methoxypsoralen, N-methyl-N-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens: N = 28	Atropine, benzyl alcohol, biphenyl, <i>d</i> -carvone, deserpidine, disodium glycyrrhizinate, emetine · 2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, β-N-[γ-l(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetic acid, <i>p</i> -hydrazinobenzoic acid, isosafrole, kaempferol, <i>d</i> -menthol, nicotine, norharman, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, turmeric oleoresin, vinblastine

^aFungal toxins are not included. ^bThese rodent carcinogens occur in: absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate milk, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, corn, coriander, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip.

Considerations

Discordance with international Regulations

The EU requires labelling to state the presence of the substance when the ingredient is > 0.001% in leave on products and 0.01% in rinse off products, but the proposed scheduling does not require this, despite skin sensitisation being a substantive driver of the scheduling. The upper limit of 0.02% is consistent with EU requirements and the IFRA standard however.

Inconsistency across similar substances

The schedule entry does not require a skin sensitisation warning at exempt levels despite the fact that isoeugenol is considerably more potent as an inducer of skin sensitisation than anise alcohol, the proposed scheduling for which does require the warning at exempt levels. (NESIL 250 µg/cm² compared to anise alcohol, 1500 µg/cm²).

There is no requirement for isoeugenol to be included on the ingredient list of cosmetic products at the exempted levels, unlike proposed scheduling for anise alcohol, cinnamaldehyde and benzyl alcohol for example. This requirement is the principle risk management mechanism to allow previously sensitised persons to avoid the product. Prevention of induction is achieved through concentration limits (0.02%) which in this case are consistent with EU requirements and the IFRA standard.

Anise Alcohol

In contrast to the scheduling proposal for this compound, the published RIFM risk assessment for anisyl alcohol (anise alcohol) on which the IFRA Standard is based utilises an exposure-based quantitative risk assessment (QRA) to establish a skin sensitisation Health Reference Value, the NESIL. This assessment considers the types of products the substance is used in, the range of concentrations, where and how those products are used, how frequently, how much and over what surface area they are used. From this assessment typical worst-case exposures are identified and form the basis of a model risk assessment. For substances with skin sensitisation

potential, designated acceptable levels of use reflect the best available science of dermal sensitisation, utilise DST where appropriate and identify levels which will not result in induction of sensitisation in naïve (ie not previously sensitised) consumers. The IFRA standard provides appropriate product type specific restrictions for anise alcohol:

- acceptable levels of use between 0.04% (lip products) and 5% (rinse-off hair conditioners) depending on the intended use and resulting exposure scenario of the finished product; and
- there are no concentration restrictions for use in products with no intended, or only incidental, skin contact as the basic exposure pre-requisites for skin sensitisation is absent for these products.

The EU Cosmetics Regulation established concentration levels for 26 identified fragrance allergens to inform consumers with a known allergy (i.e. those already sensitised) of the presence of these ingredients so they can choose to avoid certain products. They are not reflective of levels that would result in induction. Thus, the EU and IFRA standards work together to ensure levels included in products are unlikely to produce induction in naïve individuals and that their presence above levels that might cause a reaction in a sensitised person are identified through the inclusion of the fragrance substance in the ingredient list. The EU requirements for anise alcohol in cosmetics are:

- products containing greater than or equal to 0.001% anise alcohol in leave-on products, and greater than or equal to 0.01% anise alcohol in rinse-off products must include 'anise alcohol' in the ingredient list on the product label; and
- there are no restrictions on the concentration of this substance that may be used in products, and no further warnings or label statements are required on finished products

The delegate's interim decision for anise alcohol appeared to be an attempt to combine the 2 different risk management approaches of addressing sensitisation (elicitation vs induction) despite their very different basis, and to include additional, Australian unique warning statements.

The interim decision is as follows:

Schedule 6 - New Entry

ANISE ALCOHOL except:

- a) in preparations intended for therapeutic use; or
- b) in domestic preparations not intended for direct skin contact containing 5 per cent or less of anise alcohol when declared on the label; or
- c) in leave-on cosmetic and personal care preparations containing more than 0.001 and up to 2.5 per cent of anise alcohol when declared on the label and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- d) in rinse-off cosmetic and personal care preparations containing more than 0.01 and up to 5 per cent or less of anise alcohol when declared on the label and labelled with the following statement:

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals.

written in letters not less than 1.5 mm in height; or

- a) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of anise alcohol; or
- b) in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.

Appendix E, Part 2 – New Entry

ANISE ALCOHOL

Standard Statement: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)).

Appendix F, Part 3 – New Entry

ANISE ALCOHOL

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

The primary determinants of the recommended scheduling were expected eye irritation (based on benzyl alcohol data) and skin sensitisation in an LLNA assay (EC3 is 5.9 %, 1475 µg/cm²).

Discussion

Discordance with international (EU) Regulations

The EU requires only the inclusion of the substance in the ingredient list when above 0.001% in leave on products and 0.01% for rinse off products. The requirement for a warning statement above the cut offs of < 0.001% in leave on products and < 0.01% for rinse off products creates a need for separate labelling for products sold into, or imported from, the EU, compared to that required for Australia. The requirement for relabelling or over-labelling adds additional cost to affected products with questionable public health advantage. A not insignificant impact on the marketability of products required to add this labelling is also likely. There does not appear to have been explicit consideration of these impacts, or the cost benefit relationship, by either the applicant or the scheduling committee.

The warning statement ‘This product contains ingredients which may cause skin sensitisation to certain individuals’ is arguably inaccurate and potentially misleading. Firstly, it does not indicate which ingredient the warning refers to. Secondly although the substance may *elicit* a sensitisation reaction at these levels in previously sensitised individuals, the induction of sensitisation requires higher concentrations and longer periods of exposure.

Inconsistency across similar substances

Anise alcohol is a considerably weaker skin sensitiser than isoeugenol, but the proposed schedule entry requires an explicit warning regarding sensitisation, while the more potent sensitiser isoeugenol does not.

Geraniol

The IFRA Standard for geraniol sets specific cut-offs for a range of different product categories. There are no restrictions for products that are not intended for skin contact (category 11) e.g. air fresheners, candles, machine dishwashers or laundry detergents, and higher than 5% concentration cut-off for some products (categories 4 and 6) including oral care products and body lotions, creams (except baby products), foot care products and body sprays. These cut offs are intended to prevent induction of skin sensitisation in naïve individuals. The EU cosmetics directive sets lower cut off levels with a requirement to include the substance in the ingredient

list above that level, in order to allow individuals who are already sensitised to avoid products they might react to.

The acyclic terpene alcohols geraniol, linalool, and citronellol are the most important terpene alcohols used as fragrance and flavour substances. Geraniol and linalool are, in addition to nerol and lavandulol, primary products in terpene biosynthesis **Error! Reference source not found.** Geraniol [106-24-1], (2E)-3,7-dimethyl-2,6-octadien-1-ol geraniol [106-24-1], (2E)-3,7-dimethyl-2,6-octadien-1-ol, occurs in nearly all terpene-containing essential oils.

Discussion

Inconsistency across similar substances

The Schedule 6 entry for geraniol uses the full and rather cumbersome chemical name (3,7-dimethyl-2,6-octadien-1-ol) rather than the common name, in contrast to the entries for benzyl salicylate, anise alcohol and cinnamaldehyde. The index is cross-referenced to geraniol, nerol and citrol, and the reason/need for the variation is unclear.

Palmarosa oil, citronella oil and geranium oil are all included in Appendix B for any use (7.1) for reasons of low toxicity (a). Geraniol (and its isomer nerol), a major ingredient in palmarosa oil (approx. 65%) and citronella oil (10-20%) and rose oil, and a minor ingredient in geranium oil, is included in Schedule 6 if in preparations at greater than 5% (which appears to relate to the IFRA Standard). Technically speaking all these essential oils are both not scheduled (ie in Appendix B of the Poisons Standard as a constituent of palmarosa oil) and also in Schedule 6 according to the Poisons Standard entry for 3,7-dimethyl-2,6-octadien-1-ol. The second major ingredient in palmarosa oil is geranyl acetate (approx. 20%), a condensation product of geraniol and acetic acid and therefore a derivative, and presumably captured by the geraniol schedule entry as it does not exclude derivatives (and it readily converts to geraniol by hydrolysis) i.e. palmarosa oil is approx. 85% geraniol and its derivative.

Discordance with international (EU) Regulations

The EU Cosmetics Directive requires only that the substance be included in the ingredient list where it is present at concentration greater than 0.001% in leave on products and 0.01% in rinse off products.

The Poisons Standard provides a 5% cut off from S6 to exempt but with no requirement for inclusion in the ingredient list of cosmetics products.

Consideration of Cross Regulatory Impacts

The regulatory impact of the decision has not been. Citronella oil is a component of a range of insect repellents and related products registered with the APVMA. The scheduling proposal has not addressed the potential impact on these products and specific comment from the APVMA does not appear to have been sought.

The impact of the proposed scheduling on ingredients approved for inclusion in listed medicines does not appear to have been addressed.

The Poisons Standard entry for this substance is:

Schedule 6 - New Entry

3,7-DIMETHYL-2,6-OCTADIEN-1-OL and its isomers **except** in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers.

Index - New Entry

3,7-DIMETHYL-2,6-OCTADIEN-1-OL

cross reference: GERANIOL, NEROL, CITROL

Schedule 6

Appendix E, Part 2

Appendix F, Part 3

Appendix E - 3,7-DIMETHYL-2,6-OCTADIEN-1-OL

Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], E1 (if in eyes wash out immediately with water), S1 (if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F - 3,7-DIMETHYL-2,6-OCTADIEN-1-OL Warning statement: 5 (irritant).

Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).

Cinnamaldehyde

The delegate made an interim decision recommending the following schedule outcome;

Schedule 6 – New Entry

CINNAMALDEHYDE **except:**

- a. in preparations intended for therapeutic use; or
- b. in domestic preparations not intended for direct skin contact containing 0.4 per cent or less of cinnamaldehyde when declared on the label; or
- c. in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of cinnamaldehyde; or
- d. in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of cinnamaldehyde.

Issues with the Interim Decision

Inconsistency with scheduling of similar substances

The primary justification for the scheduling cut offs in the record of reasons for the interim decision is skin sensitisation. Although isoeugenol is similar or more potent as a skin sensitiser (NESIL isoeugenol 250 µg/cm² compared to 590 for cinnamaldehyde) the proposed cut offs have been set to below the levels requiring inclusion in the ingredients list by the EU, but are below the EU maximum level for isoeugenol (ie isoeugenol is *less* restrictive). The IFRA standard for cinnamaldehyde has a maximum use level of 0.05 (most dermal products) to 0.4 % (mouthwash), well above the proposed S6 cut offs.

Amyl and hexyl cinnamaldehyde, 'derivatives' of cinnamaldehyde, are in Appendix B of the Poisons Standard. As the proposed entry for cinnamaldehyde makes no mention, ie does not restrict the definition of derivatives, these compounds would appear to be both in Appendix B and in Schedule 6.

The proposed scheduling outcome is therefore discordant with previous decisions for similar materials and disproportionate to the risks being managed.

Discordance with international (EU) Regulations

The EU requires only that the substance be included in the ingredient list of cosmetics when at greater than 0.001% in leave on products and 0.01% in rinse off products. For cinnamaldehyde the cut off only applies if the concentration is below these levels, the opposite to the proposed entry for anise alcohol. In previous scheduling decisions (e.g. anise alcohol) much higher cut offs were applied, with the presence of the substance required to be declared on the label (consistent with EU requirements) but with the additional Australian specific requirement for an explicit sensitisation warning as discussed under anise alcohol.

Disproportionate Regulatory Response

Cinnamaldehyde forms 50% of the composition of cinnamon bark essential oil. Cinnamon bark contains approximately 3% of the essential oil or 1.5% of cinnamaldehyde, equal to 15 g/kg of bark (Choi, Lee, Ka, Jung, & Park, 2001; Singh, Maurya, Delampasona, & Catalan, 2007). Consequently, the proposed Schedule 6 entry requires products containing very much lower levels (1/100th or 1/1000th) of cinnamaldehyde compared to that in cinnamon bark to be labelled as 'POISON'. A requirement to label a product as POISON where the content of cinnamaldehyde is greater than 0.01 or 0.001 % would appear to be misleading, disproportionate and inappropriate.

Benzyl Salicylate

The delegate made an interim decision recommending that a new Schedule 6 entry and Appendix E and F entries be created for benzyl salicylate:

Schedule 6 – New Entry

BENZYL SALICYLATE except:

- a. in preparations intended for therapeutic use; or
- b. in domestic preparations:
 - i. intended for skin contact containing 15 per cent or less of benzyl salicylate when declared on the label; or
 - ii. not intended for direct skin contact when included in the list of ingredients; or
- c. in leave-on cosmetic and personal care preparations:
 - i. containing 0.001 per cent or less of benzyl salicylate; or
 - ii. when declared on the label; or
- d. in rinse-off cosmetic and personal care preparations:
 - i. containing 0.01 per cent or less of benzyl salicylate; or
 - ii. when declared on the label.

Appendix E, Part 2 – New Entry

BENZYL SALICYLATE

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

BENZYL SALICYLATE

Warning Statement: 28 ((Over) (Repeated) exposure may cause sensitisation).

Safety Direction: 4 (Avoid contact with skin).

Issues with the Decision

Comparison with international (EU) Regulations

The EU Cosmetics Directive does not set an upper limit for benzyl salicylate in cosmetics, but the IFRA Standard sets various limits based on product type up to 8.0% for aftershave products. The only requirement in the EU is for the compound to be included in the ingredients list when above 0.001% in leave-on products and 0.01% in rinse-off products. Thus, the EU cosmetics directive and the IFRA standard work in conjunction to set appropriate boundaries for use, a combination of Government imposed and industry self-regulation (product stewardship, legal liability management). The proposed entry is largely concordant with the EU regulations for most cosmetic products.

Ambiguity and lack of clarity

The scheduling proposal and interim decision above have a number of ambiguous or uncertain aspects. The distinction between 'domestic preparations intended for skin contact' and 'cosmetic and personal care products' can be confusing because cosmetics are thought of as domestic products, and few non-cosmetic domestic products are *intended* for skin contact. Secondly, if the presence of the compound in the product is declared there are no upper limits to the amount allowed to be present in cosmetic products but there is a limit on 'domestic' products intended for skin contact. The use of the scheduling mechanism in this case appears to be a very cumbersome method of controlling a very low risk with little evidence to support a need for regulatory intervention.

Conclusions

The Act and SPF establish the scheduling of therapeutic, domestic, agricultural and veterinary chemicals as a risk-based mechanism for managing the risks of substances at the level they are used in products available in Australia. Although the scheduling factors are hazard-based their intent is to support consistency of scheduling decisions rather than to be prescriptive. The legislation, scheduling factors, preamble to the Poisons Standard and the SPF need to be read together when considering scheduling decisions.

In reviewing the scheduling decisions/recommendations for cosmetic ingredients over the past 18 months no obvious need for, or benefit in, *de novo* assessment of fragrance materials and cosmetic ingredients is apparent in most cases. Other mechanisms to capture cosmetic ingredients to ensure they are used at internationally acceptable levels are available that would have a lower impact on Australian industry without compromising the management of the relatively low level of risk. Such mechanisms are currently used within the TGA and FSANZ and involve some level of recognition of international regulations or the decisions of authoritative bodies.

The review has identified weaknesses in a variety of more general scheduling processes that are amenable to relatively simple, procedural modifications that would substantially improve the accessibility, interpretability and effectiveness of the Poisons Standard. A routine consideration of the nature of derivatives that are intended to be captured for every new entry, with differentiation between the broader derivative definition required for drugs of abuse and addiction compared to cosmetic ingredients for example, would largely eliminate or at least substantially reduce the very considerable uncertainty associated with the current entries (unless explicitly excluded).

The establishment of an explicit cut off for impurities in cosmetic and other domestic substances of chemicals with entries in S7 to S10 would eliminate the current unintended capture of substances such as ethylene oxide when present as an impurity of synthesis in polyethoxylated surfactants.

The identification of substances captured by the Poisons Standard is frequently ambiguous due to the many synonyms that may exist for any individual substance. The routine inclusion of a CAS number (or numbers) would eliminate confusion and greatly improve identification of substance captured by Poisons Standard entries.

A clear need for improved guidance for both applicants and the scheduling committee was identified to support more consistent and proportionate decisions/recommendations and to guide applicants to address the various areas the scheduling committee and delegate are required by the legislation and government policy to give consideration to.

One area this review has identified as presenting some challenges is in determining appropriate concentration cut offs for the various acute toxicity endpoints in the absence of specific experimental demonstration of the dose response curve. Considerable information is available in the literature that would support the development of guidance documentation for estimation of appropriate cut offs for skin and eye irritation and skin sensitisation in particular. The nature of the design of the studies used to identify these end points plus the species-specific differences in physiological responses are essential considerations in extrapolating from animal studies on a pure individual ingredient to a consideration of risk in use within a product.

The use of the scheduling mechanism to manage skin sensitisation in isolation of acute systemic toxicity risks appears to be problematic. A requirement for a product that includes a skin sensitiser at low levels to carry the signal heading POISON when in S6 might be considered misleading and certainly overstates the risks presented by such products. Some consideration of the extent to which skin sensitisation, as the sole or predominant risk, should be used to drive scheduling decisions beyond Schedule 5 is appropriate.

More broadly, there appears to be a lack of, or inadequate, cross regulatory collaboration to ensure that regulatory decisions do not result in unintended high impact consequences across regulatory boundaries.

A number of options for consideration to address these issues have been proposed.

Options for Consideration

The following options are based on a preliminary assessment of the issues arising from the current approach to consideration of scheduling for cosmetic and domestic product ingredients. Most of the options identified will require further analysis to determine their viability and suitability. More specifically, the complex interaction between the many agencies with responsibility for these substances both in Australia and in major trading partners (EU and North America) is required to validate underlying assumptions and preliminary conclusions.

Procedural and policy issues

- Concordance with international regulatory approaches. Consider agency/jurisdiction policy regarding the benefits Concordance limitations and desirability of concordance with international regulatory approaches for cosmetics and domestic products
- Consider the appropriateness of a POISON Signal heading solely for sensitisation risks

Minimising Unnecessary Regulatory Impact

- Committee Structure

- Because scheduling decisions on chemicals have impact across a wide range of regulated commodities inclusion in the scheduling committee of subject experts in the areas of complementary and listed medicines, pesticides and veterinary chemicals would improve the breadth and depth of recommendations from that committee
 - Subject expertise might be drawn from either or both the relevant regulatory areas or their respective advisory committees
- Consider alternative mechanisms for regulating fragrance substances and other chemicals present at low levels in cosmetic products, e.g.
 - Establishment of an Australian standard that references the IFRA and EU standards/requirements
 - Establish an onus on industry to ensure their products are safe and provide appropriate safety advice to consumers (used in food regulation)
 - Give the EU cosmetic directive requirements and IFRA standards as examples of adequate and sufficient compliance.
 - Adopt by reference the EU Cosmetics directive (as FSANZ have done for flavours)
 - Create an Appendix B entry for perfumes and flavours when used and labelled in accordance with EU cosmetics Regulation at levels below the limits proposed by the IFRA Standards
 - Insert an amendment to the interpretation section of the Poisons Standard to exempt fragrance and flavor materials when in Appendix B.
- Consider a review of the European and US regulatory regimes to determine the extent to which the respective regimes can be adopted or leveraged by Australia to reduce resources required to manage the relatively minor risks presented by cosmetic ingredients as used in commercial practice

Identify the most appropriate Regulatory Environment for Cosmetics

- review the interaction of the multiple regulatory schemes impacting ingredients of cosmetics, consumer and household goods in Australia:
 - TGA (therapeutic goods), APVMA (all pesticides and veterinary medicines but especially insect repellents), FSANZ, ACCC, NICNAS
- consider if some types of cosmetic ingredient hazards would be better managed through the ACCC labelling standard (e.g. declaration of skin sensitizers)

Improved Guidance

- Prepare for the improved, science based, guidance for estimating acute risk of dilute preparations to provide a sound foundation for consistent decision making
- Improve the scheduling application form to require broader assessment of the impact of scheduling decisions on industry and to ensure that all affected preparations (such as essential oils) are considered

Improved Processes

- consider implementing a revision of the previous review of the scheduling of essential oils to include their constituents.
- if cosmetic ingredients are to continue to be routinely considered for scheduling, then;
 - better use might be made of existing, and higher quality, risk assessments (RIFM/IFRA, JECFA, FEMA, SCCP etc.)
 - improved engagement of industry and recognition of the costs of that engagement to industry

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- better consideration of the impact of regulation across multiple industries that use these types of substances (listed and OTC medicines, AgVet chemicals, food ingredients etc.)
 - grouping of related substances in a class review rather than ad hoc, piecemeal assessments
 - liaise with ACCC to ensure ingredient lists on cosmetic products be required to include any substance identified in the EU Cosmetics Directive in compliance with the various cut off values specified.
 - Engage other relevant advisory Committees. Where a substance proposed for scheduling has been the subject of consideration by another TGA advisory committee (e.g. ACCM), the proposal should first be sent to that committee (or at least the regulatory area responsible) for consideration and advice before a scheduling decision is made. The advice requested should include but not be limited to
 - identification of cross regulatory impacts
 - identification of any adverse incident reports
 - review of the basis for the scheduling decision

Definitions of Derivatives

- routinely define derivatives for each new entry. Consider requiring a consideration of which (types) of derivatives should be captured each time a new schedule entry is proposed
- develop standardised, contextualised definitions for derivatives. Consider developing a series of standard definitions appropriate for different toxicological or other end points driving the scheduling decision
 - e.g. for drugs of abuse the retention of the pharmacophore and interaction with a specific pharmacological receptor are the key issues
 - for a most caustic material most salts and other derivatives will not retain the caustic properties
 - where the key concern is oral toxicity a broader definition of derivative is likely to be applicable than where irritation or sensitisation are the key issues.

Develop improved options for managing Low Level Presence as impurities of substances included in Schedules 7 to 10

- designation of a generic concentration threshold for impurities (e.g. 1, 10 or 100 ppb, µg/kg) unless a specific entry specifies otherwise
 - Relatively simple and resource efficient approach
 - May not be sufficient in isolation
- explicit impurity cut offs for each substance in schedules 7 to 10
 - precise
 - resource intensive to apply retrospectively
 - may need broad and extensive consultation
- use of the TTC approach as the basis for identifying impurity cut offs for specific substances

- primarily to provide prospective guidance to the scheduling committee on where to set impurity permissions
- TTC applies to exposures rather than concentrations or amounts in a product so cannot be used as a generic limit
- case by case prospective inclusion of substances such as 1,4 butanediol and ethylene oxide in Appendix G with explicit cut offs
 - precise
 - highly resource intensive
 - likely to require extensive and broad consultation.
 - does not solve accumulated issues from the past decades

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