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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

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Date: May 23, 2022

Subject: GRAS determination and its role in the safety assessment of cosmetic ingredients

Enclosed is a draft white paper to clarify the Panel's view on Generally Recognized as Safe (GRAS) determination, as well as how to apply the GRAS status in the safety assessment of cosmetic ingredients. This iteration of the document, named *whitepaper_GRAS_062022*, is to be reviewed herein for the first time by the Panel.

The document concisely introduces FDA's current approach to the GRAS provision, with specific focus on its voluntary GRAS notification program. Notably, self-determination of GRAS status by manufacturers is allowed through FDA's notification procedure. Under GRAS notice inventory, FDA's opinion on the notified substance does not affirm the GRAS status under the conditions of its intended use. Furthermore, FDA's response must be considered in context based on the data available to reviewers at a point in time, because scientific knowledge and information about a particular ingredient can evolve over time. Therefore, when using GRAS status as a factor in the safety assessment of cosmetic ingredients, it should be considered with other relevant assessment factors that contribute to the determination of a safety margin, on a case-by-case basis.

It is requested that the Panel review the draft white paper and determine whether the document represents their view on the recognition of GRAS status based on a voluntary self-affirming mechanism, as well as how to apply the supporting materials associated with GRAS notifications in their review process of cosmetic ingredients safety. The Panel should determine how, and to what extent, the document should be revised.

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EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

White Paper

GRAS Status and the Safety Evaluation of Cosmetic Ingredients

06/2022 - DRAFT

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This resource document was prepared by Jinqiu Zhu, Ph.D., D.A.B.T., E.R.T., D.C.S.T., CIR Toxicologist.

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BACKGROUND

Under the regulations of the Food, Drug, and Cosmetic Act (FDCA), substances generally recognized as safe (GRAS) refer to a group of substances used in food that are exempted from premarket approval by the US Food and Drug Administration (FDA).[1,2] Accorded GRAS status, a substance should be generally recognized by qualified experts as having been adequately shown through scientific procedures or experience based on common use in food, to be safe under the conditions of its intended use and where the intended route of exposure is oral.[1,3,4] General recognition of safety through scientific procedures relies upon the application of scientific principles, as well as commonly available and accepted scientific data, information, or methods, which satisfy the safety standard for a food additive under the FDCA.[1] Thus, the status of a GRAS ingredient as used in food is also considered by the Expert Panel for Cosmetic Ingredient Safety (Panel) when assessing weight of evidence (WoE) in the safety evaluation of cosmetic ingredients. The Panel notes additional attention should be given when exposure routes other than oral are investigated for accessing the systemic toxic potential of a cosmetic ingredient and determining the margin of safety. The inventory of GRAS notices, under the voluntary GRAS notification program, lists self-certified GRAS substances; the FDA's no question letters on GRAS notices do not affirm the GRAS status under Title 21 of the Code of Federal Regulations (21 CFR) 170.35. Therefore, it is necessary to clarify for the Panel how a GRAS position is justified, as well as how a GRAS designation, based on available data and information, is weighted during the Panel's judgment on ingredient safety.

CURRENT REGULATIONS AND RULES ON GRAS DETERMINATION

The FDA published several lists of substances that are used in food or food packaging on the basis of the GRAS provision, appearing in 21 CFR Parts 182, 184, and 186, which serve as a reliable source to identify the GRAS status of food substances.[1] Opinions and conclusions from some GRAS substances (SCOGS) reports can also be accessed via the FDA SCOGS database.[5] However, it is impracticable to list all substances that are GRAS for their intended use because the application of a GRAS substance is not subject to review and approval by the FDA. A voluntary notification procedure allows any stakeholder to notify the FDA of a conclusion that a substance is GRAS under the conditions of its intended use.[6] This is based on the criteria for GRAS status as clarified by the final rule 81 FR 54960, which, at the same time, eliminates the petition process for GRAS affirmation.[7] The FDA would then conduct a substantive review of the GRAS notice to evaluate whether the notice provides a sufficient basis for a GRAS conclusion, including information identified from alternative sources (i.e., not covered by the notice). As the FDA clarifies in 62 FR 18938, the safety standard for a GRAS substance is identical to the safety standard for food additives. It should be noted, however, in response to a GRAS notice, that a "no questions letter" issued by the FDA does not indicate a determination has been reached regarding the GRAS status of the notified substance under the conditions of its intended use.[7] The FDA further states that it is the continuing responsibility of the notifier to ensure that marketed products are safe and compliant with all applicable legal and regulatory requirements.

Unlike food additives, a determination to justify that an ingredient is GRAS can be made by qualified experts outside of the FDA.[7] Criteria for eligibility for classification as GRAS can be satisfied either through experience based on common use in food or through scientific procedures. Scientific procedures require consideration of both the data supporting the safety of the substance and the probable exposure level (e.g., oral intake amount and patterns of use). Scientific data appropriate to establish safety, regardless of whether they are published or unpublished, should be generally accepted and publicly

available. In typical cases, a submitted GRAS application should describe a mixture of information published in peer-reviewed journals, or from reliable sources (e.g., textbooks), as well as the findings of unpublished studies to corroborate safety.

The subject matter experts, with expertise appropriate to address the applicable safety questions, may provide an opinion on whether a manufacturer's evaluation of the available data and information supports a GRAS claim. A published opinion may further serve as “generally accepted” evidence to support a conclusion of GRAS status in a notice submitted to the FDA, which announces a reviewed ingredient meets GRAS criteria.[7] A science-based safety standard for food additives should apply to a conclusion of GRAS status as claimed in a GRAS notice. Following the structured GRAS notification procedure, the FDA should evaluate all evidence involved in the submitted notice and make a decision whether this information provides a sufficient basis for a GRAS conclusion. Three types of letters might be issued based upon a case-by-case evaluation: i) the FDA has no questions about the notifier's conclusion (no questions letter); ii) the notice does not provide a sufficient basis for a GRAS determination (insufficient basis letter); and, iii) ceased to evaluate at the notifier's request (cease to evaluate letter).[6,8] The FDA has acknowledged the potential that a “no questions letter” could be misinterpreted; it does not necessarily mean the FDA has reached a conclusion of GRAS status. In fact, a GRAS notice reflects the conclusion of the notifier, not a finding by the FDA. Further, it is the notifier, rather than FDA, that should be responsible for the conclusion of GRAS status.

In every response to the notifier’s determination, the FDA clearly states they do not make the determination regarding the GRAS status of the subject use of the notified substance.[7] All GRAS notices that the FDA has received can be accessed on a web inventory,[9] which contains FDA's responses, and provides hyperlinks to the FDA's response letters and additional correspondence (e.g., a second “no questions letter” in response to the notifier’s message that supplemented its original notice, or, in some cases, the FDA may first respond with a “no questions letter,” but later determine that the GRAS notice was not complete).

It has been recognized that the regulatory significance of a “no questions letter” warrants further clarification.[7] The FDA’s response must be considered in context based on the data available to reviewers at a point in time, because scientific knowledge and information about a particular ingredient can evolve and sometimes change over time. Under any circumstances, the FDA neither indicates in a “no questions letter” that a submitted notice provides a sufficient basis for the GRAS conclusion, nor claims that such safety is generally known and accepted by qualified experts.

GRAS STAUS AS A SAFETY FACTOR CONSIDERED BY THE EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

The Panel notes that general recognition of safety, as well as evidence of GRAS status, must relate to the conditions of intended use. In addition, a substance must comply with specific usage limitations appearing in any GRAS determination. GRAS status may not be applicable if the conditions of use differ significantly from those providing the basis for eligibility. Thus, when using GRAS status as a factor in the safety assessment of cosmetic ingredients, it should be considered with other relevant assessment factors that contribute to the determination of a safety margin on a case-by-case basis (such as route of exposure, use pattern, dose level, first-pass effect/metabolism, etc). For instance, topical application of a substance in real use conditions may result in decreased systemic exposure compared with oral

ingestion. In such case, a long history of consumption of a GRAS substance in food by a significant number of people may serve as a worst-case parameter to factor in to a WoE decision-making approach.

The Panel also notes that GRAS notifications sent to the FDA typically include data and information on the notified substance that are readily accessible to the public, such as physical and chemical properties, applicable conditions of use, scientific basis for the GRAS determination (e.g., human, animal, analytical, or other scientific studies), as well as a comprehensive discussion of the evidence that the notifier relied on to establish safety. Such material may serve as complementary data and information to perform a risk analysis for a substance as applied in cosmetic products, given that it provides, to some degree, an organized profile of the current state of knowledge for the use of a substance via an estimated dietary exposure. Further, the scientific and regulatory issues, as well as safety concerns, raised by specific GRAS notices provide insight into safety evaluation against some complex endpoints. When substances are evaluated by a panel of food safety experts outside of the FDA, safety consensus should be unanimous by the entire panel on an independent conclusion of GRAS status. For example, natural flavor complexes (NFCs) determined to be GRAS under conditions of intended use as a flavoring ingredient in food by the Flavor and Extract Manufacturers Association of the United States (FEMA) expert panel[10] may rely on the threshold of toxicological concern (TTC) concept and the use of the congeneric group approach.[11-13]

As part of its mission, the Panel performs a comprehensive safety evaluation of the substance, and formally or informally, a sufficient margin of safety (MoS) based on the data available is to be determined on a case-by-case basis. This scientifically constructed procedure requires that all available relevant data should be used in evaluating the safety of a substance under conditions of intended use as an ingredient in cosmetics. For ingredients under review, the maximum concentration of use and reported function(s) and route(s) of exposure from cosmetic products should be examined. Wherever possible, other uses of the substance (e.g., in food, consumer products, and industrial products), and the concentrations involved in such uses, should be also considered. Total aggregate exposure to a substance should be calculated based on exposure scenarios by using appropriate exposure models; as a first estimate for products intended for topical use, percutaneous absorption needs to be considered relevant to the amount of a substance that is applied to, or migrates to, a specified site.

For a substance used in food before 1958, a GRAS determination can be made based on common use in food, but requires a substantial history of consumption in food by a significant number of consumers. However, such basis for GRAS classification is seldom relied on today.[6] Given that FDA GRAS notification program allows GRAS self-determination, the Panel would identify whether the GRAS status of a substance has been affirmed/recognized by the FDA, or is only self-determined by manufacturers or other stakeholders, which may be covered by FDA GRAS notice inventory. The Panel notes the conclusions on their safety should be generally based on their long history of safe use in foods combined with their likely low exposure, based on principle of self-limiting levels of use, i.e., including more of a flavoring substance in a food may adversely affect taste, thus flavor ingredients are typically used at very low concentrations in food.[13]

The Panel is aware that the FDA's response to a GRAS notice does not have the same level of authority as a listing in the regulations. A "no questions letter" based on the FDA's evaluation of the entire GRAS notice, should be considered in the contexts of both time and the available data and information; while it should also be noted, at the time it is issued, the FDA verifies such a GRAS conclusion is in compliance with the statutory requirements for GRAS criteria, which is based on data and

information that are generally accepted and accessible to the public (e.g., the conclusion is supported by the peer-reviewed scientific literature and publication in a textbook).[14] In addition, a conclusion of GRAS status claimed in a notice should be supported through the application of scientific principles for the safety assessment of food ingredients, as well as based on data, information, or methods that are generally available. Therefore, the Panel may consider the application of a WoE approach, for the oral-to-dermal extrapolation of available data and information for cosmetic uses.

KEY ELEMENTS OF SAFETY EVALUATION OF SUBSTANCES WITH AN INDEPENDENT GRAS CONCLUSION

Given GRAS status may be self-affirmed and not submitted for FDA review, further clarifications are provided herein on some of the key elements to evaluate the safety of cosmetic substances that are subject to an independent GRAS conclusion. Note, GRAS assessment is dynamic and must be re-evaluated to account for new information on ingredients and new perspectives on safety evaluation. It has also been recognized that toxicological data relating to chemical substances that are used in products other than cosmetics, such as food and medicines, can also be used for supporting safety assessment of an ingredient intended to be used in a cosmetic product.[15]

GRAS status should be considered based on its use as a food ingredient; i.e., it is only the specified use of a given substance that is GRAS, and not the substance itself. According to the uniform criteria established in the final rule for describing the basis for a GRAS determination, a conclusion based upon scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of a food additive.[7] That is, unlike judging a substance used in food prior to 1958, nowadays a conclusion of GRAS status is rarely based on common use of the substance by a significant number of consumers or a substantial history of consumption.[6,7] Thus, to support the safety of a cosmetic ingredient, the test substance should correspond to the one that is formulated in the finished cosmetic products; all routes of exposure (dermal, oral and inhalation) should be considered in view of the intended use of the product. It should also consider whether data included in a self-determined GRAS notice is relevant for evaluating the highest concentration of the substance in a typical cosmetic formulation. In addition, test dose and vehicle choice need to be representative for cosmetic in-use conditions such as contact time and location of use.

The primary route of exposure for cosmetic ingredients is generally via the skin upon topical administration, while all routes (dermal, mucous membranes, ocular, oral, and inhalation) should be considered in view of the intended use of the product, and route-specific absorption factors may apply accordingly. Note, cosmetics applied to mucous membrane, such as lipsticks, are normally not intended to be ingested (only a fraction of the orally applied products will be ingested); thus, the conservative absorption value of 100% is rarely used, unless experimentally driven data are absent. Also considered are descriptions of proposed used in specific categories and estimate average use levels in those categories. In general, the calculation of dermal exposure needs to take into account that only a fraction of the product is retained on the skin (e.g., whether the product is a rinse-off or leave-on product and which retention factor should be applied); it should also be noted that the toxicokinetics of substances may also be affected by a cosmetic formulation (e.g., penetration enhancers can be added to facilitate dermal absorption). Inhalation and ingestion are not the intended routes of exposure for cosmetic applications, and exposure assessment of cosmetic products and their ingredients should follow the basic principles an tiered approach for safety evaluation.[16] For instance, the relevant concentration to calculate

respiratory exposure is the concentration in the inhalable spray mist, but not the concentration in the formulation.[15] Data from oral animal toxicity studies are commonly used to assess the safety of human dermal exposure scenarios. In some cases, a safety evaluation based on data included in self-affirmed GRAS notice may require route-to-route extrapolation, which may be associated with considerable uncertainties.[17] Physiologically-based toxicokinetic (PBTK) modelling can be applied in oral-to-dermal extrapolation of threshold doses of cosmetic ingredients (e.g., no-observed-adverse-effect-level (NOAEL) dose can be translated to a dermal or inhalation threshold via toxicokinetic modelling).[18] In the analysis of natural complex mixtures, comparison of intake of mean percentages of each constituent to established TTC thresholds may be applied to address potential safety concerns, by utilizing data that provide an estimate of the individual daily intake of GRAS substances.[13]

CONCLUSION

It should be clarified that substances included in GRAS lists recognized in *Code of Federal Regulations*, which currently appear in 21 CFR Parts 182, 184, and 186, have different regulatory statuses compared to the ones listed on the FDA inventory of GRAS notices, or others with independent GRAS conclusions without notifying the FDA. The Panel recognizes FDA's GRAS notification process established in regulation is voluntary. It gives the food industry the ability to designate ingredients as GRAS, and thus manufacturers may self-affirm the GRAS status of an ingredient for a particular intended use without notifying the FDA. Further, the FDA does not make any determination regarding the GRAS status in their response to such notices. However, the FDA may state in their response whether the notified substance satisfied GRAS criteria clarified in the final rule. Therefore, regardless of whether a safety conclusion has been reached for a GRAS notice, the available data and information with the notified substance (as well as self-certified GRAS substances without notifying the FDA) warrant further evaluation to consider the intended use as an ingredient in cosmetic products. Whether supporting materials included in a GRAS notice satisfy the criteria for GRAS status through scientific procedures is a case-by-case determination. Thus, caution should be taken when utilizing reference points associated with self-certified GRAS conclusions, specifically when conducting safety evaluation of ingredients under their intended use in cosmetic products.

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