Australian Government

Department of Health

Therapeutic Goods Administration

Scheduling Scoping Study (Phase 1)

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TGA Health Safety Regulation

Contents

Executive Summary

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 (SPF) and scheduling process for medicines and chemicals, 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, UK and US) and to address a number of concerns raised by ACCORD Australasia Pty Ltd (ACCORD). As a result of the NICNAS IMAP Inventory Multi-tiered Assessment and Prioritisation process (IMAP), a number of cosmetic ingredients have been referred by that agency for scheduling. ACCORD have expressed concerns relating to the perceived discordance of Scheduling recommendations and decisions arising from these referral with those of comparable international regulations in major trading partners such as the EU, leading to substantial compliance costs to their industry members. ACCORD have also raised concerns relating to inconsistencies between SUSMP entries for closely similar cosmetic and fragrance substances, uncertainty around the capture of derivatives as defined in the SUSMP and problems arising from the absence of Schedule cut offs to allow impurities of substances included in Schedules 7 to 10.

In conducting this review 30 cosmetic ingredients that had been the subject of scheduling applications between March 2016 and June 2018 were reviewed. The scheduling decisions or recommendations were compared against the respective EU cosmetics Directive entries to determine the degree of concordance/discordance, 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 ACCS and the delegate was also assessed against the various matters the legislation and AHMAC guidelines require to be considered and against the Government policy for evaluating new legislation/regulation.

Of the 30 cosmetic (excluding hair dyes) 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 9 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, leading to enquires from the public concerned at the apparent incongruity of a baby wipe carrying this heading. For 12 of the compounds, the scheduling outcome is overly restrictive and discordant with the level of risk presented by the substances and require unique Australian labelling with substantial attendant costs imposed on Australian Industry. For 5 substances the scheduling outcome is inconsistent with similar substances already in the SUSMP, generally due to inconsistent management of skin sensitisation, and at least 3 result in unintended cross regulatory capture affecting a range of non-cosmetic uses such as complimentary medicines. For at least 2 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 S5 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 submitting agency 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 complimentary medicines for example includes that they are not included in a schedule of the SUSMP. The proposed Scheduling of geraniol in S6 would result in a number of essential oils included in Appendix B being both S6 and unscheduled and therefore both eligible and ineligible for approval as an ingredient in listed medicines.

Other decisions such as the proposed S6 entry for cinnamaldehyde would see products containing a 100 or a 1000-fold less cinnamaldehyde than cinnamon bark labelled as POISON primarily on the basis of skin sensitisation. Inconsistencies in labelling requirements for skin sensitisation and apparent misunderstanding of the induction versus elicitation of skin sensitisation were also identified.

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, ACCS, delegate and other stakeholders.

Neither the Advisory Committees nor the Secretariat have the resources or the depth and breadth of expertise to compensate for incomplete applications. Consequently, there is a need for agencies, corporations and individuals making applications for scheduling to gather and submit the data and analysis necessary for the ACCS and delegate to consider the range of issues they are required to have regard to. Given the resource limitations of the Secretariat and the rate of turnover of both staff and ACCS members the primary role of the Secretariat is to ensure applications contain the relevant information, collate and present the information in a form that facilitates ACCS deliberations, provide relevant information on previous decisions and document the decision-making process.

The provision of more extensive guidance has become more pressing with the introduction of the option to submit Scheduling applications for new substances in AgVet and other products directly to the Secretariat, in advance of a product approval application, rather than through the respective regulatory agencies. In the previous arrangements the respective regulatory agencies were responsible for the provision of appropriate risk assessments to provide a basis for scheduling recommendations. Under the new arrangements this responsibility may fall to the Secretariat without a mechanism to cost recover the resource necessary to undertake the task. Clear guidance on the requirements for an adequate Scheduling application would reduce the resource impacts on the TGA and Secretariat.

ACCORDs concern regarding the low level presence of impurities that are included in schedules 7-10 were considered by examining 2 case studies, ethylene oxide (S7) and 1,4-butandiol (S10). Both these substances are used industrially as reagents in the synthesis of various of cosmetic ingredients such as surfactants and polymers for example. The SUSMP permits the presence of impurities of substances included in schedules 1 to 6 at $\leq$ 10 mg per litre/kg (0.001%, 10 ppm), unless that substance is also included in Schedule 7 or 8 (in which case no tolerance is permitted), no allowance is made for any impurity from schedules 7 - 10 regardless of how low the level and regardless of whether that substance also has an S5 or S6 entry. The exemption does not explicitly mention Schedules 9 and 10 which appears to be an oversight. Appendix G – Dilute preparations – provides limited additional exemptions for low level presence of a small number of otherwise scheduled substances. The lack of a formal tolerance for low levels 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. 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).

Another concern raised by ACCORD is the uncertainty of regulatory capture inherent in the current broad and ambiguous definition of derivative. The SUSMP 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. 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. Because of the broad application of the definition it does not accommodate the very different issues each class of scheduled substance present. The current definition is also so broad it is largely

uninterpretable and is essentially as broad or as narrow as a regulatory authority wishes it to be in any given circumstance. Consequently, in a large number of circumstances, industry can potentially only gain certainty through a specific determination from the ACCS and/or delegate. The legal weight of such a determination is also uncertain. 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 ACCS 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.

Identified Process Improvement Options for Consideration

Procedural and "small p" policy issues

- Concordance with International Regulatory approaches. Consider Agency/Jurisdiction policy regarding the benefits, limitations to the extent of concordance achievable, and desirability of concordance with international Regulatory approaches for cosmetics and domestic products
- Consider the appropriateness of a POISON Signal heading solely for sensitization risks

Minimising Unnecessary Regulatory Impact

- Committee Structure
  - Because individual Scheduling decisions on chemicals have impact across a wide range of regulated commodities inclusion in the ACCS 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 regulatory arrangements/options for ingredients of cosmetic and consumer goods that can be canvassed when Scheduling applicant/proposals are being considered
- Consider alternative mechanisms for regulating fragrance substances and other chemicals present at low levels in cosmetic products, eg
  - 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 SUSMP 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

- NICNAS is a ***hazard*** assessment agency, but cosmetics scheduling is a ***risk-***based regime, other agencies have greater familiarity with both the types of ingredients in cosmetics and risk based assessments

- Review the interaction of the multiple regulatory schemes impacting ingredients of cosmetics, consumer and household goods in Australia
    - TGA all types of therapeutic goods, APVMA all pesticides and veterinary medicines but especially insect repellents, FSANZ, ACCC, NICNAS, others?

Improved Guidance to Committees and Applicants

- Prepare for the ACCS and ACMS 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.
- Conduct a regulatory impact assessment on the costs and benefits of utilizing the scheduling mechanism for the regulation of cosmetic ingredients present at low levels in consumer products.
- If cosmetic ingredients are to continue to be routinely considered for scheduling, then;
    - Consideration of the resources required to support greater input from the Secretariat may be required, or
    - 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
    - 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
    - Address the Regulatory impact in scheduling submissions even if a formal RIS is not indicated.
- Liaise with ACCC to ensure ingredient lists on cosmetic products be required to include any substance identified in the EU cosmetics directory 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 (eg 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
    - Eg 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 (eg 1, 10 or 100 ppb, ie 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 4 to 10
    - Precise
    - Resource intensive to apply retrospectively
    - May need broad and extensive consultation
- Use of the Threshold of Toxicological Concern approach as the basis for identifying impurity cut offs for specific substances
    - Primarily to provide prospective guidance to the ACCS 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

Glossary

Table 1 Glossary of Abbreviations

Acronym	Expansion
ACCORD	The national industry association representing manufacturers and suppliers of hygiene, cosmetic and specialty products, their raw material suppliers and service providers.
ACCC	Australian Competition and Consumer Commission
ACCS	Advisory Committee on Chemical Scheduling
ACD	Allergic Contact Dermatitis
ACCM	Advisory Committee on Complimentary Medicines
ACMS	Advisory Committee on Medicines Scheduling
AICS	Australian Inventory of Chemical Substances
CMEC	Complimentary Medicines Evaluation Committee
CORs	Comparable Overseas Regulators
DST	Dermal Sensitisation Threshold
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonized 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
OBPR	Office of Best Practice Review
OECD	Organisation for Economic Cooperation and Development
PMC	Department of Prime Minister and Cabinet
PPE	Personal Protective Equipment
RIS	Regulatory Impact Statement
SPF	Scheduling Policy Framework
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Agency
WoE	Weight of Evidence

General Issues

Introduction

In 2016-2017, the Department of Health (Health) reviewed the Scheduling Policy Framework (SPF) 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, UK and US). Of particular interest was an exploration of whether there are opportunities to harmonise chemical scheduling with comparable overseas regulators (CORs).

In conducting this review consideration has been given to a proposal from ACCORD Australasia Pty Ltd (ACCORD) to create a new Appendix entry in the Poisons Standard for substances used in cosmetic products, including incorporating Annexes II-VI of the European Union (EU) Cosmetics

Regulation (European Commission, 2009), which details prohibited and restricted ingredients. ACCORD has also proposed mandating compliance with the International Fragrance Association (IFRA) Standards for fragrance materials (IFRA, 2015).

The increased number of referrals of cosmetic ingredients to the Advisory Committee on Chemicals Scheduling (ACCS) and the Joint Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS) noted by ACCORD has resulted from a NICNAS program to assess existing chemicals on the Australian Inventory of Chemical Substances (AICS) that had been "grandfathered" onto the AICS at the commencement of the NICNAS scheme. This program of review is conducted under the Inventory Multi-tiered Assessment and Prioritisation process (IMAP). As a result of that process a number of cosmetic and fragrance ingredients on the AICS were identified for assessment on the basis of GHS hazard criteria. Some of these compounds have been referred individually, in the sequence in which they were reviewed, by NICNAS to the ACCS for consideration for inclusion in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSMP). The scheduling reconsiderations have given rise to concern amongst cosmetic and fragrance manufacturers in Australia, as represented by ACCORD, regarding potential unintended consequences, perceived discordance with international regulations in major export markets, and an expressed perception that the overall regulatory burden is disproportionate to the risk being managed.

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 first phase of the 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 the cosmetics industry by scheduling decisions discordant with international practice in major markets.

Before examining the nature of the information and advice provided to the ACCS in scheduling applications for cosmetic ingredients, and that committees' subsequent scheduling recommendations, 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.

What is a Cosmetic or Fragrance Chemical

In Australia and Internationally the regulation of chemicals tends to be stratified according to somewhat arbitrary divisions between drugs, food constituents/additives, pesticides and industrial chemicals. These distinctions may, and often do, have validity in terms of exposure and use patterns, and therefore risk profiles, but have no basis in reality in terms of dividing the universe of chemicals into neat regulatory boxes, and have no impact or bearing on the hazard profile of 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. Even a prescription medicine (S4) such as Deanol (also known as 2-dimethylaminoethanol) 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, complimentary 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), Figure 1. 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 Over-the-counter Medicines Branch.

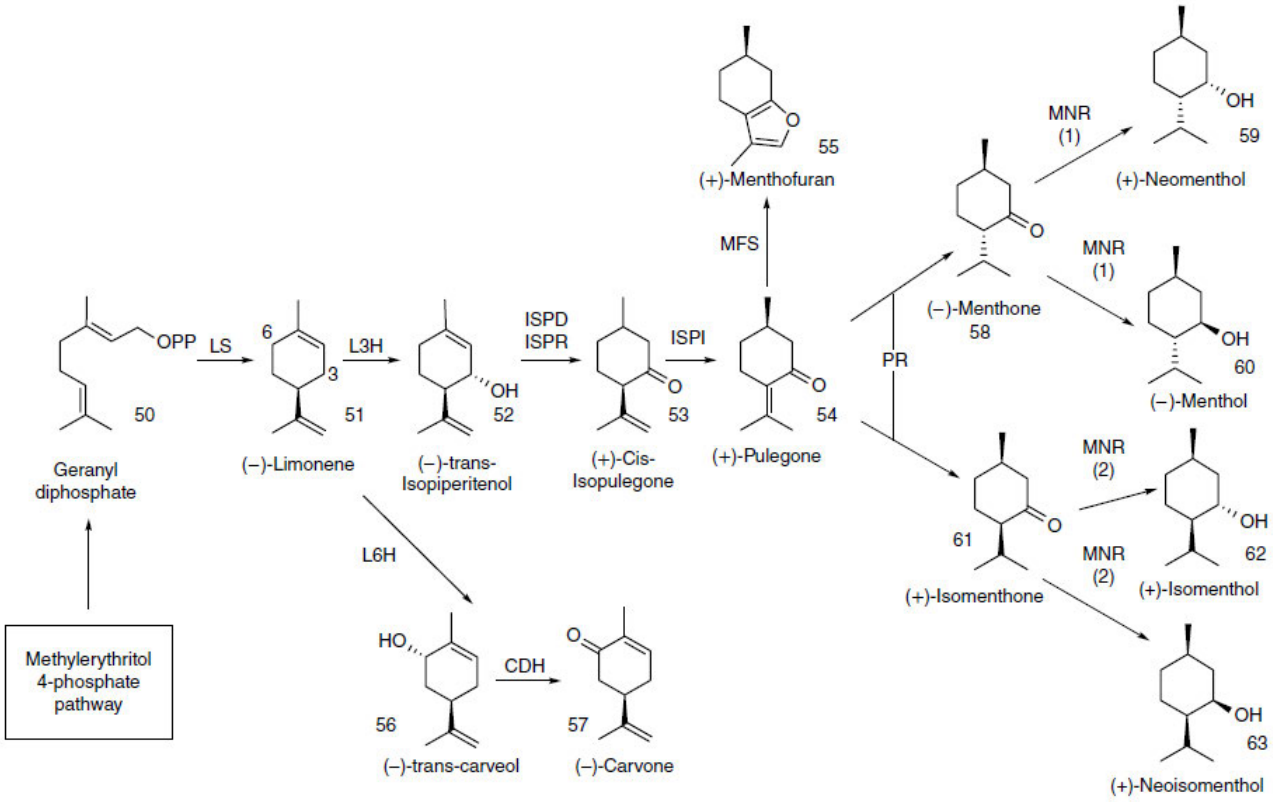

Figure 1 Geraniol (Geranyl diophosphate) in the biosynthesis of p-menthane derivatives including Menthol

There is therefore significant potential for narrowly focused, compartmentalized 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.

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 ACCS Secretariat. Isoeugenol (a component of clove oil) for example was originally proposed for scheduling as a result of an application to the APVMA for use as a farmed fish anaesthetic. Subsequent review by NICNAS under IMAP resulted in proposed amendments to the SUSMP entry. Isoeugenol is additionally a component of clove oil, 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 do not exist in isolation of the remainder of the universe of chemical substances. Every individual chemical 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. Considerations of cosmetic ingredients within classes may also; 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, complimentary 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.

The Nature of Poisons Scheduling

The Poisons schedules are legislative in nature (AHMAC, 2018) and are a Commonwealth Legislative Instrument.

> "Scheduling decisions under subsection 52D(2) are legislative in character *as they determine the future lawfulness of conduct as provided for under the Act and the Regulations*, such as in relation to advertising, as well as State and Territory legislation. Changes to the Poisons Standard alter the content of the law, and have the indirect effect of imposing or varying obligations or rights. The Federal Court in Roche Products v National Drugs and Poisons Scheduling Committee [2007] FCA 1352 held that a decision by the NDPSC to amend the Poisons Standard was legislative in nature and the Court gave several reasons to support that decision which remain applicable. As scheduling decisions are legislative in character, they cannot be the subject of an appeal under the Administrative Decisions (Judicial Review) Act 1977 in the Federal Court. Scheduling decisions under subsection 52D(2) are not "initial decisions" which are open for reconsideration under section 60 of the Act, Therefore they are not reviewable by the AAT." (TGA, 2018)

The Poisons Schedules are intended to set the level of controls on the availability, labelling and packaging of poisons primarily for domestic use. "Poisons which are packed and sold solely for industrial, manufacturing, laboratory or dispensary use are exempt from all labelling requirements included in the SUSMP as they are covered by labelling requirements under applicable jurisdictional Work Health and Safety laws, as amended from time to time." This exemption does not extend to controls on supply of these poisons however.

The scheduling decision making process is risk rather than hazard based. The introduction to the SUSMP 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.* (Department of Health, 2018)

The basis for risk categorisation of substances is detailed in the Therapeutic Goods Act (Australian Government, 2017), the AHMAC Scheduling Policy Framework (AHMAC, 2018) and the Scheduling Handbook (Dept of Health, TGA, 2018).

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 SUSMP, 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 Chapter 6, part 6-3 of the Therapeutic Goods Act. Section 52 E of the Act 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 SUSMP. In addition to AHMAC guidelines and the advice of the ACCS and ACMS 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 AHMAC guidelines. The AHMAC guidelines make 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"* [emphasis added].

The guidelines also make clear that scheduling may need to be reconsidered where knowledge ***or practice*** changes. Thus, scheduling is a risk-based process and submissions for scheduling can reasonably be required to provide the information necessary to support a risk assessment and consideration by the delegate and/or the ACCS of the matters the factors required by legislation.

Principles of Regulatory Best Practice

All regulation imposes constraints, obligations or liabilities on individuals and/or corporations and therefore a cost. In an ideal regulatory environment, such imposts are strictly proportional to the risks or potential adverse outcomes associated with the activity being restricted, and the costs of implementation and compliance are proportionate to, and commensurate with, those associated with the risks being mitigated or obviated. Consistent with these considerations, the legislative foundation for Poisons scheduling incorporates a requirement to consider both risks and benefits of substances in **products as supplied into the market,** without explicit limitation to health risks and health benefits.

The principles of proportionality more broadly are widely recognised as a foundation of National and International Law and subsidiary regulation (Cottier, 2012; Ferran, 2015; OECD, 1995; OECD, 2012). Consistent with the Governments' commitment to regulatory best practice the Office of Best Practice Review (OBPR) within the Department of Prime Minister and Cabinet (PMC) has noted the Governments' commitment to the OECD 2012 Recommendation on Regulatory Policy and Governance (OECD, 2012). This commitment has been given effect through the Office of Best Practice Review and the requirement for preparation of a Regulatory Impact Statement where new regulation is being proposed.

Regulatory Impact

Unlike provisions for review by the Administrative Appeals Tribunal (AAT), which is available only where statutes make provision for it (Administrative Review Council, 2018), the requirement for consideration of the impact of new or amended regulations through a RIS is generic across all regulatory areas and an expression of Government Policy. The Australian Government Guide to

> *If a decision is not going to Cabinet, a RIS is still required where the policy proposal is likely to have a measurable impact on business, community organisations or individuals.* ***This includes new regulations, amendments to existing regulations and, in some cases, sunsetted regulations being remade.*** (PM&C, 2014)

Regulation (PM&C, 2014) indicates that a Regulatory Impact Statement should be considered wherever a change to existing regulations is likely to have a "measurable effect on business, Community organisations or individuals".

Traditionally the TGA has not conducted Regulatory Impact Statements for scheduling proposals and OBPR has agreed to limited carve outs related to specific aspects of the scheduling process (OBPR, 2017). These carve outs however, are related to "adding new substances to the Poisons Standard" where the "*Decision maker has no discretion in terms of which schedule a new substance is added to*" and "*Does not cover amendments to the listing of an existing substance on the Poisons Standard or the removal of an existing substance from the Poisons Standard, which may require a RIS*".

Department	Proposal	Why is the proposed change an indexation, routine administrative or minor or machinery change?	OBPR reference number	Comments / limits on carve-out
Department of Health	Therapeutic Goods Administration—urgent scheduling where it relates to new substances or derivatives of existing Schedule 9 substances on the Poisons Standard	Machinery.	14416	Does not cover instances where urgent scheduling relates to up-scheduling of existing substances.
Department of Health	Therapeutic Goods Administration—annual consolidation of Standard for the Uniform Scheduling of Medicines and Poisons	Machinery.	14416	
Department of Health	Therapeutic Goods Administration—adding new substances to the Poisons Standard	Machinery: Decision maker has no discretion in terms of which schedule a new substance is added to.	14416	Does not cover amendments to the listing of an existing substance on the Poisons Standard or the removal of an existing substance from the Poisons Standard, which may require a RIS.
Department of Health	Therapeutic Goods Administration—down-scheduling of substances on the Poisons Standard	Machinery.	14416	
Department of Health	Therapeutic Goods Administration—correction of minor errors on the Poisons Standard	Machinery.	14416	
Department of Health	Therapeutic Goods Administration—correction of inadvertent scheduling errors on the Poisons Standard	Machinery.	14416	

Arguably however, where scheduling proposals are for medicines or agricultural and veterinary chemicals, the scheduling process is incidental to the broader regulatory process generally associated with a specific application for approval of a medicinal or agricultural product, therefore largely machinery in nature, and the impact of the scheduling decision is largely limited to the specific applicant. In these circumstances a RIS would not seem to be indicated, consistent with current practice and the general intent of the OBPR carve out and general RIS Guidance (OBPR, 2017). Where a substantial number of proposals are for substances used in cosmetics however (or products from any other industry supplying domestic goods not overtly regulated at the product level), are not associated with specific product applications and introduce new restrictions and imposts on that industry unrelated to the normal machinery of product or substance approval, these would not seem to be incidental or minor in their potential impact and the principles of the RIS process might at the least be addressed within the scheduling deliberations, although not explicitly required by the TGA legislation. More specifically where a substantial regulatory impost is likely, a consultation with the relevant industry would seem to be a minimal obligation to ensure that;

- the most appropriate risk proportionate regulatory response is identified,
- the most cost-efficient mechanism for addressing that response is adopted,
- a review of potential alternative approaches is undertaken.

The OBPR has produced a guide for determining where a RIS might be required (OBPR, 2017) based on COAG principles (Council of Australian Governments, 2014). The types of regulatory impacts and compliance costs on industry that OBPR indicate should be considered include;

- **Regulatory impacts including:**
  - changes to the number or type of products that businesses can offer, such as:

        - banning products or industry practices
        - changing the way products can be offered
    - impacts on consumer demand for certain products, such as:
        - increasing prices through the regulation's requirements
        - changing the information available to consumers
    - impacts on the ability of businesses to compete in the market or on their incentives to compete, such as:
        - creating a self-regulatory or co-regulatory regime
        - changing the requirements for a licence, permit or other authorisation
        - influencing the price or quantity of goods that are sold
        - setting standards for product or service quality
        - changing the prices or types of inputs available to businesses.
- **compliance costs:**
    - administrative costs
        - costs incurred by regulated entities mainly to demonstrate compliance with the regulation (usually record keeping and reporting costs)
        - costs incurred through complying with government taxes, fees, charges and levies, beyond the amount paid (for example, the time taken to pay a licence fee).
    - substantive compliance costs
        - costs that lead directly to the regulated outcomes being sought (usually purchase and maintenance costs for plant and equipment to meet regulatory requirements, fees paid to training providers, costs of providing information to third parties, and costs of operation—for example, energy costs).
- **delay costs:**
    - expenses and loss of income incurred by a regulated entity through one or both of:
    - an application delay—the time taken to complete an administrative application requirement that prevents the party from beginning its intended operations
    - an approval delay—the time taken by the regulator to communicate a decision on the administrative application that prevents the party from beginning its intended operations (this includes the time taken to asses and consider an application).
- **Costs associated with the need to engage and respond to the process** –
    - of submission preparation
    - rescheduling application to fix errors
    - monitoring of outcomes
    - provision of expertise

Many of the considerations raised by the OBPR are clearly applicable where a wide range of substances within a number of chemical and use classes are being considered for scheduling action in an area that has not previously been routinely included in the process other than for overtly high-risk chemicals. This requirement has precedence for Cosmetics in the ACCC RIS on consumer product information standards (ACCC, 2008).

Options for Consideration

For process and evaluation efficiency and effectiveness, and to limit resources required to address the regulatory impact analysis, where a number of related substances are known to require scheduling consideration these could be encompassed within class reviews such as for surfactants, perfume and flavor ingredients, colourants, preservatives etc. This approach would;

- reduce the cost to both industry and regulators by grouping related substances in the one risk analysis
    - provide opportunities for read across of data sets for related substances to compensate for missing or deficient data,
    - facilitate call in of data from potentially affected industry groups,
    - ensure unintended consequences or inconsistencies are minimized,
    - reduce the number of times that industry need to be engaged,
    - broaden the scope of industries involved and therefore distribute the burden of engagement more broadly
        - also increasing the likely availability of data
    - facilitate engagement of regulators across the broad range of chemicals to ensure a higher quality of risk assessment and consideration of unintended cross regulatory consequences.

Basic Principles of Regulatory Risk Assessment

Human Health Risk Assessment (HHRA) although founded in the scientific interpretation of toxicology and exposure data, involves elements of organisational culture, accepted paradigm and process, and both legislated and organisational policy. Very real differences in risk management can arise from these inherent differences in approach even where there is full concordance in the hazard identification for a chemical. These differences may be entirely reasonable and reflect the differences in exposure between a worker handling bulk drums of a pure chemical versus a consumer using a cosmetic containing a few micrograms of the same chemical as a fragrance, or a pharmaceutical preparation used under the supervision and advice of a medical professional. An agency which routinely assesses chemicals used in a given range of use patterns may not have the established processes, experience or familiarity necessary to adequately assess the risk management requirements appropriate for a different pattern of use.

Risk is a function of hazard and exposure. Exposure in turn is a function of the type and use pattern of the product containing the substance of interest, including its concentration in the product, how the product is used, how frequently it is used and where it is used. Risk assessment is a multi-step process that generally includes;

- Hazard identification
    - What toxicological effects can a substance cause in experimental animals and humans across the achievable exposure range
- Hazard characterization
    - What specific toxicological effects are observed at what doses (the dose response curve)
    - What studies and what species are the most relevant for humans
    - Are the studies available likely to over or under-estimate the risk to humans
    - What does previous exposure of humans tell us about the hazard in humans
- Exposure Assessment
    - By what route will people be exposed
        - Oral, dermal, inhalational, parenteral
    - To what type of products will they be exposed
        - Cosmetic, home garden, pharmaceutical
    - In what concentration will the chemical be present
    - How much of the product is used
    - Where and how is it used

    - What other sources of exposure are there for this substance
- Risk Characterisation
    - What are the risks of the chemical when used as intended, at the concentrations in actual use in products as sold to the public.
    - Are there misuse scenarios that need to be considered?

Many of the scheduling applications for cosmetic ingredients have not addressed issues beyond hazard identification at a level of detail sufficiently to provide an adequate basis for the ACCS to develop robust scheduling advice to the delegate. More extensive guidance on the information require to be provided in scheduling applications would appear to be required.

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 (relatively uncommon)
- A disconnect between the GHS hazard-based classification scheme and risk based regulatory schemes
- Too narrow a focus on individual chemical substances rather than classes (common)
- Inadequate consideration of;
    - Use patterns
    - Presentation of products
    - Familiarity of consumers with common hazards
    - The intersection of individual compounds with derivatives/extracts of natural products
    - Intersection of regulatory regimes and cross regulatory impacts
    - Exposure patterns
    - Appropriate dose metrics
    - Dose response curves
    - Consistency within chemical classes
- Lack of appropriate expertise within the group, organization or agency making a submission to the ACCS,
- Organisational culture

The NICNAS regulatory environment for example was developed to manage the introduction of industrial chemicals into Australia. Under the tiered chemicals regulatory environment in Australia any chemical or pattern of use that is not captured by a chemicals regulator at a higher tier is captured by the NICNAS legislation. Thus, if a chemical or its use pattern is not a drug (Therapeutic Goods Act), food additive or food ingredient (Food Standards Australia New Zealand Act), Agricultural or Veterinary Chemical (Agricultural and Veterinary Chemicals Code Act), then the chemical comes under the NICNAS scheme. Cosmetics and fragrances come under the responsibilities of NICNAS through this interaction of the various chemicals regulations and not through an active or considered decision that cosmetics and fragrances are most appropriately managed under an industrial chemicals paradigm. Indeed, the pattern of use and nature of the ingredients in cosmetics is more closely aligned with OTC and Complimentary medicines than with Industrial Chemicals.

The NICNAS processes and approach to chemical regulation closely, and intentionally, aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The GHS 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 minimize exposure and therefore risk.

The NICNAS approach to toxicology assessment is therefore largely procedural for most assessments and is designed to align GHS categories and hazard Statements with toxicological hazard endpoints. The IMAP assessments of chemicals which provides the principal basis of NICNAS scheduling applications, is therefore aimed at addressing the GHS requirements in order to identify occupational labelling requirements and is not primarily intended to satisfy the risk-based requirements of the ACCS or ACMS for the development of scheduling recommendations to the delegate. The remaining chemical regulatory agencies have considerably greater scope for development of risk management strategies and have greater control of use patterns and the presentation of commodities containing a specific chemical. The approach to toxicology and risk assessment in the remaining chemical regulation agencies is therefore more deeply interpretive and involves careful consideration of the nature, pattern and significance of findings in toxicology studies, and that of exposure, to ensure risk definition is appropriate for consideration of broader risk management strategies. As a consequence, assessment reports from those agencies generally provides a more substantial consideration of risk, to support their internal requirements, providing the ACMS and ACCS with a stronger basis for the formulation of scheduling recommendations.

> *Case Study* 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. The advice and interpretation required by the ACCS is the latter rather than the former.

Risk communication is a critical aspect of consumer advice. Over stating risk through hazard-based categorization 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;

> **In order to ensure the information and advice provided to the ACCS by scheduling applicants (whether individuals, Regulatory agencies or companies) is adequate and appropriate for the provision of scheduling recommendations to the delegate consideration should be given to the development of more detailed advice and guidance to applicants.**
>
> **Provision of guidance might be most effective and efficient if incorporated in the form of an online application system that captures the required information and populates a database for long term support and documentation of the scheduling process. This approach would also improve the "corporate Knowledge" of the Scheduling Secretariat and ACCMS which currently have a high turnover of personnel.**

Structuring the Review

In order to ensure sufficient opportunity for relevant stakeholders to adequately consider and comment on the outcomes of the review and to ensure final recommendation of options for consideration fully incorporate the views and needs of the relevant stakeholders, the review has been conducted in stages. These stages reflect the discussion above which identified a number of factors that clearly impact the Scheduling decision making process including;

- Is there a discordance in the assessments conducted by the principle applicant with those conducted by comparable international agencies (hazard versus risk assessment)?
- Is the analysis being presented to the ACCS by applicants sufficient to enable the members to provide adequate advice on all matters that the Delegate to the Secretary are required to have regard to?
- Are the risk management options of the SUSMP suitable for cosmetics and fragrance substance or should some other mechanism be considered?
- Are the analyses supporting the EU cosmetics Directive and the IFRA standards being adequately considered to ensure compatible regulatory outcomes where appropriate?
- Are there administrative, procedural, or organisational policy changes that can be readily implemented that would improve the alignment of Scheduling outcomes with those of major trading partners?
- Are there structural changes that are required to achieve better alignment?
- Could a mechanism for direct adoption or referencing of European standards be practicable?

Staging

To address the relevant issues this review has been staged into the following components

1. Consideration of the adequacy of the information and analysis of the Scheduling applications provided to the ACCS for cosmetic and fragrance materials to support consideration of the relevant matters.
2. A review of the regulatory environment for cosmetics in Australia
3. A review of the regulatory Requirements for Cosmetics in Europe
4. Identification of the nature and sources of practical difficulties arising from current procedures, processes and mechanisms and development of options to mitigate or remove these difficulties.

For this first stage of the review the attention has been addressed to 2 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 2, 3, 7, 8, 9 & 10
    d. Consideration of unintended regulatory impacts
    e. What types of scheduling consideration should trigger a Regulatory Impact Statement or internal equivalent
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. AHMAC Scheduling Policy Framework (AHMAC, 2018)

iii. Scheduling Handbook (TGA, 2018)
iv. Have the requirements for Regulatory Impact Assessment been considered

General Issues

In considering the adequacy and suitability of the current Scheduling procedures and ACCS & ACMS recommendations, the specific issues raised by ACCORD and the requirements of applicable legislation and AHMAC guidance are relevant and are considered in this section.

ACCORD Concerns

ACCORD 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
- **Inconsistency within the SUSMP**, inconsistency with international controls and interpretation of derivatives, for example Geraniol (Rajeswarra Rao, 2002)
- **Australian Specific Labelling**
    - 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. If the finished product is otherwise unscheduled but requires additional labelling to meet an exemption from scheduling, all of the extra labelling will need to be added.
    - Ingredient warnings should not spill over into generic product labelling.
    - The requirement for signal headers and their position on the first line of the label for scheduled substances is also unique to Australia for hair dye products and requires costly re-work of imported product labels.

Identification of Scheduled Substances

In conducting a review of recent ACCS recommendations a notable challenge was to identify unambiguously what chemical the relevant entries in the SUSMP specifically referred to. The SUSMP 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 ACCS 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 SUSMP entries is a simple low resource intensive mechanism for improving the accessibility and ease of interpretation of the SUSMP.

Presence at low levels / Impurities

The SUSMP 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 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 S7 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* ACCORD give 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 SUSMP 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 one or a combination of the following;

- Designation of a generic concentration threshold for impurities (eg 1, 10 or 100 ppb, ie 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 4 to 10
    - Precise
    - Resource intensive to apply retrospectively
    - May need broad and extensive consultation
- Use of the Threshold of Toxicological Concern approach as the basis for identifying impurity cut offs for specific substances
    - Primarily to provide prospective guidance to the ACCS 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

Derivatives

The SUSMP 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 each class of scheduled substance present. The current definition is also so broad it is largely uninterpretable and is essentially as broad or as narrow as a regulatory authority wishes it to be in any given circumstance. Consequently, in a large number of circumstances, industry can potentially only gain certainty through a specific determination from the ACCS and/or delegate. The legal weight of such a determination is also uncertain. 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 ACCS and delegate in identifying derivatives of likely concern might substantially reduce the ambiguity and reduce the potential for unintended and inappropriate capture of substances.

> *"a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise. (See Part 1, Interpretation, subparagraph 1(2)).*
>
> *It is important to note that a substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a scheduled poison relies on a balanced consideration of factors to decide if a substance has a similar nature (e.g. structurally, pharmacologically, and toxicologically) to a scheduled poison or is readily converted (either physically or chemically) to a scheduled poison."*

<u>*Case Study*</u> EtO 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, EtO 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 scheduled compounds. There is some difficulty interpreting what is intended by "on balance of consideration" in the Poisons Standard, as this has not been clarified by any regulator.

If the definition of "derivative" is not reliably and unambiguously interpretable to the average chemist, pharmacologist or toxicologist then there would at least be some doubt as to the legal enforceability of scheduling of derivatives. **Advice should be sought on this matter and the definition of "derivative" reviewed.**

In reviewing the definition of derivatives consideration should be given to the intended purpose of capturing derivatives in each schedule of the SUSMP. For drugs of abuse and addiction the principle intent is to capture compounds with a common pharmacophore (the structural element that confers the pharmacological action of concern). This concept is more important and definitive than the specific salt, ester or ether and might be given greater weight in the definition of derivatives for substances in Schedules, 4, 8, 9 and 10. For schedules 7 and 10 a core toxico-phore may be definable for some substances. For Schedules 5 and 6 and some in Schedule 7 the Scheduling decision will often be based on physicochemical irritation, or skin sensitisation rather than pharmacological or toxicological hazards. In these cases, the broad definition of derivative is toxicological inappropriate. This reality is recognised for some obvious substances such as sodium hydroxide, a corrosive skin and eye irritant, where the entry specifically excludes salts and derivatives. The most common salt of sodium hydroxide is sodium chloride, or common table salt, which is often used as an eye bath, illustrating the need for a case by case consideration of what definition of derivative is appropriate. Many entries in Schedules 5 and 6 have been based on topical skin risks such as irritation or sensitisation and not on systemic toxicity. Topical phenol for example is corrosive to the eyes and skin. The ethyl ester derivative of phenol (Phenyl acetate) is a mild irritant and its capture by the S5 entry for phenol is not appropriate.

Options

Consideration should be given to stratifying the definition of derivative across the Schedules of the SUSMP, 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)
- Topical/physicochemical properties of concern (based on the physicochemical property of concern – eg pH, solvent or surfactant strength)

Development of guidance for the ACCS, 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.

Cross Regulatory Impact

To be eligible for use in a listed medicine an ingredient, among other conditions (TGA, 2018);

> "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, Figure 2 & Figure 3 (Chizzola, 2013). Terpenoids are biosynthesised by the progressive addition of isoprene units (highlighted in bold in the figure). Geraniol and linalool are, in addition to nerol and lavandulol, primary products in terpene biosynthesis and 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 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.

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.

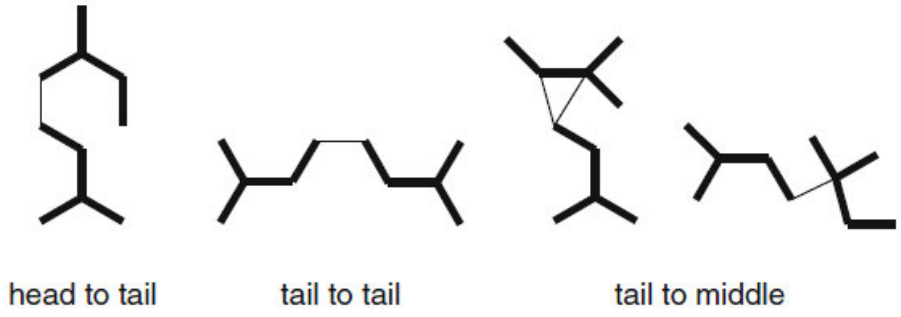

Figure 2. Terpenoids are combinations of isoprene units

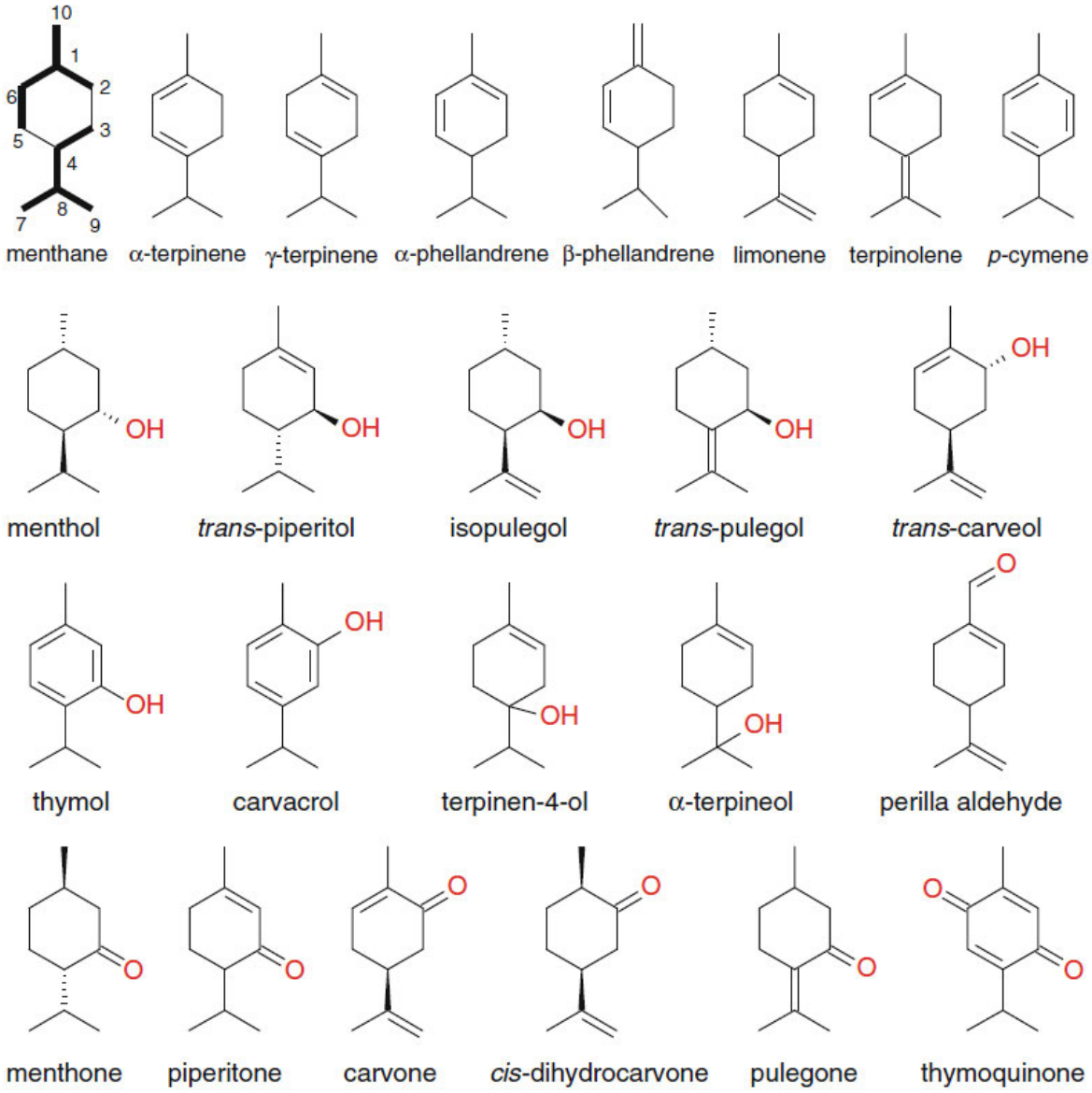

Figure 3. Monoterpenes with a menthane core structure

Recognition of International Standards – Precedence

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

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

> **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).

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 Pharmacopoeia's and for colourings:

- the Food and Agriculture Organization (FAO)/World Health Organization (WHO) Combined compendium of food additive specifications
- the European Union regulations - Laying down specifications for food additives No. 231/2012

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.

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 night 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 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 to recognise the Appendix B entry may also be required.

Review of Scheduling Application Adequacy

Neither the Advisory Committees nor the Secretariat have the resources or the depth and breadth of expertise to compensate for incomplete applications. Consequently agencies, corporations and individuals making applications for scheduling need to gather and submit the data and analysis necessary for the ACCS and delegate to consider the range of issues they are required to have regard to. Given the resource limitations of the Secretariat and the rate of turnover of staff the primary role the group is to ensure applications contain the relevant information, collate and present the information in a form that facilitates ACCS deliberations, provide relevant information on previous decisions and document the decision-making process.

Introduction

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 recommendations of the ACCS and the EC Cosmetics Directive perfume ingredients for Scheduling recommendations made between March 2016 and June 2018, Table 2. Comments provided by accord and the secretariat have identified a number of specific substances that have proved problematic and these are examined in greater detail later in this document.

Basis for Scheduling Recommendations

Cosmetic ingredients by intent are generally 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. Consequently, acute toxicity end points tend to be the primary drivers of scheduling recommendations.

The primary risk determinants of scheduling recommendations by ACCS for most cosmetic ingredients therefore, are the acute oral and dermal toxicity, skin and eye irritation and skin sensitisation. Each of these toxicological effects exhibits classical dose response relationships with a threshold for effects 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 (LD_{50}) 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 sensitized persons, versus induction of sensitisation in naive 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 11 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 lower limits of 0,001 % in leave-on products and 0,01 % in rinse-off products but requires only that where concentrations greater are than these values 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 sensitization 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 $\mu g/cm^2$. This approach reflects the principle dose metric for skin sensitisation of dose per unit area of skin. Neither total dose nor concentration 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 ca. 10 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 $\mu g/cm^2$, is a function of;

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

Various reliable sources of information are available to estimate these parameters. Skin sensitization 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 any of the NICNAS scheduling submissions to ACCS 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 – widely used internationally and within the TGA and APVMA for consideration of the toxicological significance of impurities in pharmaceuticals and pesticides.

In order to understand the basis for the threshold approach and understanding of the underlying mechanism of dermal sensitisation is required.

> Most contact allergens are small, chemically reactive compounds. As these compounds are too small to be directly immunogenic, they act as haptens; i.e. they react with higher molecular weight epidermal and/or dermal biomolecules to form immunogenic adducts. It is usually considered that the biomolecules involved are free or membrane bound proteins, which react via nucleophilic thiol, amino, and hydroxyl groups. Dendritic cells (DCs) and the local tissue microenvironment are crucial factors in the development of ACD. Langerhans cells (LCs), as epidermal DCs, and dermal DCs are pivotal for the sensitisation and the elicitation phases of ACD. During sensitisation, DCs react with the immunogenic complexes by interaction with neighbouring keratinocytes, migration to the local draining lymph nodes and the priming of naïve T-cells. These reactions are mediated by inflammatory cytokines, chemokines and adhesion molecules. Antigen specific effector T-cells are then recruited into the skin upon contact with the same hapten (elicitation). Following their recruitment these T-cells are activated by antigen-presenting skin cells, including LCs, dermal DCs and keratinocytes, and macrophages. Although most allergens can form hapten–carrier complexes directly, some

need activation, e.g. by enzyme-induced metabolic conversion or abiotic oxidation. Such compounds are termed prohaptens and prehaptens, respectively. Well known examples of prehaptens and prohaptens are limonene and eugenol. Reduced enzyme activity in certain individuals, related to genetic enzyme polymorphisms, may give an increased or reduced risk of sensitisation to prohaptens (that need enzymatic activation) in certain individuals or populations.

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 to meet the requirements of the ACCS and delegate without substantial additional resources within the Secretariat, more comprehensive guidelines are required, indicating the nature of the required data, the preferred approach of the Committee/delegate 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 and the latest understandings. 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.

The provision of more extensive guidance has become more urgent with the introduction of the option to submit Scheduling applications for new substances in AgVet and other products directly to the Secretariat, in advance of a product approval application, rather than through the respective regulatory agencies. In the previous arrangements the respective regulatory agencies were responsible for the provision of appropriate risk assessments to provide a basis for scheduling recommendations. Under the new arrangements this responsibility may fall to the Secretariat and/or the applicant.

Concordance of ACCS Advice with EU Cosmetic Requirement

ACCORD 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 the Delegates interim decision taking into account recommendations from the ACCS 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** & **Table 3.**

Of the 30 cosmetic ingredient substances (excluding those solely used in hair dyes) considered for scheduling between March 2016 and June 2018, the recommendations &/or delegates decisions (interim or final) were largely or entirely concordant with EU cosmetics regulations for 5. For 9 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 baby wipe carrying this heading.

For 12 of these compounds the scheduling outcome is overly restrictive and discordant with the level of risk presented by the substances and require unique Australian labelling. For 5 substances the scheduling outcome is inconsistent with similar substances already in the SUSMP, generally due to inconsistent management of skin sensitisation, and at least 3 result in unintended cross regulatory

capture affecting a range of non-cosmetic uses such as complimentary 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 2 of the substances the entries are ambiguous either because the capture of derivatives (Phenol) is indeterminable or and the intended capture of the proposed entry is unclear 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, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
Crystal violet & related dyes March 2016 R16/529558 BP	**Schedule 10 – new entry** METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) AND THE FOLLOWING TRIARYLMETHANE DYES– for use in hair dyes o Acid Violet 49 (CAS No. 1694-09-3) o Ethyl Violet (CAS No. 2390-59-2) o Basic Blue 7 (CAS No. 2390-60-5) o Basic Blue 26 (CI 44045) (CAS No. 2580-56-5) **Schedule 6 – New entries** METHYLROSANILINIUM CHLORIDE (formerly known as crystal violet CAS No. 548-62-9) AND THE FOLLOWING TRIARYLMETHANE DYES o Acid Violet 49 (CAS No. 1694-09-3) o Ethyl Violet (CAS No. 2390-59-2) o Basic Blue 7 (CAS No. 2390-60-5) o Methylium, 4-(dimethylamino)phenylbis4-(ethylamino)-3-methylphenyl-, acetate (CAS No. 72102-55-7) ▪ **except** when included in Schedules 4 or 10 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. **Schedule 4 – Amend entry** CRYSTAL VIOLET for human use **except** when used as a dermal marker. – replace "CRYSTAL VIOLET" with "METHYLROSANILINIUM CHLORIDE" **Index entries:** Crystal violet – see methylrosanilinium chloride Gentian violet – see methylrosanilinium chloride	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).	**Concordant for hair dyes** **Discordant for cosmetics.** EU prohibits use in cosmetics. S6 likely to have the same effect but is not an explicit prohibition. Basic Blue 26 not scheduled for cosmetics not contacting mucous membranes
Disperse Yellow 3	**Schedule 10 – New Entry** DISPERSE YELLOW 3 – for use in hair dyes (CAS 2832-40-8) **Schedule 6 – New Entry** DISPERSE YELLOW 3- except when in Schedule 10 **Appendix E, Part 2 – new entry** DISPERSE YELLOW 3 Standard statements: A, S1	EU Cosmetics Regulation 1223/2009 Annex II Prohibited	**DISCORDANT FOR COSMETICS.** EU prohibits use in cosmetics. S6 likely to have the same effect but is not an explicit prohibition.

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	Appendix F, Part 3 – new entry DISPERSE YELLOW 3 Warning Statement: 28 Safety direction: 4		
Chrysoidine base	**Schedule 6—New Entry** CHRYSOIDINE except when in Schedule 10 (CAS 495-54-5) **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)	• EU Cosmetics Regulation 1223/2009 Annex II; (CAS 495-54-5)	**DISCORDANT FOR COSMETICS.** EU prohibits use in cosmetics. S6 may discourage use but is not an explicit prohibition. Derivatives in EU more narrowly defined as "salts"
Methyldibromo glutaronitrile	**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	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 NWS R16/582422	**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	EU Cosmetic Directive 76/768/EEC – no restrictions	**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. Exceptionally unlikely to be more than a mild eye irritant at 1% The cut off alone (without FAI) likely to be adequate risk management. Scheduling application inadequate to support decision
Direct Red 254 Oct 2016 R16/740169 Azo dye for agvet use (marker)	**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	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)	**? This colour was scheduled for the purpose of an Ag spray tracer product. not a permitted EU cosmetic colourant.** **However, S5 does not explicitly prohibit use in cosmetics BUT no**

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	cross reference: 2-NAPHTHALENESULFONIC ACID, 7-AMINO-4-HYDROXY-3-[[P-[(P-SULFOPHENYL)AZO]PHENYL]AZO]-, BIS(TRIETHANOLAMINE) SALT Schedule 5 Schedule 6		**indication it is used or would be desirable to use in cosmetics**
Quinoline# CAS 91-22-5	**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 **Appendix E and F – New Entries** **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) **Appendix F –** QUINOLINE Warning statement: 79 (will irritate eyes). Safety directions: 1 (avoid contact with eyes), 4 (avoid contact with skin).	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 mg/day for 60 kg person)
Phenoxymethyl oxirane CAS 122-60-1	**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).	EU regulation (EC) No 1223/2009 Annex II prohibited As 1,2-Epoxy-3-phenoxypropane (Phenylglycidyl ether)	**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.
Amyl and hexyl cinnamaldehyde CAS 122-40-7, 101-86-0	**Appendix B – New Entries** AMYL CINNAMALDEHYDE HEXYL CINNAMALDEHYDE	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.	**DISCORDANT** EU requires name of ingredient to be on the label when above sensitisation cut off values.

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
Isoeugenol **CAS 97-54-1/ 5932-68-3**	**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). **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).	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%.	**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 Schedule entry does not require inclusion on label
Climbazole **CAS 38083-17-9**	**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.	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	**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

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
		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'.	
Butyl benzyl phthalate **Oct 2017** **D17-318988**	**Schedule 10 – New Entry** BUTYL BENZYL PHTHALATE for cosmetic use.	EC Annex II (List of substances prohibited in cosmetic products) and Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Annex XIV (List of substances subject to authorisation).	**CONCORDANT**
1-Deoxy-1-(methylamino)-d-glucitol N-C10-16 acyl derivatives **March 2018** **D17-319298** **CAS 173145-38-5**	**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 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	No known international restrictions or regulations have been identified by the applicant or the Secretariat.	**DISCORDANT** Aus restriction appears to be unique and disproportionate
Symphytum spp. (Comfrey) **Joint** **June 2016** **BP** **R16/377466** **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** Aus scheduling seems disconnected with risk

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
Geraniol & related compounds **R16/740954** **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 (TG)	**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 and other homologues of phenol. **Schedule 2 – Amend Entry** PHENOL, or any homologue boiling below 220°C for human therapeutic use, except: 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. **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)],	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 xylenol 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 contain phenol as an impurity.	**DISCORDANT** **There are millions of "derivatives" of phenol, cresol and xylenols – which of these are intended to be captured?**

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	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). **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).		
1-Deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives CAS 1591783-13-9	**Schedule 6 – New Entry** 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES except: 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. **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). 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) **Index – New Entry** 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL N-COCO ACYL DERIVATIVES cross reference: cocoyl methyl glucamaide Schedule 6 **Appendix E, Part 2** **Appendix F, Part 3**	No restriction In CosIng as COCOYL METHYL GLUCAMIDE	**DISCORDANT EU no labelling required** **Schedule entry appears disproportionate and disconnected to meaningful risk**
o-Toluidine and o-anisidine	**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 preparations containing 0.001 per cent or less of o anisidine. (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.)	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; 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	**CONCORDANT**

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	(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')	leather or textile articles. 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. 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). o-Toluidine and o-anisidine are listed on the following (Galleria Chemica): • 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. 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'.	
Epidermal Growth Factor	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): **Schedule 7** EPIDERMAL GROWTH FACTOR except in preparations for human therapeutic use.	CosIing lists multiple epidermal growth factor preparations from various animal and plant sources that are permitted without restriction. Named as [source] SH-Oligopeptide-1. Eg potatoe-SH-Oligopeptide-1 Public submissions: Plant-made EGF for topical cosmetic use is	**DISCORDANT EU no restriction for cosmetic use**

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	Appendix J EPIDERMAL GROWTH FACTOR, Condition 1 (Not to be available except to authorised or licensed persons).	currently permitted in EU, USA and Canada	
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	**CONCORDANT**

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
		-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; 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** **D17-367223** **CAS 94-96-2**	**Schedule 10 – Delete Entry** **Schedule 6 – New Entry** ETHYL HEXANEDIOL in cosmetic preparations 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 cosmetic 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	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	**PARTIALLY CONCORDANT** S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	(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	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.	
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) Date of entry: February 1970 Reason for Entry – a, low toxicity Area of Use – 7.1, general, any use	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 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.	**CONCORDANT**
Methylisothiazolinone CAS 2682-20-4	**Schedule 6 – Amend Entry** METHYLISOTHIAZOLINONE except: a) in rinse-off cosmetic preparations or therapeutic goods intended for topical rinse-off application containing 0.0015 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.	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	**PARTIALLY CONCORDANT** S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	Unchanged: **Appendix F, Part 3** METHYLISOTHIAZOLINONE Warning Statement: 28 (Over) (Repeated) exposure may cause sensitisation.	(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	
Chloracetamide **Oct 2017** **CAS 79-07-2**	**Schedule 6 – New Entry** CHLOROACETAMIDE except d) in preparations for cosmetic use; or e) in preparations for topical therapeutic use; or f) in other preparations containing more than 0.3 per cent of chloroacetamide. **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)). **Appendix F, Part 1– New Entry** CHLOROACETAMIDE Warning Statement: 28 (Repeated exposure may cause sensitisation). Safety Direction: 4 (Avoid contact with the skin).	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 Commission, 2015). A decision had not been finalised at the time of the preparation of this assessment report.	**DISCORDANT** EU requires labelling with ingredient name. cut off is the same. Prohibited in cosmetics at higher concentrations S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions
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	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	**PARTIALLY CONCORDANT** for cosmetics S6 may discourage use but is not an explicit prohibition at concentrations > than EU permissions

Substance; Decision Date, TRIM Ref	Scheduling Decision	EU/international (at the time of scheduling)	Analysis
	Appendix E, Part 2 **Appendix F, Part 3**	was recommended, but this has not yet been finalised, nor implemented in legislation.	

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	Product type, body part	Max conc	Other	Wording of conditions of use and warnings	*Differences to ACCS proposed Schedule*
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	[none]*	**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 Aus 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	[none]	**Consistent** ≤ 0.001% in leave on products & ≤ 0.01% for rinse off products (no labeling or restrictions)
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	[none]	**DISCORDANT & inconsistent** EU requires labelling to state presence of the substance when ingredient is > 0.001% in leave on

Ref No	Chemical Name	Common Name	CAS No	EC No	Product type, body part	Max conc	Other	Wording of conditions of use and warnings	*Differences to ACCS proposed Schedule*
							19(1)(g) when its concentration exceeds: 0,001 % in leave-on products — 0,01 % in rinse-off products		products and 0.01% in rinse of products Schedule entry does not require inclusion on label No warning statement for skin sensitization ? NESIL 250 µg/cm2 compared to Benzyl Salicylate 17700 µg /cm² Anise Alcohol 1500 µg/cm²
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	[none]	**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 sensitization. NESIL 11800 µg/cm²
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 —	[none]	**DISCORDANT.** No requirement to include name on ingredients list in Australia

Ref No	Chemical Name	Common Name	CAS No	EC No	Product type, body part	Max conc	Other	Wording of conditions of use and warnings	*Differences to ACCS proposed Schedule*
							0,01 % in rinse-off products		
76	2-Propenal, 3-phenyl-	Cinnamal [Cinnamaldehyde]	104-55-2	203-213-9			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	[none]	**DISCORDANT AND INCONSISTENT** S6 at greater than the EU cut offs. In EU only requirement is for inclusion in ingredient list. No exemption when labelled with warning statement re sensitization. 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	[none]	**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 compond is included in the ingredients list then previously sensitised individuals can avoid contact.

Table 4. Assessment of the Adequacy of Scheduling Application to 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 Substance Identification	√	√	√	√	√	Generally adequate
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 Acute Oral Toxicity	√	√	√	√	√	Straight forward
Acute Dermal Toxicity	√	√	√	√	√	Straight forward

Acute inhalation toxicity	√	-	√	√	√	Straight forward
Skin irritation	√	√	√	√	√	Straight forward
Eye irritation	√	√	√	√	√	Straight forward
Skin sensitization	√	√	√	√	√	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/cm² (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 ACCS, ACMS and Secretariat rely on the information provided in the scheduling application to provide the basis for balanced, consistent and robust recommendations. Although the Secretariat is able to add further information, particularly in terms of scheduling history and collation of public comments, neither the Secretariat nor the Advisory Committees have the resources, personnel stability or range of expertise to compensate for inadequate or incomplete scheduling applications. The quality of the advice provided by the Advisory committees is therefore dependent on the quality of the Scheduling Request and in particular whether the request adequately addresses each of the matters to which the ACCS 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 ACCS/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.

In considering the adequacy of the Scheduling requests provided to the ACCS therefore the content of the advice provided in the Scheduling application is compared to the matters the legislation and Government policy requires to be considered ('have regard to', OBPR requirements). The scheduling proposals for the following fragrance materials have been assessed for their adequacy to support ACCS/Delegate deliberations, Table 4, for the following fragrance materials;

- Isoeugenol,
- Anise Alcohol,
- Geraniol,
- Cinnamaldehyde, and
- Benzyl Salicylate.

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 ACCS 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, and
- Alternative mechanisms for achieving the regulatory intent.
- 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 sensitization (amount applied per surface area, μg/cm^2 rather than concentration in product). No consideration of dermal sensitization 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

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 categorization*** 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 ACCS is the latter rather than the former. Although the Cat3 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 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-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid·HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-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, *d*-carvone, deserpidine, disodium glycyrrhizinate, emetine·2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, β-*N*-[γ-*l*(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *d*-menthol, nicotine, norharman, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, turmeric oleoresin, vinblastine

[a] Fungal toxins are not included. [b] These 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.

The Scheduling delegates final decision, June 2017, was;

Schedule 6 - Amend Entry

ISOEUGENOL **except**:

1. when included in Schedule 5; or
2. in preparations intended for contact with skin containing 0.5 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 0.5 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).

Issues with the decision

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 of products but the proposed scheduling does not require this despite skin sensitisation being a substantive driver of the scheduling.

Inconsistency across similar substances

The proposed schedule does not require a skin sensitisation warning despite the fact that isoeugenol is considerably more potent as an inducer of skin sensitisation than benzyl salicylate and Anise alcohol which do require the warning. (NESIL 250 µg/cm2 compared to Benzyl Salicylate 17700 µg /cm2 Anise Alcohol 1500 µg/cm2).

There is no requirement for Isoeugenol to be included on the ingredient list of cosmetic products, unlike Anise 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 application for this compound the published RIFM risk assessment for Anisyl alcohol (anise alcohol) on which the IFRA Standard is based, utilizes an exposure-based quantitative risk assessment (QRA). 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, utilize 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.
- 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 in harmony together to ensure levels included in products will not 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.
- 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 ACCS/delegates 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

e) in leave-on cosmetic and personal care preparations containing 0.001 per cent or less of anise alcohol; or

f) 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 sensitization in an LLNA assay (EC3 is 5.9 %, 1475 μg/cm^2).

Issues with the Decision

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 & 0.01% for rinse off products. The requirement for a Warning statement above the cut offs of < 0.001% in leave on products & < 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 ACCS.

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 (or causing) 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 that 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 after 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, Figure 1. 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.

Issues with the Decision

Inconsistency across similar substances

The schedule entry for Geraniol uses the full and rather cumbersome chemical name rather than the common name, in contrast to the entries for benzyl salicylate, anise alcohol and cinnamaldehyde. Although the index is cross referenced 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% (appears to relate to the IFRA Standard). 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

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 SUSMP provides a 5% cut off from S6 to exempt but with no requirement for inclusion in the ingredient list of cosmetics and no requirement for a skin sensitisation warning as for Anise Alcohol.

Consideration of Cross Regulatory Impacts

The regulatory impact of the proposal has not been addressed by either the applicant or the ACCS. 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 SUSMP 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 Decision

Inconsistency with Scheduling of similar substances

The primary justification for the scheduling cut offs in the record of reasons is skin sensitisation. Although isoeugenol is similar or more potent as a skin sensitiser (NESIL isoeugenol 250 μg/cm^2 compared to 590 for cinnamaldehyde) the cut offs have been set as below the levels requiring only inclusion in the ingredients list for cinnamaldehyde by the EU but as 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 SUSMP. As the proposed entry for cinnamaldehyde makes no mention, ie does not restrict the definition, of derivatives these compounds would be both in appendix B and in S6.

The proposed Scheduling outcome is therefore entirely 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 entry for Anise alcohol. In previous Scheduling decisions (eg Anise alcohol) much higher cut offs were applied and with declaration of presence required on the label, consistent with EU requirements, but with the additional Australia 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). So, **the proposed S6 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

Discordance 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).

Ambiguity and lack of clarity

The ACCS proposed scheduling and the Delegates interim decision, above, have a number of ambiguous or uncertain aspects. Firstly, the distinction between “domestic preparations

intended for skin contact" and "cosmetic and personal care products" is unclear. Cosmetics are 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. 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 Therapeutic Goods Act and AHMAC guidance 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 scheduling factors, preamble to the SUSMP and the AHMAC guidance need to be read together when considering scheduling decisions. Additionally, as scheduling decisions are legislative in nature, the requirements and guidance of the OBPR, best practice regulation guidance and the RIS process requirements should be considered when making decisions/recommendations likely to have a significant impact on industry and consumers.

In reviewing the scheduling decisions/recommendations for cosmetic ingredients over tha 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 scheduling submissions for cosmetic ingredients arising from the IMAP process are predominantly a hazard assessment and are not adequate to support the risk based Scheduling process leading to inconsistencies between similar substances, unintended cross regulatory consequences and discordance with major international regulatory requirements, potentially impacting significantly on the competitiveness of Australian industry. The assessments are less useful for scheduling than the RIFM and SCCP assessments and these would provide a better basis for scheduling considerations.

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 SUSMP. 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 current vague definition applicable to all 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 SUSMP 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 SUSMP entries.

A clear need for improved guidance for both applicants and the ACCS was identified to support more consistent and proportionate decisions/recommendations and to guide applicants to address the various areas the ACCS 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.

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.

None of the issues identified as problematic in this review would seem to require legislative changes at either the State or Commonwealth levels, being largely procedural in nature.

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 "small p" 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 sensitization risks

Minimising Unnecessary Regulatory Impact

- Committee Structure
  - Because Scheduling decisions on chemicals have impact across a wide range of regulated commodities inclusion in the ACCS 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 regulatory arrangements/options for ingredients of cosmetic and consumer goods that can be canvassed when Scheduling applicant/proposals are being considered
- Consider alternative mechanisms for regulating fragrance substances and other chemicals present at low levels in cosmetic products, eg
  - 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 SUSMP 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

- NICNAS is a ***hazard*** assessment agency, but cosmetics scheduling is a ***risk-***based regime, other agencies have greater familiarity with both the types of ingredients in cosmetics and risk based assessments
- Review the interaction of the multiple regulatory schemes impacting ingredients of cosmetics, consumer and household goods in Australia
  - TGA all types of therapeutic goods, APVMA all pesticides and veterinary medicines but especially insect repellents, FSANZ, ACCC, NICNAS, others?

Improved Guidance to Committees and Applicants

- Prepare for the ACCS and ACMS 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.
- Conduct a regulatory impact assessment on the costs and benefits of utilizing the scheduling mechanism for the regulation of cosmetic ingredients present at low levels in consumer products.
- If cosmetic ingredients are to continue to be routinely considered for scheduling, then;
  - Consideration of the resources required to support greater input from the Secretariat may be required, or
  - 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
  - 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

    - Address the Regulatory impact in scheduling submissions even if a formal RIS is not indicated.
- Liaise with ACCC to ensure ingredient lists on cosmetic products be required to include any substance identified in the EU cosmetics directory 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 (eg 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
    - Eg 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 (eg 1, 10 or 100 ppb, ie 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 4 to 10
    - Precise
    - Resource intensive to apply retrospectively
    - May need broad and extensive consultation
- Use of the Threshold of Toxicological Concern approach as the basis for identifying impurity cut offs for specific substances
    - Primarily to provide prospective guidance to the ACCS 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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Information placeholder not for final version

Cosmetic ingredients “derivatives” of Phenol in the European Commission database for information on cosmetic substances and ingredients

Name or CAS/EC # phenol Version EC Regulation

Scope All Status Active

Go »

(*) Not in the annexes of the Directive/Regulation as published in the Official Journal of the European Union
(**) Not officially an INCI Name but Perfuming Name 1 - 100 Total: 258

#	INCI Name/Substance Name	CAS No.	EC No.	Restriction/ Annex/Ref #
1.	4-[(2-Nitrophenyl)amino]phenol	54381-08-7	259-132-4	III/256
(*) 2.	(E)-3-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenol	82413-20-5	428-010-4	Article 15/CMR
3.	1-Hydroxy-2,4-diaminobenzene (2,4-Diaminophenol) and its dihydrochloride salts (2,4-Diaminophenol HCl) when used as a substance in hair dye products	95-86-3 -- 137-09-7	202-459-4 -- 205-279-4	II/1338
4.	1-Hydroxy-3-nitro-4-(3-hydroxypropylamino)benzene (see note 17)	92952-81-3	406-305-9	III/205
5.	2,2'-(6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl)bis(5-((2-ethylhexyl)oxy)phenol) / Bemotrizinol	187393-00-6		VI/25

cription

Advertising, labelling and packaging of therapeutic goods and agricultural and veterinary chemicals are also dealt with through the respective product registration schemes provided for in Commonwealth legislation

From QRA report

The EC3 value has recently been demonstrated to closely correlate with the NOEL from human sensitization tests designed to confirm lack of induction (Basketter et al., 2000; 2005; Gerberick et al., 2001; 2001a; 2004; Griem et al., 2003; Schneider and Akkan, 2004).

For Anise Alcohol the No Expected Sensitisation Induction Level (NESIL) is 1500 µg/cm^2. Taking a hand cream as an example, the typical area of application is 890 cm^2 and approximately 2.2 g is applied (SCCS, 2016) resulting in an application of 2.47 mg/cm^2 of product. To reach the NESIL of 1.5 mg/cm^2 the concentration of For a hand cream containing 5% anise alcohol the dermal exposure would be 124 µg/cm^2 (2200 mg * 0.05 /890 cm^2 = 123.6 µg/cm^2). An exposure of 124 µg/cm^2 is well below the NESIL for this compound. Where a specific NESIL has not been calculated due to insufficient data the concept of the Dermal Sensitisation threshold (DST - analogous to the TTC for systemic toxicity) is appropriate. The Dermal Sensitisation threshold for reactive chemicals is 64 µg /cm^2 (Safford, Api, Robets, & Lalko, 2015). The IFRA standard (IFRA, 2015) for anise alcohol sets a concentration limit for anise alcohol in category 5 products (hand creams) of 0.36%, for induction of skin sensitisation and reflecting their use of safety factors.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Section/Office	XX/XX/XXXX

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Reference/Publication #