ADMIN

Boilerplate Guidance Document and Re-Review Summary Formats

EXPERT PANEL MEETING

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume MMF
Senior Director, CIR
Date: May 19, 2023
Subject: Boilerplate Guidance Document and Re-Review Summary Formats

At the September 2022 meeting, a document capturing standard language used in CIR reports, and the standard operating procedures (SOPs) used to develop that language, was provided for review. At that time, comments were made on several of the boilerplates. Accordingly, an update to those boilerplates is provided for review and comment (*BoilerplateGuidance_Format-SOPs_062023*). Please note, the document contained herein only includes those boilerplates for which there were comments. The entire document that was originally provided in September is available on the CIR website (https://www.cir-safety.org/meeting/162nd-expert-panel-meeting).

Additionally, over the last few meetings, there have been discussions regarding the wording of re-review summaries. Consequently, included herein, are templates proposed for use with re-review summaries for consideration and comment. Please note that 2 templates are provided – 1 for reports being reviewed for the first time (*RRSummaryTemplate_Format-SOPs_062023*), and the other for reports for which a re-review was previously considered and the original conclusion reaffirmed (*RRSummary-Previous RR-Template_Format-SOPs_062023*).

Botanicals

Concern for multiple exposures to constituents of concern

ABSTRACT

[*Genus species***]**-derived ingredients comprise, in part, constituents that may cause adverse effects. Because final product formulations may contain multiple botanicals, each possibly 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 **[**potential adverse effect (e.g., constituents of concern)**]** in cosmetics. Additionally, industry should use good manufacturing practices to limit impurities, such as heavy metals and pesticide residues, in cosmetic formulations.

DISCUSSION

Because final product formulations may contain multiple botanicals, each possibly 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. For **[***Genus species***]**-derived ingredients, the Panel was concerned about the presence of [give examples of constituents of concern] in cosmetics, which could result in **[**list adverse effects/endpoints**]**. Therefore, when formulating cosmetic products, manufacturers should avoid reaching levels of plant constituents that may cause sensitization or other adverse health effects.

Contaminants, Residues, Impurities

Aflatoxin

DISCUSSION

While aflatoxin has been detected in **[**plant (part) where aflatoxins were found**]**, the Panel believes that aflatoxin should not be present in **[**botanical/ingredient**]**. 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]

Other/Previous Examples of Discussion Language

- 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

DISCUSSION

To Be Used in Most Cases

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 **[**ingredient(s)**]** before blending them into cosmetic formulations. [For examples, see: Alkyl PEG Ethers; PEGs Distearate reports]

Another Possibility

The Panel was concerned about the possibility of the presence of residual starting materials (i.e., ethylene oxide and propylene oxide) used in the manufacture of **[**ingredient/family**]** 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 limit these impurities from the ingredients before blending them into cosmetic formulations.

Appropriate for use with Ethoxylated Ingredients

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]

Examples of Discussion Language that have been Used

- 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] [updated language suggested, as given above]
- 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

ABSTRACT

Industry should continue to use good manufacturing practices to limit impurities, such as heavy metals, in cosmetic formulations.

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 formulations.

Boilerplate - botanicals

ABSTRACT (if there are no constituents of concern)

Industry should use good manufacturing practices to limit impurities, such as heavy metals and pesticide residues, that could be present in cosmetic formulations. **[if there are constituents of concern, see that boilerplate, under 'Botanicals']**

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 in cosmetic formulations.

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.

Endocrine Activity

Background

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

DISCUSSION

To Be Used

The Panel reviewed data suggesting potential endocrine activity in in vitro and/or in vivo studies [as appropriate] with **[**ingredient**]**; however, the levels required or reported are not relevant to cosmetic use. 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.

OR

The Panel reviewed data suggesting potential endocrine activity in studies conducted with [ingredient] and concluded the results did not support characterizing this ingredient as demonstrating endocrine activity. 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.

Example of Discussion Language Used Previously

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

Boilerplates

DISCUSSION – developed using information from the 2013 formaldehyde report (IJT 32 (S4), 5-32)

According to **[**information source**]** on **[**ingredient**],** this chemical may contain formaldehyde at a maximum level of **[**x%**]**. The Panel noted that this level is less than the 0.074% formaldehyde limit established by the Panel in the final safety assessment of formaldehyde published in 2013 and is well below the threshold for toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by **[**ingredient**]** in formulation would be even lower, considering that this ingredient is being used at concentrations up to **[**y%**]** in rinse-off products and at concentrations up to [z%] in leave-on products. At the maximum use concentration of **[**y or z%, whichever is greater**]**, the formaldehyde concentration would be no more than **[**n%**]**.

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

ABSTRACT

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 rationale 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 the report is on a botanical, and there are constituents of concern, include:

- **[***Genus/species***]**-derived ingredients comprise, in part, constituents that may cause adverse effects. 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 **[**identify potential concern (e.g., potential sensitizers) and give examples of constituents of concern**]** in cosmetics. Additionally, industry should continue to use good manufacturing practices to minimize impurities, such as heavy metals and pesticide residues.

When decision is based on read-across, include:

- 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.

CONCLUSION

Boilerplates

If the number of ingredients in a group is 3 or less, list all ingredients in the conclusion sentence. If there are more than 3 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 this caveat for sensitization is typically in botanical reports, due to concern for aggregate exposure to constituents of concern from multiple botanical ingredients in a single formulation)
- … formulated to be non-sensitizing, which may be based on a quantitative risk assessment (QRA)
- …formulated to be non-irritating.
- … formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA)
- … 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 of safety for [LIST ALL INGREDIENTS] under the intended conditions of use in cosmetic formulations.

For ingredients not in use, identify with asterisk (*), 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.

Unsafe:

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 [ingredient(s)] is/are not safe for use as [a] cosmetic ingredient(s).

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:

Examples:

The Expert Panel for Cosmetic Ingredient Safety concluded that **[**ingredient(s)**]** is/are safe for use as **[**function**]** in cosmetic formulations, and that the available data are insufficient to determine the safety of [ingredient(s)] for any other functions.

The Expert Panel for Cosmetic Ingredient Safety concluded that Polysilicone-2, Polysilicone-4, and Polysilicone-5 are safe when used to coat metal oxide particles and that the data are insufficient to determine safety if these ingredients are used independently in cosmetics.

The Expert Panel for Cosmetic Ingredient Safety concluded that Pyrocatechol is unsafe for use in leave-on products, and that the available data are insufficient to support the safety of Pyrocatechol as used in hair dyes.

Hair Dyes

Coal Tar Hair Dyes

COSMETIC USE section (Hair Dye Caution Statement - FDA labeling)

[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

HAIR DYE EPIDEMIOLOGY section of report*:*

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*:*

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 Panel 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.

Nitrosamine formation caveat

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.

DISCUSSION

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

CONCLUSION (include this statement as part of the conclusion)

The Panel cautions that ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed.

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 (the caveat is not included in the Conclusion)

pH Adjusters

DISCUSSION

For an acid

While **[**ingredient**]** 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 **[**ingredient**]** used is dependent on the alkaline content of the formulations. In any case, the concentration of free [ingredient] is expected to be low, and systemic toxicity is not expected to be a relevant issue. The safety of [ingredient] as a pH adjuster, therefore, should not be based on the concentration of use, but on the amount of free [ingredient] that remains after neutralizing the formulation.

For inorganic hydroxides

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. [As appropriate: The concentration of free hydroxide ions is expected to be low in cosmetic formulations, except in some depilatory and hair-straightening formulations.]

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.

[INGREDIENT/FAMILY NAME]

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the [REPORT TITLE] in [YEAR].[citation] The Panel concluded [state conclusion]. Upon re-review in [MONTH YEAR, if known], the Panel reaffirmed the original conclusion, as published in [YEAR].[citation]

Because it has been at least 15 years since the prior re-review was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel again considered whether the safety assessment should be reopened. At its [MONTH YEAR] meeting, the Panel considered updated [YEAR] information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database[citation] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council (Council)[citation] [Provide comparison of current and historical use (using the year(s) given in previous RR) data).] The cumulative frequency and concentration of use data are presented in Table 1.

In [month year], an extensive search of the world's literature was performed for studies dated [YYYY (5 yr prior to previous re-review)] forward, and new data were found.[all citations] [Include sentence(s) to identify anything of note.] **[**Or, if appropriate: In [month year], an extensive search of the world's literature was performed for studies dated [YYYY] forward. No relevant new data were found.**]**

In summary, the Panel reviewed [YEAR] frequency and concentration of use data, in addition to any new, available, relevant safety data. [**Or, if appropriate:** The Panel reviewed [YEAR] frequency and concentration of use data and noted the lack of any new, available, relevant safety data.] Considering this information, as well as the information provided in the original safety assessment and the prior re-review document, the Panel once again reaffirmed the [YEAR of original report] conclusion.

Table 1. Frequency (YYYY/YYYY) and concentration (YYYY/YYYY) of use according to likely duration and exposure by product category. [**See \\PCPC-Store\Department$\CIR\New N Drive\Boilerplates & SOPs\templates to get template for use table**]

REFERENCES

[include all citations, including all references that were reviewed by the Panel for the RR]

[INGREDIENT(S)/FAMILY NAME]

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published the [REPORT TITLE] in [YEAR].[citation] The Panel concluded [state conclusion].

Because it has been at least 15 years since the final report was published, in accordance with Cosmetic Ingredient Review (CIR) Procedures, the Panel considered whether the safety assessment should be reopened. At its [month year] meeting, the Panel reviewed updated [YYYY] information regarding product types and ingredient use frequencies as reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database[citation] and maximum use concentrations provided in response to the survey conducted by the Personal Care Products Council (Council).[citation] [Provide comparison of current and historical use data.] The cumulative frequency and concentration of use data are presented in Table 1.

In [month year], an extensive search of the world's literature was performed for studies dated [YYYY (5 yr prior to original report)] forward, and new data were found.[all citations] [Include sentence(s) to identify anything of note.] **[**Or, if appropriate: In [month year], an extensive search of the world's literature was performed for studies dated [YYYY] forward. No relevant new data were found.**]**

In summary, the Panel reviewed [YEAR] frequency and concentration of use data, in addition to any new, available, relevant safety data. **[**Or, if appropriate: The Panel reviewed [YEAR] frequency and concentration of use data and noted the lack of any new, available, relevant safety data.] Considering this information, as well as the information provided in the original safety assessment, the Panel reaffirmed the [YYYY] conclusion for [ingredient(s)/family].[citation]

Table 1. Frequency (YYYY/YYYY) and concentration (YYYY/YYYY) of use according to likely duration and exposure by product category. [**See \\PCPC-Store\Department$\CIR\New N Drive\Boilerplates & SOPs\templates to get template for use table**]

REFERENCES

[include **all** citations, including all references that were reviewed by the Panel for the RR]