Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Review of chemical scheduling in relation to cosmetic and fragrance ingredients

Version 1.0, March 2019

TGA Health Safety Regulation

Contents

Executive summary

This review of current processes and scheduling decisions in relation to cosmetic and fragrance ingredients has been conducted as part of a project to implement the review of the Scheduling Policy Framework (SPF) and scheduling process for medicines and chemicals. The review also directly addresses a number of concerns raised by stakeholders relating to particular scheduling decisions and limitations of current scheduling arrangements. These include:

- consistency of scheduling decisions across related substances
- clarity of definition of 'derivatives' of scheduled substances
- the capture of low-level impurities by schedule entries

Concerns have also been expressed about the creation of unique Australian restrictions which can lead to particular labelling requirements for cosmetic products.

The scheduling decisions or recommendations for thirty cosmetic ingredients that had been the subject of scheduling applications between March 2016 and June 2018 were compared against the corresponding EU Cosmetics Regulation entries to determine the degree of concordance or discordance with the European position. The consistency across decisions for related substances was assessed, and evaluated for proportionality with the risks arising from their use. Selected scheduling applications were also examined against the various matters the legislation and SPF required to be considered to determine whether they provided sufficient information to support the deliberations of the scheduling committee and the delegate.

Of the 30 cosmetic (excluding hair dyes) ingredient substances considered for scheduling between March 2016 and June 2018, four ingredient substances were not strictly cosmetic ingredients while three others were assessed as 'new' chemicals and had no EU restrictions. For four other substances, no final decisions have yet been made by the scheduling delegate so concordance could not be judged. For five substances, the recommendations and/or delegate's decisions (interim or final) were largely or entirely concordant with EU cosmetics regulations. For nine substances that the EU has prohibited for use in cosmetics, the scheduling decision, while clearly intended to restrict use in cosmetics, allows their continued use as Schedule 6[1] entries. However it is noted that it is the preference of the scheduling committees to use Schedule 6 rather than Schedule 10 to restrict use in cosmetics and thus the decisions are considered to be aligned with the EU in practice. In the case of methylisothiazolinone for example, its use in personal skin wipes has continued with the product carrying the signal heading of POISON, leading to enquiries from the public concerned at the apparent incongruity of a personal wipe carrying this heading.

For twelve of the ingredient substances, the scheduling outcome may be seen as discordant with the level of risk presented by the substances. As a result, products containing the substance require unique Australian labelling, with additional costs imposed on Australian industry. For five substances the scheduling outcome was inconsistent with similar substances already in the *Poisons Standard*; in particular there was inconsistent management of skin sensitisation. At least three scheduling decisions resulted in unintended effects on a range of non-cosmetic uses, including forbidding potential use of the substance in complementary medicines. For at least one of the substances, phenol, the entry is ambiguous since the capture of derivatives in the schedule is not clearly specified.

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

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, supporting information in applications for the scheduling of cosmetic ingredients did not adequately address issues related to risk, or the regulatory (and cross-regulatory) impact of the proposed scheduling.

The requirement for ingredients permitted for use in complementary medicines, includes that they are not included in any schedule of the *Poisons Standard*. For example, the scheduling of geraniol in Schedule 6 (**except** in products containing 5 per cent or less 3,7-dimethyl-2,6-octadien-1-ol and its isomers) may have resulted in a number of essential oils that are currently included in Appendix B[2] (such as geranium oil and citronella oil) that contain geraniol, possibly being both Schedule 6 and unscheduled (depending on the levels of geraniol present). Therefore, simultaneously, these substances became both eligible and ineligible for approval as an ingredient in listed medicines.

The assessments underpinning many of the scheduling applications also raised issues of public perception and confidence in the process. For example, although one substance was explicitly identified as a carcinogen from a hazard categorisation, from a risk perspective it was (appropriately) recommended for inclusion in Schedule 5[3] and Schedule 6.

Many issues identified reflect insufficient guidance documentation to support applicants in the preparation of the documentation required for robust scheduling deliberations. The provision of guidance for applicants and the maintenance of readily accessible records of decisions for the secretariat, scheduling committee, delegate and other stakeholders would aid in the transparency and consistency of the chemicals scheduling process.

Stakeholder concerns regarding the low-level presence of impurities that are included in Schedules 7-10 were considered by examining two case studies, ethylene oxide (S7[4]) and 1,4-butanediol (S10[5]). Both these substances are used industrially as reagents in the synthesis of various cosmetic ingredients such as surfactants and polymers, and low level or trace impurities are therefore not unusual, but are not covered by standard exemptions, which exist for impurities of Schedules 1 to 6 substances. The lack of a formal tolerance for low levels of S7 – S10 impurities of synthesis is inconsistent with the detection sensitivity of modern analytical techniques and the general tolerance granted for impurities in agricultural and veterinary chemicals. This could be addressed through the development of appropriate impurity cut-offs for S7 to S10 substances.

Another stakeholder concern considered is the uncertainty of the scope of substances captured in the current broad and ambiguous definition of derivatives. The scope of the current derivative definition collectively covers drugs of abuse, drugs of addiction, potent poisons and the wide range of consumer and domestic chemicals with much narrower spectrums of concern. Relatively simple procedural modifications combined with a more nuanced range of definitions for 'derivatives', which provide guidance to the scheduling committee[6] and delegate in identifying derivatives of likely concern, would substantially reduce the potential for unintended or inappropriate capture of substances.

[2] Appendix B: 'substances considered not to require control by scheduling'
[3] Schedule 5: **Caution** – Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.
[4] Schedule 7: **Dangerous Poison** – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.
[5] Schedule 10: **Substances of such danger to health as to warrant prohibition of sale, supply and use** - Substances which are prohibited for the purpose or purposes listed for each poison.
[6] The Advisory Committee on Chemicals Scheduling, ACCS

Options for consideration

In identifying options for scheduling process improvements, preference has been given to those that do not require changes to enabling legislation or to the overarching scheduling policy framework. Substantial improvements in the scheduling outcomes for cosmetic and consumer product ingredients can also be achieved through procedural reforms and the provision of improved guidance to applicants, delegate and the committee members.

The following changes are proposed:

1. Policy improvements

- Align scheduling decisions with international regulatory requirements where practicable and appropriate, in particular for cosmetic and household chemicals.
- Increase use of existing overseas risk assessments (Research Institute of Fragrance Materials [RIFM] /International Fragrance Association [IFRA], Scientific Committee on Consumer Safety [SCCS], Scientific Committee on Consumer Products [SCCP] etc.) where available.
- Consider whether use of a POISON Signal heading solely to advise of skin sensitisation risks is appropriate. In these cases assignment to Schedule 5 with additional controls may be more appropriate.
- Develop administrative processes to improve engagement of stakeholders in providing feedback on chemicals scheduling proposals.
- More systematic consideration of the impact of scheduling proposals for particular substances where multiple industries use these types of substances (e.g. listed and OTC medicines, AgVet chemicals, food ingredients, etc.).
- Grouping of related substances in a class review for the purposes of scheduling rather than carrying out *ad hoc* assessments of individual substances.

2. Improved processes

- Provide improved guidance to applicants on the information requirements for scheduling applications.
- Implement enhanced systems to record and analyse prior scheduling decisions and data supporting these decisions.
- Improve the scheduling application form to require broader assessment of the impact of scheduling decisions on users of the chemicals (industry and consumers), to ensure that all affected preparations containing the chemical to be scheduled (such as essential oils) are considered.
- Develop improved science-based guidance for estimating the acute risk of particular substances when in dilute preparations.
- Review the scheduling of essential oils to include their constituent substances (where known).
- Make greater use of subject matter experts in complementary and listed medicines, pesticides and veterinary chemicals to improve the breadth and depth of advice to the scheduling committee.
- Improve engagement between relevant TGA advisory committees (Advisory Committee on Complementary Medicines, Advisory Committee on Medicines, and Advisory Committee on Medical Devices) where a substance under consideration crosses

regulatory boundaries. For instance, where a substance proposed for scheduling forms part of a product under consideration by another TGA advisory committee, advice should be sought before a scheduling decision is made.

- Improve liaison with the Australian Competition and Consumer Commission (ACCC) to ensure ingredient lists on cosmetic products must contain any substance identified in the EU cosmetics directory as requiring inclusion on the label in compliance with the various cut-off values specified.

3. Derivatives

- An explicit definition of derivatives of individual substances should be routinely captured for each new entry (i.e. through use of CAS numbers for derivatives).
- Develop standardised, contextualised definitions for derivatives appropriate for different toxicological or other end points driving the scheduling decision.

4. Managing the 'low level presence' of impurities

- Develop improved options for managing 'low level presence' as impurities of substances included in Schedules 7 to 10:

Glossary

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

Introduction

Following decisions by the Australian Government in response to the Expert Panel Review of Medicines and Medical Devices Regulation, in 2016-2017, the Department of Health reviewed the Scheduling Policy Framework (SPF) and the scheduling process for medicines and chemicals. That review identified that improvements were required to streamline the process by which chemicals are scheduled.

We have conducted a review of current processes (and some recent scheduling decisions) in relation to cosmetic and fragrance ingredients to identify how closely Australia's decisions align with other regulators (in particular the EU). Of particular interest was an exploration of whether there are opportunities to harmonise chemical scheduling outcomes with requirements of comparable overseas regulators. Consideration has also been given to concerns raised by a number of stakeholders, and options to improve particular processes have been proposed.

In reviewing the scheduling process for cosmetic ingredients, a distinction is made between substances generally present in very low concentrations (such as fragrances and flavours) and other ingredients (such as surfactants), which may be present at considerably higher levels. This review has focused primarily on the former in recognition of the low levels present in cosmetic products and the low level of risk generally presented by these substances.

This review addresses two broad groups of issues:

1. **General issues related to the operation of the Poisons Schedules**
   - interpretation and suitability of derivatives definition for substances in the various schedules
   - unambiguous identification of scheduled substances
   - capture of low level impurities by Schedules 7, 8, 9 & 10
   - consideration of unintended regulatory impacts
2. **Adequacy of Scheduling submissions**
   - whether the matters the committee must have regard to have been adequately addressed to support the recommendations of the Committee and the decision(s) made by the delegate, including Section 52(e) of the *Therapeutic Goods Act 1989*, the SPF and the Scheduling Handbook

Stakeholder concerns

Stakeholders have raised a number of concerns with the current approach to chemicals scheduling, including:

- no provision to exempt trace levels (impurities) of Schedules 7, 8, 9, or 10 substances in cosmetic or fragrance materials from these schedules
- inconsistencies in the scheduling decisions made for related substances or substances with similar risk profiles
- inconsistencies between Australian chemicals scheduling decisions and those made for the same substances by other regulators internationally
- requirements for Australian-specific labelling and warning statements resulting from scheduling decisions

The regulatory environment

In Australia (and internationally) the regulation of chemicals intersects with the regulation of medicines, food constituents and additives, pesticides and industrial chemicals. For example, surfactants used in cosmetics or pharmaceuticals are likely to be found in drilling muds, fracking fluids, pesticide formulations or a myriad of other industrial and domestic uses. Furthermore, the Schedule 4 substance deanol (2-dimethylaminoethanol) also has uses in cosmetics, paints, lacquers and varnishes. Thus, the regulatory environment for chemicals in Australia is complex, duplicative and fragmented.

The poisons scheduling process is only one component of this regulatory environment and, at the Commonwealth level, intersects with the regulatory regimes for:

- consumer products (Australian Competition and Consumer Commission [ACCC])
- pesticides and veterinary chemicals (Australian Pesticides and Veterinary Medicines Authority [APVMA])
- human pharmaceuticals, complementary medicines and medical devices (Therapeutic Goods Administration [TGA])
- industrial chemicals (National Industrial Chemicals Assessment Scheme [NICNAS] and enHealth).

Any individual chemical may fall under the responsibilities of more than one of these agencies. There is potential for 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 regulators. For example, isoeugenol (a component of clove oil) was originally proposed for scheduling as a result of an application to the APVMA for use as a farmed fish anaesthetic. Isoeugenol is additionally used as a food, and is also used medicinally as a local anaesthetic.

In addition to the overlap of individual substances across regulatory jurisdictions, individual chemicals will exist as a member of broad classes or groups with similar functions, 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 member of a class may simply shift usage to closely related members with 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 class, or be considered in the context of the class of compounds as a whole.

What is a cosmetic or fragrance chemical?

The Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991 prescribes the requirements for a mandatory standard, which defines cosmetic products as substances or preparations intended for placement in contact with any external part of the body, including the mouth and teeth, for the purpose of:

- altering the odours of the body
- changing the appearance of the body
- cleansing the body

- maintaining the body in good condition
- perfuming the body
- protecting the body

They are usually made up of mixtures of chemical substances. Fragrance chemicals are organic compounds that add odours, usually pleasant ones, to cosmetics such as perfumes. They are not only used in cosmetics, but are also found in detergents, fabric softeners and other products to mask unpleasant odours from raw materials. They can also be found naturally in foods such as herbs and spices, complementary medicines, and over-the-counter (OTC) products, sometimes at higher levels than may be used in a fragrance. For example, geraniol is a simple monoterpene composed of two isoprene subunits, formed early in the biosynthesis pathway of more complex terpenoids (Eslahi, Fahimi & Sardarian, 2018). Consequently, geraniol occurs at significant levels in a range of essential oils that are an approved ingredient for listed medicines by TGA.

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

Cosmetics regulation in Europe

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

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

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

Cosmetic ingredients are also subject to a range of other legislative requirements under various EU chemicals regulations (e.g. the Registration, Evaluation and Authorisation of Chemicals [REACH] regulation).

To assist manufacturers to utilise fragrance ingredients at levels that are unlikely to be hazardous, the IFRA has created ingredient monographs that identify potential hazards and indicate safe levels of the individual substances in various categories of cosmetic products. The recommendations of IFRA are based on the advice of an expert toxicology assessment panel of RIFM which publishes detailed risk assessments in peer reviewed journals (e.g. Food and

Chemical Toxicology). RIFM was formed in 1966 to analyse, evaluate and distribute scientific data, cooperate with official agencies and encourage safety standards for the use of fragrance ingredients.

RIFM risk assessments also utilise extensive exposure data based on robust surveys of actual use of cosmetics by consumers. These surveys have identified the quantity of various cosmetic products applied, and the area and location of application and the frequency of use. These data provide the basis for exposure assessment underpinning the RIFM evaluations and the IFRA standards (Cadby & Troy, 2002). Members of IFRA that supply fragrance ingredients to cosmetic manufacturers are required to provide a copy of the IFRA monograph for the ingredient to the purchaser to support safe use in cosmetic products, and therefore support compliance with EU regulations by the 'Responsible Person'.

The nature of poisons scheduling

The *Poisons Standard* schedules are legislative in nature (although the Scheduling Policy Framework [SPF] is set by AHMAC, the Australian Health Ministers' Advisory Committee) and are a Commonwealth Legislative Instrument (see the Scheduling Handbook).

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

The introduction to the *Poisons Standard* indicates that:

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

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

Legislative requirements for scheduling

An understanding of the legislative basis for the Poisons Standard, and in particular the matters that must be considered in determining the need to include a substance in the *Poisons Standard*, in some cases provides the context for potential discordance with international regulations, and to identify any opportunities for improvement in the current process. The legislative basis for poisons scheduling is established in Section 52 E of the *Therapeutic Goods Act 1989*, which specifies the matters that the Secretary (in practice, their delegate) must have regard to when considering the inclusion of a substance in a schedule of the *Poisons Standard*. In addition to the SPF and the advice of the scheduling committees (Advisory Committee on Chemicals Scheduling [ACCS] and/or Advisory Committee on Medicines Scheduling [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 *Therapeutic Goods Act 1989* directs that in having regard to these matters the delegate must comply with the SPF. The SPF makes clear that 'poisons include medicines for human therapeutic use, veterinary medicines, agricultural, domestic and industrial chemicals where there is a potential risk to public health and safety' and that 'Poisons are scheduled according to the risk of harm and the level of access control required to protect consumers.'

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

Potential sources of discordance

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

Discordance can occur through any one of the following:

- a disconnect between hazard-based classification systems such as the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) and risk-based regulatory schemes such as the scheduling process
- an excessively narrow focus on individual chemical substances rather than classes
- inadequate consideration of actual patterns of use and resultant exposures of the substance, lack of consideration of the users of the substance to self-manage risk (e.g. skin sensitisation)
- a too narrow consideration of the use of the substance by several industries, and its regulation through a number of schemes

The GHS forms the basis of industrial chemical labelling and regulation. It 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.

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

Case study 1	Isoeugenol is non-genotoxic, but produces tumours in old rats and mice at high life time doses without affecting survival. Although the chemical is correctly *hazard* classified under the GHS as 'Category 3 – limited evidence of carcinogenic effect', *a risk categorisation* would state that the chemical is unlikely to present a carcinogenic risk to humans at the concentrations used, and the resultant exposures, in food and consumer products. The advice and interpretation required by the delegate is the latter rather than the former. Although an equivocal/possible *hazard* has been identified in animals under extreme exposure conditions a *risk* to humans under realistic exposure scenarios is implausible.

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

Potential improvements

Identification of scheduled substances

In reviewing some recent chemical scheduling recommendations or decisions, it was difficult to identify unambiguously which chemical some entries in the *Poisons Standard* specifically referred to. The *Poisons Standard* generally does not include an extensive range of chemical synonyms and only rarely includes a CAS number. In order to cross reference substances considered by the scheduling delegate with the same substance considered by the EU SCCP/SCCS and those included in the EU regulation (EC) No. 1223/2009 it was often necessary to extract the CAS number from the scheduling decision documentation and search on that term in the EU documents and database.

Option for consideration	The routine inclusion of a CAS number in the *Poisons Standard* entries to improve the ease of interpretation.

Presence at low levels of impurities

The *Poisons Standard* allows the presence of impurities of substances included in Schedules 2 to 6 at a concentration not exceeding 10 mg per litre or 10 mg per kilogram (i.e. 0.001%, 10 ppm), unless that substance is also included in Schedules 7, 8, 9 or 10 (in which case no tolerance is permitted for any substance in Schedules 2 to 6). Any substance present as an impurity in a pesticide must be at no greater a level identified in the *Standards for Active Constituents*, as published by the APVMA. 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, enabling impurities to be detected and identified at levels in the parts per billion (ppb) or trillion (ppt).

Case study 2	Ethylene oxide is an S7 substance with no cut-off or use exemption. It is used in the manufacture of poly-ethoxylated surfactants, and is consequently a low-level residue in many commonly used surfactants, e.g. alkylphenol ethoxylates. A strict application of the *Poisons Standard* would make products using these surfactants S7 and thus tightly (and unreasonably) limit its use. This is not the intent of the scheduling process.
Case study 3	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 (or a precursor to the manufacture of drugs 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 the plastics products are also technically Schedule 10, which is not the intent of the scheduling process.

Options for consideration	In order to manage the 'low level presence' of impurities, one or more of the following is suggested: • greater use of Appendix G • designation of a generic concentration threshold for impurities (e.g. 1, 10 or 100 ppb, i.e. µg/kg) unless a specific entry specifies otherwise • explicit impurity cut-offs for certain substances (or alternatively each substance) in Schedules 7 to 10

Derivatives

The *Poisons Standard* includes in Part 1 – Interpretation – a 'definition' of derivatives that extends the scheduling of specific substances to related compounds that share significant structural, toxicological or pharmacological characteristics with the specific scheduled substance. The definition is necessarily broad in order:

- to prevent deliberate circumvention of restrictive scheduling, especially of drugs of abuse or addiction or potent toxicants,
- to avoid repetitive schedule entries for the various salts of a specific substance
- to ensure that structurally related substances with predictably similar toxicological/pharmacological properties are captured with a single entry.

The scope of the current derivative definition collectively covers drugs of abuse, drugs of addiction, potent poisons and the wide range of consumer and domestic chemicals with much narrower spectrums of concern. Because of the broad application of the definition it does not accommodate the very different issues that each class of scheduled substance present. The current definition is also so broad it is largely uninterpretable, creating considerable regulatory uncertainty.

A small number of schedule entries explicitly define the derivatives covered by that entry which substantially reduces or eliminates potential ambiguity for those entries.

Some relatively simple procedural modifications together with a more nuanced range of definitions for derivatives that provide guidance to the delegate in identifying derivatives of likely concern might substantially reduce the ambiguity and reduce the potential for unintended and inappropriate capture of substances.

Case study 4	Ethylene oxide is used as a reagent in the production of a wide range of cosmetic products. The question arises as to whether these ethoxylated surfactants are 'derivatives' of ethylene oxide. Although chemically speaking ethylene oxide is a reagent, the vagueness of the definition of derivative creates uncertainty, even though the toxicological profile of the surfactant/polymer is significantly different to the scheduled compounds.

The breadth of the derivatives definition leads to unintended consequences. For example, to be eligible for use in a listed medicine, an ingredient, among other conditions:

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

All essential oils consist of a mixture of a range of terpenoids and related compounds (Chizzola, 2013). Terpenoids are biosynthesised by the progressive addition of isoprene units. Geraniol and linalool are, in addition to nerol and lavandulol, primary products in terpene biosynthesis. Geraniol and nerol occur at some level in nearly all terpene-containing essential oils. The scheduling of geraniol may have created a range of potential unintended and inappropriate consequences (see Example 3 – Geraniol).

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 prevented from being ingredients in listed medicines.

Options for consideration	Consideration could be given to stratifying the definition of derivative across the schedules of the *Poisons Standard*, differentiating between substances that are included due to the various types of risks 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 toxicophore) • topical and physicochemical properties of concern (based on the physicochemical property of concern – e.g., pH, solvent or surfactant strength) Development of guidance could support consideration of which range of derivatives are appropriate to capture based on the nature of the risks determining the scheduling decisions.

Recognition of international standards – precedence

Some stakeholders have proposed that Australia should adopt by reference, or incorporate in the *Poisons Standard*, the EU Cosmetics Regulation. There is precedence for recognising international regulatory requirements for flavours and fragrances in Australian regulatory Instruments. The Food Standards Code recognises international approvals or safety assessments of flavouring agents, e.g. in Food Standard 1.3.1.

Permitted flavouring substances, for the purposes of Food Standard 1.3.1

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

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

Additionally, the TGA utilises the monographs of recognised pharmacopoeias, and for colourings:

- the Food and Agriculture Organisation (FAO)/World Health Organisation (WHO) Combined Compendium of Food Additive 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 for consideration	A relatively simple approach to exempting cosmetic ingredients from the application of the *Poisons Standard* schedules while adopting the provisions of the EU cosmetics guidelines and IFRA standards might be to include in Appendix B an entry along the following lines: 'Fragrance compounds in cosmetic products when used at levels permitted by, and where the product is labelled in accordance with, the EU Cosmetics Regulation (specify latest version) and when the levels used in the product are below the limits specified by the IFRA standard (specify latest version).' Some recognition of the US FDA cosmetics regulations as an alternative may also be appropriate. Flavour compounds and other cosmetic ingredients might be similarly managed. An additional amendment to the interpretation section of the *Poisons Standard* to recognise the Appendix B entry may also be required.

Scheduling application adequacy

In order to explore any differences between the outcomes of scheduling decisions and the provisions of the EU Cosmetics Regulation, a direct comparison of cosmetic ingredients proposed for scheduling has been undertaken focusing on perfume ingredients initially for scheduling recommendations made between March 2016 and June 2018. The basis of delegate decisions and of scheduling committee advice to the delegate is the scheduling application. The adequacy of this advice and the delegate's decision is dependent on the quality and adequacy of the application. The scheduling applications and consequent decisions or proposals for a number of specific substances are examined in greater detail later in this document.

Basis for scheduling recommendations

Dermal cosmetic ingredients generally are of low systemic toxicity via the dermal route. Frank carcinogens or reproductive toxicants are unlikely to be knowingly used in cosmetic products by reputable manufacturers. Acute toxicity end points tend to be the primary drivers of most scheduling decisions.

The primary risk determinants of scheduling decisions for most cosmetic ingredients are the acute oral and dermal toxicity, skin and eye irritation and skin sensitisation. Each of these toxicological effects exhibit classical dose response relationships with a threshold for effect occurring at some dose (acute systemic toxicity) or level of dilution (irritation) or dose per unit area (sensitisation). Determination of the likely threshold for effect is a critical aspect of scheduling decisions and a key requirement for acceptable scheduling applications.

Acute systemic toxicity through oral and dermal exposure is relatively straight forward to extrapolate across dilutions. For a product containing 10% of a substance with an oral LD_{50} of 1000 mg/kg body weight, the product as a whole will have an LD_{50} of 10,000 mg/kg body weight (10 x 1000 mg/kg) provided other ingredients do not contribute significantly to the toxicity of the product. However, the dose that results in the death of 50% of animals (LD_{50}), although used as a basis for SPF criteria, is not an especially appropriate dose metric for consumer risk assessments. A more appropriate metric might be the highest non-toxic or highest non-lethal dose (if known), 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 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 depends primarily on the activation of allergen-specific T cells. A clear distinction needs to be made between *elicitation* of a skin sensitisation reaction in previously sensitised persons versus *induction* of sensitisation in naïve individuals. The EU (Cosmetics) Regulation is intended to address the former and the IFRA guidance the latter. The two standards work in combination to ensure that products compliant with the IFRA standard will not induce sensitisation in naïve individuals, and sensitive individuals will have the necessary information to be able to avoid a product that might elicit sensitisation. Limits for both standards 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 the concentration of a substance in a preparation provides a usable basis for *risk* estimation (unless combined with an application rate for the product that gives an exposure per unit area of skin). The entire process of the induction phase requires approximately ten days to several weeks, whereas an elicitation phase reaction develops within 1–2 days.

Thus, the purpose of labelling is to alert a sensitive person to the presence of the ingredient and to enable anyone having a reaction to identify the ingredient(s) that might be responsible. The purpose of the IFRA standard conversely is to ensure that 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:

- concentration of the substance in a product
- amount of product applied
- area of skin product is applied to

Various reliable sources of information are available to estimate these parameters. Skin sensitisation is a threshold effect. Sufficient of a substance must be applied per cm2 of skin to initiate an effective immune response to lead to induction of sensitisation. A key concept that does not appear to have been addressed in scheduling submissions is that of the Dermal Sensitisation Threshold (DST). The DST has been derived utilising an analogous approach to that used for the derivation of TTC – widely used internationally and within the TGA and APVMA for consideration of the toxicological significance of impurities in pharmaceuticals and pesticides.

Options for consideration	Not all applicants submitting scheduling applications will be familiar with the risk based requirements for scheduling of a substance. In order that scheduling applications contain sufficient information for decision making, more comprehensive guidelines are required, indicating the nature of the required data, the preferred approach to risk assessment and the appropriate depth of analysis expected. The guidance to applicants might consist of a more guided and extensive application form, in combination with comprehensive guidance documents on assessing risks associated with the principal hazards driving scheduling decisions (eye and skin irritation, acute oral, dermal, and inhalational toxicity and skin sensitisation) and incorporate current best practice. The application form could provide a means for electronic capture of the data to support the scheduling process into the future.

Level of concordance of scheduling decisions with EU Cosmetics Regulation

Some stakeholders have expressed concern that some outcomes from scheduling deliberations on cosmetic ingredients are substantially divergent from the requirements of the international regulations, most notably those of the EU Cosmetics Regulation. A comparison of recent scheduling decisions for cosmetic ingredients with the requirements of the EU Cosmetics Regulation was therefore conducted to gauge the extent and frequency of such divergence.

Of the thirty cosmetic ingredient substances (excluding those solely used in hair dyes) considered for scheduling between March 2016 and June 2018, four ingredient substances were not strictly cosmetic ingredients while three others were assessed as 'new' chemicals and had no EU restrictions. For four other substances, no final decisions have yet been made by the scheduling delegate so concordance could not be judged.

- For five substances, the recommendations and/or delegate's decisions (interim or final) were largely or entirely concordant with EU cosmetics regulations.
- For nine substances that the EU has prohibited for use in cosmetics the scheduling decision, while clearly intended to restrict use in cosmetics, allows their continued use as Schedule 6 entries. However, it should be noted that the preference of the advisory committees has been that inclusion of a chemical in Schedule 6 precludes its use in cosmetic products. This decision is considered by the committee to be aligned with the EU in practice. In the case of methylisothiazolinone for example, its use in baby wipes has continued with the product carrying the signal heading of POISON. This outcome has elicited enquires from the public concerned at the apparent incongruity of a personal wipe carrying this heading.
- For twelve of these ingredient substances, the scheduling outcome is overly restrictive and discordant with the level of risk presented by the substances, and requires unique Australian labelling.
- For five substances, the scheduling outcome is inconsistent with similar substances already in the *Poisons Standard*, generally due to inconsistent management of skin sensitisation.
- At least three decisions resulted in unintended impacts on other regulatory schemes affecting non-cosmetic uses, such as complementary medicines. The Schedule 6 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 one of the substances the entry is ambiguous, since the capture of derivatives (phenol) is indeterminable.

As some entries have more than one issue, the numbers above sum to more than the 30 substances considered.

Analysis of some recent scheduling decisions

The quality of the advice provided by the advisory committees, and the decisions of the delegate, are dependent on the quality of the scheduling request and in particular whether the request adequately addresses each of the matters to which the scheduling committees and the delegate must have regard to in formulating their advice and decisions, respectively. Some applicants may lack the experience to understand the needs of the scheduling committees and delegate and the requirements of the legislation in terms of the data and analysis required to support the decision-making process. The current scheduling application form and application handbook provide limited advice and guidance in this regard.

Deficiencies common to most cosmetic ingredient proposals reviewed

Most of the scheduling submissions relating to cosmetic ingredients are essentially hazard based classification proposals. The proposals may not have adequately explored the critical aspects for scheduling recommendations, such as:

- 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 (e.g. shampoo and soap hurt when in the eye)
- the impact of proposals on stakeholders
- cross regulatory impacts of proposals
- alternative mechanisms for achieving the regulatory intent
- which derivatives should be captured by the entry.

The scheduling submissions also may not adequately consider the dose response pattern for the hazards they are seeking to control, and have generally not used appropriate dose metrics for skin sensitisation (amount applied per surface area, µg/cm2 rather than concentration in product). No consideration of dermal sensitisation thresholds (DST) may have been included in the assessments, and the regulatory impact on industry of the collective scheduling proposals for cosmetic chemicals has not been addressed.

These common deficiencies are not further commented on in the reviews of the individual submissions below.

Example 1: Isoeugenol

Scheduling delegate's final decision, June 2017

Schedule 6 - Amend Entry

ISOEUGENOL **except**:

a. when included in Schedule 5; or

b. in preparations not intended for contact with skin containing 10 per cent or less of isoeugenol; 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 intended for contact with skin containing 10 per cent or less of isoeugenol.

Appendix E, Part 2 - New Entry

ISOEUGENOL

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

Appendix F, Part 3 - New Entry

ISOEUGENOL

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

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

Discussion

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

QSAR analysis, as has been used for related substances in scheduling applications from the same applicant.

The scheduling submission is in the public domain. The submission and documentation supporting the delegate's decision did not comment on the significance of the carcinogenicity classification to human health and safety; this 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. 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 (Ames & Gold, 1997).

Discordance with international Regulations

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

Inconsistency across similar substances

The schedule entry does not require a skin sensitisation warning at exempt levels despite the fact that isoeugenol is considerably more potent as an inducer of skin sensitisation than anise alcohol, the proposed scheduling for which does require the warning at exempt levels. (NESIL 250 μg/cm^2 compared to anise alcohol, 1500 μg/cm^2).

There is no requirement for isoeugenol to be included on the ingredient list of cosmetic products at the exempted levels, unlike proposed scheduling for anise alcohol, cinnamaldehyde and benzyl alcohol for example. This requirement is the principal 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.

Example 2: Anise Alcohol

Scheduling delegate's interim decision

The delegate made an interim decision recommending that a new Schedule 6 entry and Appendix E and F entries be created for anise alcohol.

The primary determinants of the recommended scheduling were expected eye irritation (based on benzyl alcohol data) and skin sensitisation in an LLNA assay (EC3 is 5.9 %, 1475 μg/cm^2).

Schedule 6 - New Entry

ANISE ALCOHOL **except**:

a. in preparations intended for therapeutic use; or

b. in domestic preparations not intended for direct skin contact containing 5 per cent or less of anise alcohol when declared on the label; or

c. in leave-on cosmetic and personal care preparations containing more than 0.001 and up to 2.5 per cent of anise alcohol when declared on the label and labelled with the following statement:

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

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

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

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

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

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

b. in rinse-off cosmetic and personal care preparations containing 0.01 per cent or less of anise alcohol.

Appendix E, Part 2 – New Entry

ANISE ALCOHOL

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

Appendix F, Part 3 – New Entry

ANISE ALCOHOL

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

Safety Direction: 4 (Avoid contact with skin).

Discussion

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

For substances with skin sensitisation potential, designated acceptable levels of use reflect the best available science of dermal sensitisation, utilise DST where appropriate and identify levels which will not result in induction of sensitisation in naïve (ie not previously sensitised) consumers.

The IFRA standard provides product type specific restrictions for anise alcohol:

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

The EU Cosmetics Regulation established concentration levels for 26 identified fragrance allergens to inform consumers with a known allergy (i.e. those already sensitised) of the

presence of these ingredients so they can choose to avoid certain products. They are not reflective of levels that would result in induction. Thus, the EU and IFRA standards work together to ensure levels included in products are unlikely to produce induction in naïve individuals and that their presence above levels that might cause a reaction in a sensitised person are identified through the inclusion of the fragrance substance in the ingredient list. The EU requirements for anise alcohol in cosmetics are:

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

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

Discordance with international (EU) Regulations

The EU requires only the inclusion of the substance in the ingredient list when above 0.001% in leave-on products and 0.01% for rinse-off products. The requirement for a warning statement above the cut-offs of < 0.001% in leave-on products and < 0.01% for rinse-off products creates a need for separate labelling for products sold into, or imported from, the EU, compared to that required for Australia.

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

Inconsistency across similar substances

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

Example 3: Geraniol

The Poisons Standard entry

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).

Discussion

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 Regulation sets lower cut-off levels with a requirement to include the substance in the ingredient list above that level, in order to allow individuals who are already sensitised to avoid products they might react to.

The acyclic terpene alcohols geraniol, linalool, and citronellol are the most important terpene alcohols used as fragrance and flavour substances. Geraniol and linalool are, in addition to nerol and lavandulol, primary products in terpene biosynthesis. 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.

Inconsistency across similar substances

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

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

Discordance with international (EU) Regulations

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

The *Poisons Standard* provides a 5% cut-off from Schedule 6 to exempt but with no requirement for inclusion in the ingredient list of cosmetics products.

Consideration of impacts on other regulatory schemes

The regulatory impact of the decision has not been fully considered. 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.

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

Example 4: Cinnamaldehyde

Scheduling delegate's interim decision

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.

Discussion

Inconsistency with scheduling of similar substances

The primary justification for the scheduling cut-offs in the record of reasons for the interim decision is skin sensitisation. Although isoeugenol is similar or more potent as a skin sensitiser (NESIL isoeugenol 250 µg/cm2 compared to 590 for cinnamaldehyde) the proposed cut-offs have been set to below the levels requiring inclusion in the ingredients list by the EU, but are below the EU maximum level for isoeugenol (ie isoeugenol is less restrictive). The IFRA standard for cinnamaldehyde has a maximum use level of 0.05% (most dermal products) to 0.4% (mouthwash), well above the proposed Schedule 6 cut-offs.

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

The proposed scheduling outcome thus may be discordant with previous decisions for similar materials and potentially disproportionate to the risks being managed.

Discordance with international (EU) Regulations

The EU requires only that the substance be included in the ingredient list of cosmetics when at greater than 0.001% in leave-on products and 0.01% in rinse-off products. For cinnamaldehyde the cut-off only applies if the concentration is below these levels, the opposite to the proposed entry for anise alcohol. In previous scheduling decisions (e.g. anise alcohol) much higher cut-offs

were applied, with the presence of the substance required to be declared on the label (consistent with EU requirements) but with the additional Australian specific requirement for an explicit sensitisation warning as discussed under anise alcohol.

Potentially Disproportionate Regulatory Response

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

Example 5: Benzyl Salicylate

Scheduling delegate's interim decision

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).

Discussion

Comparison with international (EU) Regulations

The EU Cosmetics Regulation 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 Regulation and the IFRA standard work in conjunction to set appropriate boundaries for use, a combination of Government imposed and industry self-regulation (product stewardship, legal liability management). The proposed entry is largely concordant with the EU regulations for most cosmetic products.

Ambiguity and lack of clarity

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

Conclusions

The *Therapeutic Goods Act 1989* and SPF establish the scheduling of therapeutic, domestic, agricultural and veterinary chemicals as a risk-based mechanism for managing the risks of substances at the level they are used in products available in Australia. Although the scheduling factors are hazard-based their intent is to support consistency of scheduling decisions rather than to be prescriptive. The legislation, scheduling factors, preamble to the *Poisons Standard* and the SPF need to be read together when considering scheduling decisions.

In reviewing some recent scheduling decisions or recommendations for cosmetic ingredients, there appears to be no obvious need for *de novo* assessment of fragrance materials. 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 for managing other risks and involve some level of recognition of international regulations or the decisions of authoritative bodies.

The review has identified room for improvement in a variety of more general scheduling processes that are amenable to relatively simple, procedural modifications that would substantially improve the accessibility, interpretability and effectiveness of the *Poisons Standard*. For example, 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, would largely eliminate, or at least substantially reduce, the very considerable uncertainty associated with the current entries (unless explicitly excluded).

The establishment of an explicit cut-off for impurities in cosmetic and other domestic substances for chemicals with entries in S7 to S10 would eliminate the current unintended capture of

substances such as ethylene oxide when present as an impurity of synthesis in polyethoxylated surfactants.

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

A clear need has been identified for improved guidance, which would support more consistent and proportionate decisions and guide applicants to address the various areas the scheduling committee and delegate are required to give consideration to.

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

The use of the scheduling mechanism to manage skin sensitisation in isolation of acute systemic toxicity risks appears to be problematic. A requirement for a product that includes a skin sensitiser at low levels to carry the signal heading POISON when in Schedule 6 might be considered misleading and certainly overstates the risks presented by such products. Some consideration of the extent to which skin sensitisation, as the sole or predominant risk, should be used to drive scheduling decisions beyond Schedule 5 is appropriate.

More broadly, improvements to scheduling decision-making processes could be made for substances that cross regulatory boundaries to ensure that regulatory decisions do not result in unintended consequences that add cost to industry and may prevent Australians having access to particular products that have been used safety for some time overseas.

References

ACCC. (2008). *Review of the Trade Practices (consumer Product Information Standards) (Cosmetics) REgulations 1991 (Cosmetic Regulations)*. RIS, ACCC.

Administrative Review Council. (2018, Aug). *Overview of the Commonwealth System of Administrative Review*. Retrieved from Attorney Generals Department: https://www.arc.ag.gov.au/Aboutus/Pages/OverviewoftheCommonwealthSystemofAdminReview.aspx#a2

Ames, B., & Gold, L. (1997). Environmental Pollution, Pesticides, and the Prevention of cancer: Misconceptions. *The FASEB Journal*, 11, 1041 - 1052.

Australian Government. (2017, July 13). *Federal Register of Legislation*. Retrieved from Therapeutic Goods Act 1989: https://www.legislation.gov.au/Details/C2017C00226

Cadby, P., & Troy, W. V. (2002). Consumer exposure to fragrance ingredients: Providing estimates for safety evaluation. *Regulatory Toxicology and Pharmacology*, 36, 246-252.

Chizzola, R. (2013). Ch 96 Regular Monoterpenes and Sesquiterpenes (Essential Oils). In J. M. K.G. Ramawat (Ed.), *Natural Products* (pp. 2973-3008). Berlin: Springer Verlag.

Choi, J., Lee, K., Ka, H., Jung, W., & Park, H. (2001). Constituents of the essential oil of theCinnamomum cassia stem bark and the Biological Properties. *Archives of Pharmacal Research*, 24(5), 418-423.

Cosmetic Ingredient Review Panel. (1997). Final Report on the Safety Assessment of p-Chloro-m-Cresol. *International Journal of TOxicology*, 16(3), 235-268.

Cottier, T. E.-A.-G. (2012). *The principle of proportionality in international law*. Swiss National Centre of Competence in Research.

Council of Australian Governments. (2014, November 18). *Best Practice Regulation: A guide for Ministerial Councils and National Standard Setting Bodies*. Retrieved from Prime Minister and Cabinet.

Department of Health. (2018). *Poisons Standard June 2018*. Department of Health, Therapeutic Goods Administration.

Dept of Health, TGA. (2018). *Scheduling handbook Guidance for amending the Poisons Standard*. Canberra: TGA.

ECHA. (2018). *Chlorocresol, EC number: 200-431-6*. Retrieved June 25, 2018, from ECHA REACH Dossiers: https://echa.europa.eu/registration-dossier/-/registered-dossier/10359/7/4/3

Eslahi, H., Fahimi, N., & Sardarian, A. (2018). Chemical Composition of Essential Oils. In A. M. Seyed Mohammad Bagher Hashemi (Ed.), *Essential Oils in Food Processing: Chemistry, Safety and Applications* (1st ed., pp. 119-171). John Wiley and Sons.

European Commission. (2009). *REGULATION (EC) No 1223/2009 of the European parliament and of the CounciL on cosmetic products*. Retrieved June 25, 2018, from https://ec.europa.eu/health/sites/health/files/endocrine_disruptors/docs/cosmetic_1223_2009_regulation_en.pdf

Ferran, E. (2015). *Principle of Proportionality*. Retrieved from https://www.eba.europa.eu/documents/10180/1044289/Session+1.+Proportionality+vs+simplicity+-+Prof+Eilis+Ferran.pdf

IFRA. (2015). *IFRA Standard 48th Amendment*. Retrieved June 25, 2018, from IFRA: http://www.ifraorg.org/Upload/DownloadButtonDocuments/c7b29dc8-19d2-4ffd-8aae-bb35ec2ae95b/IFRA-RIFM%20QRA%20Information%20booklet%20V7.1%20(July%209,%202015).pdf

IFRA. (2015). *IFRA Standards, 48th Amendment*. Retrieved June 25, 2018, from IFRA: http://www.ifraorg.org/Upload/DownloadButtonDocuments/a13f9a09-ec56-4aab-a33b-ec66528d5330/booklet%20FINAL.pdf

Kim, J., Liu, K., Yoon, Y., Sornnuwat, Y., Kitirattrakarn, T., & Anantachoke, C. (2005). ESSENTIAL LEAF OILS FROM MELALEUCA CAJUPUTI. *Acta Horticulturae*, 680, 65-72.

OBPR. (2017, September 30). *Australian Government RIS Preliminary Assessment Form: Is a RIS required?* Retrieved from Department of Prime Minister and Cabinet: https://www.pmc.gov.au/resource-centre/regulation/australian-government-ris-preliminary-assessment-form-ris-required

OBPR. (2017, Feb 22). *Carve-outs Guidance Note*. Retrieved from Department of Prime Minister and Cabinet: https://www.pmc.gov.au/resource-centre/regulation/carve-outs-guidance-note

OECD. (1995). *RECOMMENDATION OF THE COUNCIL OF THE OECD ON IMPROVING THE QUALITY OF GOVERNMENT REGULATION*. Paris.

OECD. (2012). *RECOMMENDATION OF THE COUNCIL ON R EGULATORY POLICY AND GOVERNANCE*. Paris: OECD.

PM&C. (2014). *The Australian Government Guide to Regulation*. Commonwealth of Australia, Prime Minister and Cabinet. Commonwealth of Australia.

Rajeswarra Rao, B. (2002). Biomass yield, essential oil yield and essential oil composition of rose scented geranium (pelargonium species) as influenced by row spacings and intercropping with cornmint (mentha arvensis L.f. piperascens Malinv. ex Holmes. *Industrial Crops and Products*, 16, 133-144.

Safford, R., Api, M., Robets, D., & Lalko, J. (2015). Extension of the Dermal Sensitisation Threshold (DST) approach to incorporate chemicals classified as reactive. *Regulatory Toxicology and Pharmacology*, 72, 694-701.

SCCS. (2016). *THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION*. European Commission.

(2018). *Scheduling Policy Framework*. TGA.

Singh, G., Maurya, S., Delampasona, M., & Catalan, C. (2007). A comparison of chemical, antioxidant and antimicrobial studies of cinnamon leaf and bark volatile oils, oleoresins and their constituents. *Food and Chemical Toxicology*, 45(9), 1650-1661.

TGA. (2017). *Minor variations to prescription medicines*. Retrieved June 25, 2018, from https://www.tga.gov.au/sites/default/files/guidance-minor-variations-chemical-entities.pdf

TGA. (2018). *Australian regulatory guidelines for complementary medicines*. Retrieved June 25, 2018, from TGA: https://www.tga.gov.au/sites/default/files/australian-regulatory-guidelines-complementary-medicines-argcm-v8.0.pdf

TGA. (2018). Scheduling handbook Guidance for amending the Poisons Standard. *Ver 1.0*. Department of Health.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Therapeutic Goods Administration	01/03/2019

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication # D19-5241647