ADMIN

Report Format Outline and Boilerplate/SOPs Guidance Document

EXPERT PANEL MEETING
September 26-27, 2022

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume MMF
Senior Director, CIR
Date: September 1, 2022
Subject: Report Format Outline and Boilerplate/SOPs Guidance Document

CIR reports follow a standard format. In that we have several new members of the Expert Panel for Cosmetic Ingredient Safety, the outline that is used is being provided to help familiarize everyone with that format (*ReportFormatOutline_Format-SOPs_092022*).

Additionally, there is boilerplate language that has been developed over the years that is used regularly in reports issued by the Panel, as well as certain standard operating procedures (SOPs). A document capturing that language and these SOPs is included for your review (*BoilerplateGuidance_Format-SOPs_092022*). In addition to the "boilerplates" and SOPs, in some instances background regarding these common matters is also provided. [Please note: This document is used as a reference by CIR staff, and as such, there are links to files in the guidance document that are only accessible internally; therefore, please know that as you review this Guidance document, these links are not accessible.]

REPORT FORMAT (updated 10/29/2020)

ABBREVIATIONS *(include all abbreviations here, as well as first mention in text)*

ABSTRACT *(included from draft TR on)*

INTRODUCTION

CHEMISTRY

- **Definition and Structure** *(non-botanicals*), or **Definition and Plant Identification** *(botanical reports*)
- **Chemical Properties** *(present measured properties first, computational second)*
- **Method of Manufacture**
- **Impurities** (*non-botanicals*), or **Composition and Impurities** *(botanical reports)*
- **Other Sub-Sections as Appropriate** (for example: Natural Occurrence; UV Absorption; Nitrosation)

USE

- **Cosmetic**
- **Non-Cosmetic**

TOXICOKINETIC STUDIES

- **Dermal Penetration**
  - In Vitro
  - Animal
  - Human
- **Penetration Enhancement**
- **Absorption, Distribution, Metabolism, and Excretion (ADME)**
  - In Vitro
    - Skin Samples
    - Cell Cultures
  - Animal
    - Dermal
    - Oral
    - Inhalation
    - Other Routes, when relevant
  - Human
    - Dermal
    - Oral
    - Inhalation
    - Other Routes, when relevant
  - Computational (examples provided here)
    - Physiologically Based Pharmacokinetic (PBPK) Modelling
    - In Vitro/In Vivo Extrapolation (IVIVE)
    - Quantitative Structure-Activity Relationship (QSAR)/Quantitative Structure-Property Relationship (QSPR) Calculations

TOXICOLOGICAL STUDIES (for this section, if there are <u>only</u> animal studies, "Animal" is <u>not needed</u> as a subheading)

- **Acute Toxicity Studies** (*single exposure*)
  - Dermal
  - Oral
  - Inhalation
  - Other (when relevant)
- **Short-Term Toxicity Studies (***includes 0 - < 3 mo exposure; does <u>not</u> include 90-d/13 wk/3 mo exposures – those are Subchronic*)
  - Animal
    - Dermal

- Oral
- Inhalation
- Other (when relevant)

Human
- Dermal
- Oral
- Inhalation
- Other (when relevant)

Subchronic Toxicity Studies (*includes ≥ 3 - < 6 mo exposure; does <u>not</u> include 6 mo exposures – those are Chronic*)

Animal
- Dermal
- Oral
- Inhalation
- Other (when relevant)

Human
- Dermal
- Oral
- Inhalation
- Other (when relevant)

Chronic Toxicity Studies *(includes ≥ 6 mo exposure*)

Animal
- Dermal
- Oral
- Inhalation
- Other (when relevant)

Human
- Dermal
- Oral
- Inhalation
- Other (when relevant)

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES
- Dermal
- Oral
- Inhalation

Computational Analyses/ Predictions (as these tools become available and validated)

GENOTOXICITY STUDIES

In Vitro

In Vivo

Computational Analyses/Predictions

CARCINOGENICITY STUDIES
- Dermal
- Oral
- Inhalation

Co-Carcinogenicity
- Dermal
- Oral
- Inhalation

Tumor Promotion (these are in vivo studies**)**
- Dermal
- Oral
- Inhalation

In Vitro Cell Transformation (these are in vitro studies examining effect on tumor cells)
Computational Analyses/ Predictions (as these tools become available and validated)

ANTI-CARCINOGENICITY STUDIES (only included when data are relevant/available)

OTHER RELEVANT STUDIES (only included when applicable)
Comedogenicity
Effects on Pigmentation
Endocrine Activity
Cytotoxicity
Anti-Microbial
Other Endpoints, <u>when relevant</u> (for example, Neurotoxicity, Immunotoxicity, Behavioral Toxicity)

DERMAL IRRITATION AND SENSITIZATION STUDIES
Irritation
In Vitro/In Chemico
Animal
Human
Sensitization
In Vitro (or In Vitro/In Chemico, if appropriate; e.g., DPRA)
Animal
Human
Photosensitization/Phototoxicity (only included when relevant data are available)
In Vitro
Animal
Human
Computational Analyses/Predictions (as these tools become available and validated)

OCULAR IRRITATION STUDIES
In Vitro
Animal
Human (including use studies)
Computational Analyses/Predictions (as these tools become available and validated)

MUCOUS MEMBRANE IRRITATION STUDIES (only included when relevant data are available)
In Vitro
Animal
Human

CLINICAL STUDIES (only included when relevant data are available)
Retrospective and Multicenter Studies
Case Reports
Adverse Event Reports
Other Clinical Reports, if relevant

RISK ASSESSMENT (included when review docs have MOE or MOS relating to cosmetic use)

OCCUPATIONAL EXPOSURE (only included when relevant data are available)

EPIDEMIOLOGICAL STUDIES (only included when appropriate; typically, in hair dye reports)

SUMMARY

DISCUSSION

CONCLUSION

TABLES (or, FIGURES AND TABLES)

REFERENCES

PLEASE NOTE:

Risk Assessment data: risk assessment data are included when appropriate

- When risk assessment data are available and appropriate for inclusion, that information should be included in the relevant section of the report
    - if Quantitative Risk Assessment (QRA) for dermal sensitization is to be included, that information should be included in the **Sensitization** section of the report

Analogs: Analogs are included in the report as a source of read-across data when appropriate, and when approved by the Panel.

- When used, it is important to identify the analog, the endpoints that the analog address, and the rationale as to why it is appropriate for use (this information may be provided in a table)

Threshold of Toxicological Concern: TTC may be appropriate at times

- When it is appropriate to included TTC, a link to a description of the methodology should be included

Aerosols/Sprays/Powders and Airbrush

Aerosol Propellant Dilution

As aerosols, Isobutane, Propane, Isopentane, and n-Butane are so greatly diluted when discharged that the amount coming into contact with the skin is much less than the stated amounts used in the clinical tests. Since alkanes are highly volatile and have low water solubility, it is estimated that, as propellants, they would remain on the skin no longer than 10 seconds. Such a short period of contact makes the absence of sensitization, phototoxicity, and photosensitization studies relatively unimportant.

Sprays/aerosols/powders – particle size and airbrush use

Updated 6/2022

Background

see Respiratory Exposure Resource Document - https://www.cir-safety.org/cir-findings

Boilerplates

USE Section

in all documents – first paragraph of Cosmetic Use section

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

route of exposure type paragraph, when exposure via inhalation is known

In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. [**if there are known spray deodorant uses**: There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.] [**if there are known powder uses**: Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.]

in all documents, following route of exposure paragraph

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

DISCUSSION

standard inhalation bp (modify as necessary)

The Panel discussed the issue of incidental inhalation exposure resulting from these ingredients (e.g., …). Inhalation toxicity data were not available. [*modify previous sentence, as appropriate*] However, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore,

droplets/particles deposited in the nasopharyngeal or tracheobronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the low concentrations at which these ingredients are used (or expected to be used) in potentially inhaled products, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. [*modify previous sentence, if appropriate*.] A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Possible modifications that may be applicable for use in the preceding paragraph

[NOTE INHALATION TOXICITY DATA, **IF APPLICAPLE**: Examples: (1) The limited data available from inhalation studies, including acute and chronic exposure data, suggest little potential for respiratory effects at relevant doses OR (2) The data available from multiple inhalation studies, including acute and chronic exposure data, indicate little potential for respiratory effects at relevant doses.]

The Panel considered other data available to characterize the potential for [INGREDIENT(S)] to cause [LIST PERTINENT TOXICITIES EVALUATED; EXAMPLES: (1) irritation and sensitization OR (2) systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity.]

[SUM UP PERTINENT TOXICOLOGY RESULTS; EXAMPLES: (1) They noted the lack of systemic toxicity at high doses in several acute and subchronic oral exposure studies and one chronic oral exposure study, little or no irritation or sensitization in multiple tests of dermal and ocular exposure, the absence of genotoxicity in multiple Ames tests and a Chinese hamster ovary test, and lack of carcinogenicity in a lifetime oral exposure study OR (2) They noted the lack of irritation or sensitization in tests of dermal exposure, no systemic toxicity at 5000 mg/kg, and the absence of genotoxicity in an Ames test of a related chemical.]

[SUM UP PERTINANT PHYSICOCHEMICAL PROPERTIES, **IF APPLICABLE**; EXAMPLES: (1) [INGREDIENT(S) is/are chemically inert and thus not systemically toxic OR (2) In addition, these ingredients are large macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract.]

DISCUSSION (always in the Discussion; follows the inhalation paragraph, if it is used)

The Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings [***or, when the inhalation bp language is used in the previous paragraph, state instead: see link above]*** notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

Alternatives to "28-day dermal toxicity" study

Boilerplate

DISCUSSION

...while the Expert Panel for Cosmetic Ingredient Safety has specified a "28-day dermal toxicity study," there is concern that specifying a type of study may inhibit those who want to gather data using other study designs. The types of data the Panel is seeking include the gross pathology and histopathology in skin and other major organ systems, along with certain other toxicity parameters, associated with repeated exposures. A 28-day dermal toxicity study would generate the needed data; but there are other approaches. For example, the Panel would consider a dermal reproductive and developmental study in which gross pathology and histopathology data are gathered on the F_0 generation to be sufficient to meet both the "28-day dermal toxicity" and "reproductive and developmental toxicity" data requested, if done at or above current concentrations of use of the ingredient.

Botanicals

see Botanicals report template N:\CIR\New N Drive\Boilerplates & SOPs\templates\SLR Outline & Details - Botanical report_updated post-June 2022 mtg.docx

General Guidance for Developing INTRODUCTION Language in Botanical Ingredient Reports

There are paragraphs that are included in the Introduction of all botanical reports. One addresses the fact that the Panel is evaluating the ingredient(s) as a whole substance, and not evaluating the safety of the individual constituents. The second addresses the fact that often it is not known how the substance being tested compares to the ingredient as used in cosmetics. These boilerplates are included in the Introduction of all botanical reports.

Sometimes, the only function reported in the *Dictionary* is as a fragrance ingredient. According to the CIR Procedures, review of a fragrance is commonly under the purview of RIFM. The Expert Panel for Cosmetic Ingredient Safety may, in order to avoid duplication of effort, exclude such a fragrance-only ingredient from their review. However, if it is known that RIFM did not evaluate safety of the botanical that is reported to function as a fragrance (only), and there are no plans in the near future to do so, the Panel may opt to include that ingredient in their safety assessment(s).

Boilerplates [always included in the Introduction]

Botanicals, such as [botanical family], may contain hundreds of constituents. [If some constituents are known to have adverse effect, the following can use used instead: [Botanical] contains over 100 constituents, some of which have the potential to cause adverse effects. For example, [name component and adverse effect].] In this assessment, the Panel is evaluating the potential toxicity of each of the [botanical group name] ingredients as a whole, complex substance; toxicity from single components may not predict the potential toxicity of botanical ingredients.

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics and without abbreviations. When referring to the plant from which these ingredients are derived, the standard scientific practice of using italics will be followed (i.e., [*genus/species*]). Often in the published literature, the general name [generic name for botanical] is used. If it is not known whether the substance being discussed is equivalent to the cosmetic ingredient, the test substance will be identified by the name used in the publication that is being cited. However, if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature (e.g., [give example of INCI name]) will be used.

Boilerplate [when appropriate]

The Expert Panel for Cosmetic Ingredient Safety (Panel) does not typically review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). [Ingredient(s)] in this report is reported to function only as a fragrance ingredient(s) in cosmetics, according to the wINCI *Dictionary* (see Table N). [then as appropriate: However, according to personal communications with RIFM [DATE], [this ingredient is not included in their review process,] OR [it is unknown when the safety assessment of this ingredient will be prepared], OR [the RIFM review status of these ingredients is currently being sought] therefore, the Panel is reviewing the safety of this ingredient.

Toxicokinetics Section

Because botanicals are complex mixtures of constituents, toxicokinetics data are often absent. The following should be included in the report.

Boilerplate

No relevant toxicokinetic studies on [INGREDIENTS] were found in the published literature, and unpublished data were not submitted. In general, toxicokinetic data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

General Guidance For Developing DISCUSSION Language For Botanical Ingredients

The Discussion should include a succinct summary of the key issues for the botanical ingredients. In general, the Discussion section for plant-derived ingredients should be developed in a case-by-case manner to present and evaluate cogent information specific for each plant under review.

If the boilerplate statements under [Concerns for multiple exposures], [Constituents], or any other boilerplates regarding botanicals, are applicable to the safety assessment of a botanical ingredient or group, then the Discussion following these statements should be developed to include the following information, as well as other relevant information, as applicable:

- Identity of the constituents of concern to the Panel in the botanical ingredient(s)
- Specific adverse toxicological endpoint(s) of concern (e.g., carcinogenicity, neurotoxicity, sensitization…) for each constituent of concern
- Concentration limits and other relevant qualifications that have been recommended for specific constituents of concern in the current or other Expert Panel for Cosmetic Ingredient Safety assessments, IFRA, or other sources, and the nature or magnitude and basis or rationale for each limit or qualification...

Concern for multiple exposures

Background

The Panel has acknowledged that different botanical ingredients may have similar constituents of concern, and, if different botanical ingredients with the same constituents of concern are used in a single formulation, the effect could be additive. Therefore, the Panel acknowledges that concern in the **ABSTRACT** and **DISCUSSION**, and often in the **CONCLUSION**.

When a botanical contains constituents of concern, the following statements may be incorporated, as appropriate (and modified, as needed), into the indicated sections (**ABSTRACT**, **DISCUSSION**) of safety assessment reports for botanical ingredients to convey the Panel's caveats and concerns about such ingredients, when applicable. When the constituents of concern are sensitizers, a caveat is placed in the **CONCLUSION**. **It should be noted** that the caveat for sensitization is due to concern for multiple exposure; it is not appropriate to include this caveat due to lack of data/clarity on sensitization potential for a single ingredient.

The Discussion should be clear whether constituents of concern to the Panel were identified by analysis of the whole plant/plant part(s), or by analysis of the cosmetic ingredients derived from the plant/plant part(s) (e.g., analysis of the oil from pressed leaves or aqueous extracts of the flowers used as a cosmetic ingredient). If the constituents of concern were identified by analysis of whole-plant or plant-part samples (rather than by analysis of the cosmetic ingredients), and the ingredients may be derived from more than one plant species, then the discussion should :

- specify the constituents of concern associated with each species, and
- note that the levels of constituents of concern in the cosmetic ingredients derived from the plant(s) can vary widely, and may even be undetectable in the ingredients, depending on the growing conditions of the plant, the methods of manufacturing of the ingredient, and other factors.

When a botanical does not contain any constituents of concern, the boilerplate statements stated below for use in the **ABSTRACT DISCUSSION,** and **CONCLUSION** are typically not needed because, for instance, (1) the ingredients are derived from well-characterized parts of plant species that are commonly used as food or food ingredients in which the constituents of concern are known to be absent (e.g., soy beans), or, (2) the cosmetic-ingredient manufacturing process ensures that the cosmetic ingredients contain no constituents of concern. For example, the boilerplate statements were not needed in the safety assessment report for the Phytosterols.

Boilerplates

ABSTRACT

Because final product formulations may contain multiple botanicals, each containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With [*Genus species*]-derived ingredients, the Panel was concerned about the presence of [*list constituents of concern*] in cosmetics. Industry should use good manufacturing practices to limit impurities.

DISCUSSION

Because final product formulations may contain multiple botanicals, each possibly containing the same constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. For [*Genus species*]-derived ingredients, the Panel was concerned about the presence of [*list constituents of concern*] in cosmetics, which could result in [*list adverse effects/endpoints*, *respectively*]. Therefore, when formulating products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that [INGREDIENT/ FAMILY] is/are safe in cosmetics in the present practices of use and concentration described in this safety assessment when formulated to be non-sensitizing.

Plant extracts – equivalency

Boilerplate

DISCUSSION

Concern, however, was expressed about alternative approaches to extraction that might not produce material with the same safety profile described in this safety assessment, especially if pesticides were used on the plants. While extracts from pesticide-free plants were not genotoxic and there do not appear to be any components that could be carcinogenic, pesticide residues could raise this issue. The Panel urged that manufacturers limit pesticide residues to the limit previously used for lanolin of not more than 40 ppm (with not more than 10 ppm for any one residue).

The conclusion regarding safety is valid only for extracts prepared in a manner that produces a similar chemical profile as that described in this report, particularly as regards to diosgenin. Prepared in this manner, the Panel's conclusion is that these extracts do not have significant estrogenic activity. Extracts not prepared in a manner that produces a similar chemical profile, would be considered safe if they have a similar safety test profile.

ALSO See : Contaminants, Residues, Impurities

Contaminants, Residues, Impurities

Aflatoxin

Examples of Discussion Language

- While aflatoxin has been detected in [*plant (part) where aflatoxins were found*], the Panel believes that aflatoxin should not be present in [*botanical/ingredient/group*]. The Panel has adopted the US Department of Agriculture (USDA) designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content. [for example, see: wheat-derived ingredients]
- Aflatoxins have been detected in [*plant (part) where aflatoxins were found*]. The Panel believes that aflatoxins will not be present at levels of toxicological concern in [*botanical/ingredient group*]. The Panel recognizes the USDA designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content. [for example, see: *Camellia sinensis*-derived ingredients]
- The Panel noted that aflatoxins have been detected in [*plant (part) where aflatoxins were found*]. They recognized the US Department of Agriculture designation of ≤ 15 ppb as corresponding to "negative" aflatoxin content and concluded that aflatoxins will not be present at levels of toxicological concern in [*botanica/ ingredient/group*].[for example, see: *Avena sativa*-derived ingredients]

1,4-Dioxane and Ethylene Oxide

Examples of Discussion Language

- Also of concern to the Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from the [ingredients] before blending them into cosmetic formulations. [for examples, see: Alkyl PEG Ethers; PEGs Distearate reports]
- The Panel noted the possible presence of 1,4-dioxane and ethylene oxide impurities in [ingredient/family]. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities from [ingredient/family] blending them into cosmetic formulations. [for an example, see: Butyl Polyoxyalkylene Ethers report]
- Because some of these ingredients are ethoxylated, the Panel was concerned about the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from [ingredient/family] before blending them into cosmetic formulations. [for an example, see: Monoalkylglycol Dialkyl Acid Esters report]
- The Panel also addressed the potential for ethylene oxide and 1,4-dioxane impurities in [ingredient/family]. Due to the volatility of ethylene oxide, it would be unexpected to find any appreciable quantity of the chemical residing as an impurity in these ingredients. The available data bear out that current methods of manufacture do not result in significant levels of ethylene oxide. The available data have demonstrated contaminant levels of 1,4-dioxane to be less than 10 ppm in these ingredients, again supporting that current methods of manufacture do not result in significant levels of 1,4-dioxane. Because of the toxicity of ethylene oxide and 1,4-dioxane, the Panel stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from [ingredient/these ingredients] before blending them into cosmetic formulations. [for example, see: Alkyl PEG Sulfosuccinates report]

- The Panel was concerned about the possibility of the presence of residual starting materials used in the manufacture of [ingredient/family] (i.e., ethylene oxide and propylene oxide) and of the residual by-product, 1,4-dioxane. These compounds are potentially carcinogenic. The Panel noted these are volatile compounds, and therefore, levels of these compounds in cosmetics are expected to be below the level of toxicological concern. Although levels may be low, the Panel stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from the ingredients before blending them into cosmetic formulations. [for an example, see: Alkyl PEG/PPG Ethers report]
- Further, in the absence of impurities data, the Panel cautioned [ingredient/family] should not contain 1,4-dioxane or ethylene oxide, which are possible oxidation products. [for an example, see: Ceteths report]

Pesticide and heavy metal limits

Boilerplate – non-botanicals

DISCUSSION

The Panel expressed concern regarding heavy metals that may be present in this/these ingredient(s). They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in this/these ingredient(s) before blending into cosmetic formulation.

Boilerplate - botanicals

ABSTRACT (if there are no constituents of concern)

Industry should continue to use good manufacturing practices to limit impurities that could be present in these botanical ingredients. **[if there are constituents of concern, see that boilerplate]**

DISCUSSION

[Note: if there are constituents of concern, this paragraph follows the one addressing that]

The Panel also expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities. [Inclusion of "other plant species" was added following the Sept 2016 meeting.]

Note: previously, the Expert Panel for Cosmetic Ingredient Safety had specified limits, and examples are provided here:

- The Expert Panel for Cosmetic Ingredient Safety expressed concern about toxic metal residues that may be present in (ingredient name) and advised industry that this ingredient should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb).
- In its safety assessment of Acid Violet 43 (Andersen 2001a), the Expert Panel for Cosmetic Ingredient Safety adopted limitations established by the Food and Drug Administration for certification of Ext. D & C No. 2 as a color additive (FDA 1976). In its safety assessment of the Lard Glycerides group of ingredients (Andersen 2001b), the Expert Panel for Cosmetic Ingredient Safety adopted the Food Chemicals Codex limit for lead in unhydrogenated lard (National Academy of Sciences 1996).
- The Panel recognizes that these limits were developed for uses other than cosmetics, but considers that such limits would assure that any cosmetic product with these ingredients can be used safely.
- In 2001, the Environmental Protection Agency established a limit of 10 ppb for arsenic in drinking water (40 CFR 141.6). The Expert Panel for Cosmetic Ingredient Safety considered this EPA determination as it might relate to cosmetics such as lipsticks that may be ingested. According to Loretz et al. (2005), the mean application per day of lipstick is 24 mg. Recognizing that not all of that application would be ingested and that not all ingredients in a lipstick product would contain arsenic up to 3 ppm, the Panel determined that the daily ingestion of arsenic from lipstick would be less than that received from the ingestion of 2 liters of drinking water per day at the 10 ppb level established by EPA.

Ingredients from Processed Botanical Sources

Boilerplate

The heavy metals and pesticide boilerplate language for botanical ingredients was left out of this report. While plants are the source of some components in the ingredients of this report, they result from significant processing, and as such are

not expected to contain residual pesticides or heavy metals.

Endocrine Activity

Background

see Endocrine Activity resource document. https://www.cir-safety.org/cir-findings

Example of Discussion Language

The Panel discussed the endocrine disruption potential of [ingredient/family] in available in vitro and in vivo studies, and determined that the results were not sufficient to characterize this ingredient as an endocrine disrupting chemical. For further explanation of what qualifies as endocrine activity or disruption, please refer to the CIR resource document: https://www.cir-safety.org/supplementaldoc/cir-precedents-endocrine-activity. [For an example, see: Triphenyl Phosphate]

Formaldehyde Releasers

Background

DISCUSSION (excerpts from the most recent Formaldehyde report; IJT 22(S4): 5-32, 2013; see report for entire Discussion)

Based on the available data, the Panel considered that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail-hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair-smoothing products. …

… The Panel adopted a suggestion to include limits for formalin concentration because formalin is what formulators actually add to cosmetic products. Formalin is an aqueous solution typically containing 37% (w/w) formaldehyde. Formalin contains both formaldehyde and methylene glycol because of the equilibrium between formaldehyde and methylene glycol in aqueous solution. While retaining the concept that formaldehyde and methylene glycol should be used only at the minimal effective concentration, the Panel stated that in no case should the formalin concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Although these numbers appear to be disparate, they are not. The value of 0.074% (w/w) of formaldehyde simply reflects that formalin typically contains 37% formaldehyde (0.2% (w/w) formalin multiplied by 0.37 = 0.074%, w/w formaldehyde). The value of 0.118% (w/w) for methylene glycol simply reflects the difference in molecular weight between formaldehyde and methylene glycol. …

… The Panel reasoned that the term ‘‘formaldehyde equivalents’’ best captures the idea that methylene glycol is continuously converted to formaldehyde, and vice versa, even at equilibrium, which can be easily shifted by heating, drying, and other conditions to increase the amount of formaldehyde. Any other term would not distinguish the rapid, reversible formaldehyde/methylene glycol equilibrium from the slow, irreversible release of formaldehyde resulting from the so-called formaldehyde releaser preservatives (e.g., diazolidinyl urea). Formaldehyde releaser preservatives are not addressed in this safety assessment. The formaldehyde releasers may continue to be safely used in cosmetics at the levels established in their individual CIR safety assessments.

CONCLUSION (from the 2013 report)

The Expert Panel for Cosmetic Ingredient Safety concluded that formaldehyde and methylene glycol are safe for use in cosmetics when formulated to ensure use at the minimal effective concentration, but in no case should the formalin† concentration exceed 0.2% (w/w), which would be 0.074% (w/w) calculated as formaldehyde or 0.118% (w/w) calculated as methylene glycol. Additionally, formaldehyde and methylene glycol are safe in the present practices of use and concentration in nail hardening products. However, formaldehyde and methylene glycol are unsafe in the present practices of use and concentration in hair smoothing products (a.k.a. hair straightening products).

†Formalin is an aqueous solution wherein formaldehyde (gas) has been added to water to a saturation point, which is typically 37% formaldehyde (w/w). Because of the equilibrium between formaldehyde and methylene glycol in aqueous solution, formalin is composed of both formaldehyde and methylene glycol.

Boilerplates

DISCUSSION – example based on updated formaldehyde report

According to an MSDS on Disodium Laureth Sulfosuccinate, this chemical may contain formaldehyde at a maximum level of 0.056%. The Panel noted that this level is less than the 0.076% formaldehyde limit established by the Panel in its final safety assessment on this ingredient, and is well below the threshold for any toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by disodium laureth sulfosuccinate in formulation would be even lower, considering that this ingredient is being used at concentrations up to 10% in rinse-off products and at concentrations up to 2% in leave-on products. At the maximum use concentration of 10%, the formaldehyde concentration would be no more than 0.006%. [IJT 34(S2): 70-83, 2015.]

Note: previously, the Panel had stated:

- Diazolidinyl Urea; 2008 RRsummary: Diazolidinyl Urea is a formaldehyde-releasing preservative, and the presence of free formaldehyde in cosmetic products preserved with this ingredient was addressed in the original discussion by noting that, due to the skin sensitivity of some individuals to formaldehyde, this ingredient should be used at the minimum effective concentration (not to exceed 0.2%) and that there was no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations that would exceed the limits recommended for formaldehyde (Elder 1990).

  In a presentation at the December 4 - 5, 2006 Panel meeting, Dr. John Merianos, with International Specialty Products, reviewed the chemistry of formaldehyde releasing preservatives. He emphasized the fundamental equilibrium that exists between these compounds and free formaldehyde itself, resulting in a steady state of availability of formaldehyde in aqueous solutions. Knowing the chemistry, he suggested, allows a calculation of the amount of free formaldehyde, which exists in a low balance. For example, at a use level of 0.6% Imidazolidinyl Urea (aq.), the steady state concentration of free formaldehyde is only 0.23 ppm, and for Diazolidinyl Urea at 0.5% (aq.), the level of free formaldehyde is only 0.40 ppm. Dr. Merianos concluded that not all formaldehyde releasing preservatives are equivalent, but, in all cases, the level of free formaldehyde is sufficiently low that maximum use levels of the preservatives cannot result in hazardous levels of formaldehyde.[IJT 27(S1): 98,101, 104, 2008.]

  - From original report: The Expert Panel for Cosmetic Ingredient Safety noted that Diazolidinyl Urea is a formaldehyde releaser. The Panel has previously concluded that the use of formaldehyde in cosmetic products is safe to the great majority of consumers. However, due to skin sensitivity of some individuals to formaldehyde it should be used at the minimum effective concentration (not to exceed 0.2 percent). There is no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations which would exceed the limits recommended for formaldehyde. The Panel noted that the results of tests with Diazolidinyl Urea, at low concentrations, were indicative of a potential for sensitization. [JACT 9(2): 229-45, 1990]

- DMDM Hydantoin; 2008 RRsummary: The Panel noted that the present practices of use of DMDM Hydantoin would not result in more than 0.2% free formaldehyde, which is the concentration limit for free formaldehyde in cosmetic products that was previously established by the Panel. The Panel also noted that the North American Contact Dermatitis Group (NACDG) patch test results for DMDM Hydantoin in large populations of patients with suspected allergic contact dermatitis indicated that the frequency of allergic reactions to DMDM Hydantoin has not increased over time. [IJT 77(S1): 105 107, 2008]

  - From original report: DMDM Hydantoin is a formaldehyde donor in aqueous media. A comparison of Ames test results from studies of a 55% DMDM Hydantoin product and formaldehyde indicates a similar number of revertants per formaldehyde equivalent. Furthermore, positive Ames test results were obtained for both substances with *Salmonella* strain TA98 in these studies. Because of similar mutagenic potencies and the observation of positive results in the same bacterial strain, it is probable that the mutagenic activity of the product is attributable to formaldehyde release. This probability is further supported by comparable mutagenic potencies of formaldehyde and a 55% DMDM Hydantoin product in the mouse lymphoma assay and positive results for the two in the chromosome aberrations assay. The possibility that preparations may contain, in addition to formaldehyde, other genotoxic agents has not been ruled out.

    Clinical studies revealed some observations of skin irritation subsequent to induction and challenge applications of DMDM Hydantoin formulations. Authors have suggested that such clinical findings are related to the release of formaldehyde from DMDM Hydantoin. The Panel has previously reviewed the safety of formaldehyde in cosmetic products and concluded: …

    … Use of DMDM Hydantoin at its current concentration of use in cosmetic products would not expose the consumer to concentrations of formaldehyde above the limit previously stated. [JACT 7(3): 245-77, 1988]

- Methenamine; 2011 RRsummary: The Expert Panel noted that methenamine functions as a formaldehyde releaser. A fundamental equilibrium exists between these releasers and free formaldehyde itself, resulting in a steady state of availability of formaldehyde in aqueous solutions. Data in the original safety assessment, along with all of the new data available since then, confirmed that, if the level of preservative is kept low, then the level of formaldehyde will not present any safety concerns. [IJT 30(S2): 106S-107S, 2011]
    - From original report: The Panel based their conclusion for Methenamine, in part, on the fact that Methenamine decomposes to ammonia and formaldehyde. Formaldehyde was previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Elder, 1984) and it was concluded by the Panel that the maximum concentration of formaldehyde considered safe for cosmetic use was 0.2%. Methenamine was approved for cosmetic use at a concentration not to exceed 0.16% so that the released formaldehyde concentration would not exceed 0.2% in formulation. An additional restriction on Methenamine is that it should not be used in products intended to be aerosolized since it was not concluded that formaldehyde is safe in aerosolized products. [JACT 11(4): 531-58, 1992]
- Polyoxymethylene Urea, 2011 RRsummary: The Expert Panel determined to not reopen this safety assessment and confirmed That Polyoxymethylene Urea is safe as a cosmetic ingredient, except those that are intended to be aerosolized, when formulated to ensure that concentrations of free formaldehyde do not exceed 0.2%. [IJT 30(S2): 117S-118S, 2011]
    - From original report; DISCUSSION: The Panel was concerned about the release of formaldehyde from Polyoxymethylene Urea. In their review of formaldehyde in 1984, the Panel determined that formaldehyde is an irritant at low concentrations, especially to the eyes and respiratory tract. Under experimental conditions it was teratogenic, mutagenic, and induced neoplasms. The Panel concluded in 1984 that the formulation and manufacture of cosmetic products should be such as to ensure use at the minimal effective concentration of formaldehyde, not to exceed 0.2% measured as free formaldehyde. That limitation was considered appropriate for Polyoxymethylene Urea as well.

      It could not be concluded in 1984 that formaldehyde is safe in cosmetic products intended to be aerosolized. Since the potential exists for formaldehyde to be released from Polyoxymethylene Urea, the Expert Panel for Cosmetic Ingredient Safety considers it inappropriate to use Polyoxymethylene Urea in aerosolized products.
    - From original report; CONCLUSION: On the basis of the animal, clinical, and use data presented in this report, the Panel concludes that Polyoxymethylene Urea is safe for use as a cosmetic ingredient. Cosmetics containing Polyoxymethylene Urea should be formulated to ensure that concentrations of free formaldehyde not exceed 0.2%. It cannot be concluded that Polyoxymethylene Urea is safe for use in cosmetic products intended to be aerosolized. [JACT 14(3): 204-20, 1995

Formats

(updated 10/29/2020)

Refer to report format outline: CIR Report Format Outline - updated 10-29-2020.docx, and to the report development outlines N:\CIR\New N Drive\Boilerplates & SOPs\templates\SLR Outline & Details_updated post-June 2022 mtg.docx; N:\CIR\New N Drive\Boilerplates & SOPs\templates\SLR Outline & Details - Botanical report_updated post-June 2022 mtg.docx

Abstract

Background

To convey relevant information in a consistent manner, the Expert Panel for Cosmetic Ingredient Safety has recommended that all Abstracts follow the same format. The Abstract should include a description of the ingredient or group of ingredients that were reviewed, a statement that the Panel reviewed the relevant data, and a summary of the conclusion. In some cases, additional information may be included.

In describing the ingredient group, all reviewed ingredients do not need to be listed; they will be listed in the conclusion. For example, “Silica and the related cosmetic ingredients” rather than “Silica and the related cosmetic ingredients Alumina Magnesium Metasilicate, Aluminum Calcium Sodium Silicate, Aluminum Iron Silicate, Hydrated Silica, and Sodium Potassium Aluminum Silicate”.

Boilerplates

Safe as Used (Without restrictions) Conclusion:

- Sentence 1: What was reviewed [NAME OF INGREDIENT OR INGREDIENT GROUP] as used in cosmetic formulations, and its FUNCTION.
- Sentence 2: The Panel reviewed relevant data related to the(se) ingredient(s).
- Sentence 3: Optional, as needed.
- Sentence 4: The Panel concluded that [NAME OF INGREDIENT OR INGREDIENT GROUP] was/were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment.
- NOTE: The Panel may ask to discuss a specific topic in the abstract. That discussion would comprise Sentence 3.

For Safe with Qualifications Conclusion:

- As above, but also include nature of and reason for qualification in Sentence 3.

For Insufficient Data Conclusion:

- As above, but include short statement about the nature of the insufficiencies in Sentence 3. The report discussion will contain the detailed listing of data needs.

For Unsafe Conclusion:

As above, but:

- Sentence 3 could include brief reason for unsafe decision, as stated in the conclusion.
- Sentence 4 should read: The Panel concluded that [NAME OF INGREDIENT OR INGREDIENT GROUP] is/are not safe under its/their intended conditions of use.

When decision is based on read-across:

- The Panel noted gaps in the available safety data for some of the [ingredient group] in this safety assessment. The available data on many of the ingredients are sufficient, however, and similarity between structure activity relationships and biologic functions in cosmetic concentrations of use and can be extrapolated to support the safety of the entire group.

When the report is on a botanical:

- Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With [*genus species*]-derived ingredients, the Panel was concerned about the presence of [*list constituents of concern*] in cosmetics. Industry should use good manufacturing practices to limit impurities.

Conclusion

Boilerplates

If the number of ingredients in a group is 5 or less, list all ingredients in the conclusion sentence. If there are more than 5 ingredients in a group, refer to the ingredients as "the following:" and list the ingredients in a bulleted list following the sentence. An example is provided in the Safe as Used section, below.

Safe as Used:

Three ingredients or less:

The Expert Panel for Cosmetic Ingredient Safety concluded that [LIST ALL INGREDIENTS]* are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

More than 3 ingredients:

The Expert Panel for Cosmetic Ingredient Safety concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

[LIST ALL INGREDIENTS]

For ingredients not in use, identify with an asterisk (*), and include the following footnote:

** Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

For hair dyes:

The Expert Panel for Cosmetic Ingredient Safety concluded that [ingredient] is safe for use as a hair dye ingredient in the present practices of use and concentration described in this safety assessment.

Safe with Qualifications:

The Expert Panel for Cosmetic Ingredient Safety concluded that [LIST ALL INGREDIENTS] are safe in cosmetics in the present practices of use and concentration described in this safety assessment when [LIST QUALIFICATION].

Examples of qualifications include:

- …formulated to be non-sensitizing. (**It should be noted** that the caveat for sensitization is typically due to concern for multiple exposure)
- …formulated to be non-irritating.
- … safe for use as pH adjusters in cosmetic formulations
- … The Panel cautions that ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.
- …formulated to be non-respirable.
- …the concentration of [x] does not exceed [%].

Also include asterisk and footnote (given above) for ingredients not in use.

Insufficient Data:

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination that [LIST ALL INGREDIENTS] is/are safe under the intended conditions of use in cosmetic formulations.

For ingredients not in use, identify with1 or 2 asterisks (*), as appropriate, and include the following footnote:

** There are currently no uses reported for these ingredients.*

NOTE: A detailed description of the data needs should be included in the discussion section of the report, preferably in bulleted format.

Not Safe:

Based on the data included in this report, and [provide brief summary of reason for decision], the Expert Panel for Cosmetic Ingredient Safety concluded that [LIST ALL INGREDIENTS] is not safe for use as a cosmetic ingredient.

Examples of reasons for decision include:

…X is a potential human sensitizer at use concentrations,…

…X has been found to be a human carcinogen…

Mixed Conclusion:

The Expert Panel for Cosmetic Ingredient Safety concluded that [LIST ALL INGREDIENTS] is/are unsafe for use in leave-on products, and that the available data are insufficient to make a determination that [LIST ALL INGREDIENTS] is/are safe under the intended conditions of use.

If Decision is different than a previous decision of the Expert Panel for Cosmetic Ingredient Safety, add following statement:

This conclusion supersedes the earlier conclusion issued by the Panel in [year of publication of previous decision].

Re-Review Summary

First Paragraph

In a safety assessment of (insert name/names) published in [YEAR], the Expert Panel for Cosmetic Ingredient Safety

(Panel) stated that (this ingredient/these ingredients) (is/are[give conclusion]. (citation)). The Panel reviewed newly available studies since that assessment, along with updated information regarding product types and concentrations of use, and did not reopen this safety assessment. The Panel confirmed that (insert name/names) (is/are) safe as (a) cosmetic ingredient(s) in the practices of use and concentration as given in Table 1.

Hair Dyes

Hair dyes as "consumables"

Example of Discussion Language

...the Panel noted that data supplied by industry indicate that during the hair dyeing procedure, Hydroquinone is a "consumable." This means that the actual concentration of Hydroquinone decreases sharply as the color-forming reaction proceeds. Therefore, the amount of Hydroquinone that may be absorbed during the hair dyeing process is limited both by the decreasing concentration of available Hydroquinone and by the length of time the hair dye is applied before being rinsed off.

Hair Dye Ingredients

(**updated 9/2009**)

Coal Tar Hair Dyes

Background

Hair dye ingredients containing coal tar are not subject to the same FDA requirements as other hair dyes. Since 1938, FDA law exempts coal tar hair dye products from the principal adulteration and color additive provisions in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation.[FDA, 1979] The caution statement reads as follows:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

In 1991-1992, the Panel addressed the question of sensitization testing for coal tar hair dye products. There was a general consensus among dermatologists that screening of patients for sensitization (allergic contact dermatitis) should be conducted by the procedures used by the North American Contact Dermatitis Group and the International Contact Dermatitis Group.[North American Contact Dermatitis Group 1980; Eiermann et al. 1982; Adams et al. 1985] Basically, these procedures state that the test material should be applied at an acceptable concentration to the patient, covered with an appropriate occlusive patch, and evaluated for sensitization at 48 and 72 hours after application. The Expert Panel for Cosmetic Ingredient Safety has cited the results of these studies in its safety assessments of cosmetic ingredients. The Panel advised the cosmetics industry to recommend that the open patch test be evaluated 48 hours after application of the test material.

References

Adams, R.M., H.I. Maibach, W.W. Clendenning, et al. 1985. A five-year study of cosmetic reactions. *J Am Acad Dermatol* 13:1062-1069.

Eiermann, H.J. W. Larsen, H.I. Maibach, et al. 1982. Prospective study of cosmetic reactions: 1977-1980. *J Am Acad Dermatol* 6:909-917.

Food and Drug Administration (FDA). 1979. Cosmetic product warning statements: coal tar hair dyes containing 4-methoxy-m-phenylenediamine (2,4-diaminanisole) or 4-methoxy-m-phenylenediamine sulfate (2,4-diaminoanisole sulfate). *Federal Register* 44:59509-59510.

North American Contact Dermatitis Group. 1980. Patch testing in allergic contact dermatitis. Evaston IL:American Academy of Dermatology.

Boilerplates

Hair Dye Caution Statement - FDA labeling

COSMETIC USE section:

[INGREDIENT] is considered a coal tar hair dye for which regulations require caution statements and instructions regarding patch tests in order to be exempt from certain adulteration and color additive provisions of the of the Federal Food, Drug, and Cosmetic Act. In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Product labels shall also bear patch test instructions for determining whether the product causes skin irritation. However, whether or not patch testing prior to use is appropriate is not universally agreed upon. The Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 h after application of the test material and prior to the use of a hair dye formulation. Conversely, a report in Europe suggests that self-testing has severe limitations, and may even cause morbidity in consumers.[Thyssen et al., 2012; Goossens, 2012] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the Food, Drug, and Cosmetic Act.

References

Thyssen JP, Sosted H, Uter W, et al. Self-testing for contact sensitization to hair dyes - scientific considerations and clinical concerns of an industry-led screening programme. Contact Dermatitis. 2012;66(6):300.

Goossens A. Self-testing for contact sensitization to hair dyes. Contact Dermatitis. 2012;66(6):299.

Hair dye adulteration exemption:

DISCUSSION

[The Panel has determined that the data are sufficient to support safety of this ingredient in hair dye products, which are rinsed-off after application. The Panel recognizes that**] OR [**The Panel recognizes that [INGREDIENT] is used as a hair dye ingredient and that irritation and sensitization data are not available in all cases. However**,]** hair dyes containing [INGREDIENT], as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that [ingredient] is safe for use as a hair dye ingredient in the present practices of use and concentration described in this safety assessment.

Hair Dye Epidemiology

Updated 12/2018

Background

see Hair Dye Epidemiology Resource Document https://www.cir-safety.org/sites/default/files/Hair_Dye_Epi_12-2018.pdf

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct dyes consist of preformed colors. Epidemiology studies that seek to determine links, if any, between hair dye use and disease provide broad information and have been considered by the Expert Panel, although these studies do not specifically address the safety of individual hair dye ingredients.

The Panel reviews new epidemiological studies addressing the personal use of hair dyes as these studies become available. Table 1 summarizes the studies specifically addressing bladder cancer, lymphoma, leukemia, bladder, and breast cancer. Relevant meta-analytical studies included here address glioma and breast cancer, in addition to bladder and blood cancers. Occupation as a hairdresser, barber, or cosmetologist involves exposures to multiple products used during work, making it difficult to use the results of such studies to inform the assessment of the risk, if any, associated specifically with hair dyes. Accordingly, such studies are not summarized in the resource document.

Boilerplates

HAIR DYE EPIDEMIOLOGY*:*

Hair dyes may be broadly grouped into oxidative (permanent) and direct (temporary or semi-permanent) hair dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color. [INGREDEINT] is a direct, non-oxidative hair dye ingredient. While the safety of individual hair dye ingredients is not

addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. A detailed summary of the available hair dye epidemiology data is available at https://www.cir-safety.org/cir-findings.

SUMMARY Section*:*

The most recent comprehensive review of available epidemiology studies concluded that there is insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. A summary of the available hair dye epidemiology data is available at https://www.cir-safety.org/cir-findings.

DISCUSSION:

In considering hair dye epidemiology data, the Expert Panel for Cosmetic Ingredient Safety concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints, based on lack of strength of the associations and inconsistency of findings. Use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies.

Information Sources BP language (7/12/17)

Background

At the December 2016 meeting, the Panel stated that the information sources used to identify information for use in Expert Panel for Cosmetic Ingredient Safety reports should be included in our safety assessments. Based on that request, the following statements were developed for inclusion in the Introduction of every report, and a listing of the typical search engines and websites are listed on the CIR webpage.

Boilerplate

INTRODUCTION:

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR)website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Irritation Potential

Background

Although studies may demonstrate the potential for dermal or ocular irritation, a product can be formulated so that irritation does not occur. The concern for irritation potential is addressed in the Discussion and the Conclusion.

Boilerplates

DISCUSSION

The Panel was concerned that the potential exists for dermal irritation with the use of products formulated using [INGREDIENT(S)]. The Panel specified that products containing [INGREDIENT(S)] must be formulated to be non-irritating.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that [INGREDIENT(S)] is/are safe in the present practices of use and concentration when formulated to be non-irritating.

Leave-on and Rinse-off definitions

In response to the Expert Panel for Cosmetic Ingredient Safety's request for a statement discriminating between "rinse-off" and "leave-on" products, the following statement has been recommended by the CTFA Scientific Advisory Committee's Executive Committee:

- A "rinse-off" product is one designed to be applied to the hair or body in diluted or undiluted form for a short period of time (less than 1 hour) followed by thorough rinsing. Operational examples include shampoos, hair conditioners, and depilatories.
- A "leave-on" product is a product intended to be applied to the skin and left in place for a long enough time to achieve the desired benefit.

Nitrosamine formation caveats

BACKGROUND

The ingredient being reviewed has an amine group that can react with NO_2 to form the N-N=O moiety, which can be carcinogenic....

Where the concern is over nitrosamine formation and possible presence of nitrosamines as impurities, we have to handle it differently. The safety assessment of morpholine presented that issue: easy nitrosation to form *N*-nitrosomorpholine and the presence of *N*-hydroxyethylmorpholine as an impurity, independent of subsequent use in a formulation that would contain an *N*-nitrosating agent. Unfortunately, we only captured the former in the discussion, and it was an insufficient data finding, so nothing was said in the conclusion.

BOILERPLATE

The current language is:

DISCUSSION

[INGREDIENT(S)] should not be used in cosmetic products in which *N*-nitroso compounds can be formed. **[*Discuss rationale*.]**

CONCLUSION

The Panel cautions that ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. **[the Panel has included, and has not included, this in the Conclusion; the Panel needs to specify]**

The nitrosamine formation caveat has been variously expressed as:

- …should be formulated to avoid the formation of nitrosamines
- ... should not be used with N-nitrosating agents
- ... should not be used in products containing N-nitrosating agents

for hairdyes: unless the Panel instructs otherwise, the issue of nitrosamine formation, and the caveat, are addressed in the Discussion section, but the caveat is not included in the Conclusion.

pH Adjusters

Examples of Discussion Language

- While Maleic Acid may function in cosmetics as a fragrance ingredient or a pH adjuster, this safety assessment considered only its use as a pH adjuster. The Expert Panel for Cosmetic Ingredient Safety recognized that while Maleic Acid itself may be a dermal and/or ocular irritant, its use as a pH adjustor in cosmetic formulations dictates that most of the acid will be neutralized into various maleate salts. Furthermore, the concentration of Maleic Acid used is dependent on the alkaline content of the formulations. Therefore, the concentration of free Maleic Acid is expected to be low, and systemic toxicity is not expected to be a concern. The safety of Maleic Acid as a pH adjustor should not be based on the concentration of use, but on the amount of free Maleic Acid that remains after neutralizing the formulation.

- ...while Formic Acid itself may be a dermal and/or an ocular irritant, its use as a pH adjuster in cosmetic formulations dictates that most of the acid will be neutralized into various formate salts. Furthermore, the concentration of Formic Acid used is dependent on the alkaline content of the formulations. In any case, the concentration of free Formic Acid is expected to be low, and systemic toxicity is not expected to be a relevant issue. The safety of Formic Acid as a pH adjuster, therefore, should not be based on the concentration of use, but on the amount of free Formic Acid that remains after neutralizing the formulation.
- The Panel noted that the only significant toxic effect of Malic Acid was irritation to the skin and eyes, which would be predicted based on their pH. Since Malic Acid is used as a pH adjuster in cosmetics, the irritating property of the acid would be minimized in formulated products.
- The safety of inorganic hydroxide ingredients as pH adjusters should not be based on the concentration of use, but on the concentration of free hydroxide ions that remain in a formulation. In general, the concentration of free hydroxide ion in a formulation depends on the acidity of the other ingredients in the formulation. The concentration of free hydroxide ions is expected to be low in cosmetic formulations, except in some depilatory and hair-straightening formulations.

CONCLUSION (when specified by the Panel)

On the basis of the animal and clinical data included in this report, the Panel concludes that [ingredient(s)/ group] is/are safe for use as pH adjusters in cosmetic formulations

Phototoxicity

Example of Discussion Language

With increasing ethoxylation, the fatty acid components of the Stearic Acid moiety have less potential to produce phototoxicity and photosensitivity in humans and animals. Since there were no phototoxicity or photosensitivity reactions in subjects tested with PEG-2 Stearate and PEG-8 Stearate, the Panel concluded that it is reasonable to extrapolate these data to the higher molecular weight species (e.g. PEG-20, -32, -40, -50, -100, and -150 Stearates). The converse of this latter statement, that is, the extrapolation of high molecular weight species to lower molecular weight species, may or may not be true.

Read-Across Data

Boilerplate

ABSTRACT and DISCUSSION

The Panel noted gaps in the available safety data for some of the [ingredient group] in this safety assessment. The available data on many of the ingredients are sufficient, however, and similarity between structural activity relationships and biologic functions in cosmetic concentrations of use and can be extrapolated to support the safety of the entire group.

Skin penetration studies

Study Design Preferences

The Panel stated that skin penetration studies using viable skin are preferable to those using cadaver skin. Studies using cadaver skin measure penetration of unmodified compounds only, and do not provide information on the influence of other factors such as skin metabolism. Therefore, studies using viable skin are more useful in assessing the safety of cosmetic ingredients.

Penetration Enhancement

Boilerplate

DISCUSSION

[INGREDIENT/FAMILY] can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients

whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

Transmission of Infectious Disease

(BSE, HIV, Other)

updated 11/2010

BACKGROUND

The Panel has expressed concern about the inherent danger of transmission of infectious agents with use of human or animal derived cosmetic ingredients. For example, cosmetics may include cattle derived ingredients, including tallow and its derivatives, albumin, brain extract, brain lipid, cholesterol, fibronectin, sphingolipids, and collagen. Bovine Spongiform Encephalopathy (BSE) is an example of a pathogenic agent that may be transmitted through use of animal derived ingredients containing pathogenic viruses or infectious agents. For cosmetic ingredients of human origin, Human Immunodeficiency Virus (HIV), and Creutzfeldt-Jacob disease (CJD) are examples of pathogenic agents that may be of concern.

In evaluating the safety of those cosmetic ingredients that are derived from animal or human sources, the specific sources, processing and manufacturing procedures and routes of potential exposure should be considered. The Panel believes that these ingredients must be free of detectible pathogenic viruses or infectious agents.

Not all animal or human derived cosmetic ingredients raise the same levels of concern. Tallow derivatives, particularly fatty acids and glycerin, are the predominant bovine ingredient used by the cosmetic industry. Tallow is an animal (mostly cattle) derived fat that is heat processed, during which the protein components and fat components are separated. The protein component is part of the insoluble impurities fraction that remains in the tallow after rendering. Any risk of disease transmission is a result of protein that is present as an impurity in the tallow. Tallow containing no more than 0.15 % hexane-insoluble impurities is considered to be protein-free tallow and is considered safe for consumption by animals. FDA concluded that tallow has negligible risk of transmitting BSE and that tallow derivatives, which undergo additional processing, do not pose a risk of transmitting the agent that causes BSE to humans.

Panel assessments of tallow containing ingredients do not need to include cautions about the transmission of infectious diseases. The reports, however, should state that tallow derivatives which may be used to make cosmetic ingredients must be made from tallow containing a maximum level of insoluble impurities of 0.15% in weight.

In discussing the potential for transmission in Expert Panel for Cosmetic Ingredient Safety reports, the writer should take care to specify the source of the potentially infectious material, distinguish between human or animal derived cosmetic ingredients, and word the discussion accordingly.

References

Federal Register: September 7, 2005 (Volume 7, Number 172).

Boilerplates

For Animal-derived cosmetic ingredients:

DISCUSSION

The Panel was also concerned with the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. The Expert Panel for Cosmetic Ingredient Safety stressed that these ingredients must be free of detectible pathogenic viruses or infectious agents (e.g. Bovine Spongiform Encephalopathy (BSE)). Suppliers and users of these ingredients must accept responsibility for assuring that these ingredients are risk-free. Tests to assure the absence of a pathogenic agent in the ingredients, or controls to assure derivation from pathogen-free sources are two approaches that should be considered.

For Human-derived cosmetic ingredients:

DISCUSSION

The Panel was also concerned with the risks inherent in using human-derived ingredients, namely the transmission of infectious agents. The Expert Panel for Cosmetic Ingredient Safety stressed that these ingredients must be free of detectible pathogenic viruses or infectious agents (e.g. Human Immunodeficiency Virus (HIV), and Creutzfeld-Jacob disease (CJD)). Suppliers and users of these ingredients must accept responsibility for assuring that these ingredients are risk-free. Tests to assure the absence of a pathogenic agent in the ingredients, or controls to assure derivation from pathogen-free sources are two approaches that should be considered.

For Tallow-derived cosmetic ingredients:

DISCUSSION

updated -- use: The Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. Although tallow may be used in the manufacture of [INGREDIENTS] in this report and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

old: To assure the absence of a pathogenic agent in the ingredients, [LIST TALLOW CONTAINING INGREDIENTS] must be made from tallow containing a maximum level of insoluble impurities of 0.15% in weight.

For Plant- and Tallow-derived cosmetic ingredients (combined wording):

DISCUSSION

The Panel acknowledged that some of the [INGREDIENTS] may be formed from plant-derived or animal-derived constituents. The Panel thus expressed concern regarding pesticide residues and heavy metal that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to sufficiently limit amounts of such impurities in an ingredient before blending them into cosmetic formulations. Additionally, the Panel considered the risks inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal-derived, the Panel notes that tallow is highly processed, and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

Usage Data Gaps

Note: put early in the Discussion section, when directed by the Panel

Boilerplates

DISCUSSION

The Expert Panel for Cosmetic Ingredient Safety recognizes that there are data gaps regarding use and concentration of this/these ingredient(s). However, the overall information available on the types of products in which this ingredient is used, and at what concentration, indicate a pattern of use, which was considered by the Panel in assessing safety.

CONCLUSION

*Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group. **[this is used as a footnote in the Conclusion]**