Personal Care Products Council
Committed to Safety, Quality & Innovation

CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

February 22, 2016

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

RE: Comments on *"Over-the-Counter Sunscreens: Safety and Effectiveness Data Draft Guidance for Industry"* [Docket No. FDA-2015-D-4021]

Dear Madam or Sir,

The Personal Care Products Council (Council) (formerly the Cosmetic, Toiletry, and Fragrance Association)[1] and the Consumer Healthcare Products Association (CHPA)[2] (collectively, we) play a major role in advancing the science of sunscreen safety and efficacy and are pleased to submit the following comments in response to the Food and Drug Administration's (FDA) Over-the-Counter Sunscreens: Safety and Effectiveness Data Draft Guidance for Industry (Draft Guidance) pertaining to sunscreen ingredients requesting inclusion into the over-the-counter (OTC) sunscreen monograph via a Time and Extent Application (TEA) (Sunscreen TEA active ingredients). 80 Fed. Reg. 72975 (November 23, 2015).

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1 Founded in 1894, the Council is the national trade association representing the personal care products industry. Our membership includes approximately 300 active member companies that manufacture or distribute personal care products, including OTC sunscreens. We also represent approximately 300 additional associate members who provide goods and services to manufacturers and distributors of personal care products.

2 The Consumer Healthcare Products Association (CHPA) is the 135-year-old national trade association representing the leading manufacturers and marketers of over-the-counter (OTC) medicines and dietary supplements. CHPA is committed to empowering consumer self-care by preserving and expanding choice and availability of consumer healthcare products.

We acknowledge the Agency's work towards providing industry with its current thinking on this technical, multifaceted, and rapidly evolving science. We also appreciate FDA's willingness to seek input from industry and other stakeholders to ensure the Draft Guidance reflects the most current, sound science. By its very nature, such input is best served through written comments as well as direct dialogue among FDA, industry, and independent and relevant experts in the field.

We request a working meeting with FDA (*e.g.*, workshop or symposium) where the Agency can engage with us to determine how the Guidance can incorporate flexibility appropriate and in keeping with 21st Century Toxicology.

We understand that the Sunscreen Innovation Act[3] requires FDA to finalize the Draft Guidance by November 26, 2016; however, it is our hope that FDA continues to update its thinking (and the Guidance) as the science evolves, noting that:

> Guidance documents represent the Agency's *current* thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. *An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.*[4] Emphasis added.

Sunscreens Have Clear Public Health Benefits

Consideration of the above approach is particularly important given what the Agency and industry know about the dangers of solar ultraviolet (UV) exposure and the benefits that sunscreen ingredients provide. Mainly:

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3 Sunscreen Innovation Act (Public Law 113-195).

4 FDA information on drug guidances documents: http://www.fda.gov/Drugs/%20GuidanceComplianceRegulatoryInformation/Guidances/default.htm

- UV radiation is a known carcinogen and sun exposure is linked to 65% of melanoma skin cancers in the U.S.[5]
- Melanoma, the most deadly form of skin cancer, causes nearly 9,000 deaths each year.[6]
- Every year in the United States, nearly 5 million people are treated for skin cancer, at an estimated cost of $8.1 billion.
- FDA recognizes sunscreens for their effectiveness in protecting the skin against solar UV exposure, their ability to prevent sunburn, in reducing the risk of skin cancer, and in mitigating premature skin aging.[7]
- Use of sunscreens is a simple procedure, inexpensive, with demonstrated health benefits and limited associated sequelae; and as such is an important measure to limit the overall healthcare burden in the U.S.
- Today only 37% of women / 16% of men indicate using a sunscreen product always or most of the time.[8]
- Inconvenience and product aesthetics are the main reasons that consumers do not use sunscreen products on a regular basis.[9]

Having an array of safe and effective sunscreen active ingredients allows sunscreen manufacturers to formulate safe and effective products that meet the differing needs of

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5 Armstrong BK and Kricker A. (1993) How much melanoma is caused by sun exposure? Melanoma Res. 3(6):395-401; Pleasance et al. (2010). A comprehensive catalogue of somatic mutations from a human cancer genome. Nature 463: 191–196.

6 Surgeon General Report 2014: Call to Action to Prevent Skin Cancer.

7 76 Fed. Reg. 117 35620 (June 17, 2011) FDA Final Rule: Labeling and Effectiveness Testing; Sunscreen Drug Products for OTC Human Use (2011).

8 Hartman AM et al. (2012) Sunburn and Sun Protective Behaviors Among Adults Aged 18–29 Years – United States, 2000-2010. MMWR 15:317-322.

9 Solky BA et al., (2007) Patient preferences for facial sunscreens: A split-face, randomized, blinded trial. J Am Acad Dermatol, ; 57(1):67-72.

individuals and their families, while providing necessary protection against the damaging effects of the sun, including premature skin aging and skin cancer. Ensuring that consumers have access to products containing a broad variety of sunscreen active ingredients is critical and in furtherance of FDA's public health mission.

There is a Public Health Need for New Sunscreen Active Ingredients

In addition, it is important to note that currently in the U.S., we have a limited palette of sunscreen filters available to use in developing high protection broad spectrum products. The FDA monograph lists 16 Sunscreen Active Ingredients, but only nine are commonly used in U.S. formulations today due to limited UV absorbance range, difficulty in formulation, low absorbance efficiency, poor aesthetics or solubility, etc. Formulating to develop sunscreens in the higher Sun Protection Factor (SPF) range that are also broad spectrum takes a combination of UV filters.

Both the OTC Review, and the TEA process that later followed, recognized the value of extensive and continued human use in substantiating safety. The value placed on human experience with a drug with few associated serious adverse events has roots in other areas of policy for FDA. This includes a policy that some regularly consumed foods may be considered generally recognized as safe based on common use.[10]

FDA developed the TEA process to permit extensive foreign marketing experience with over-the-counter drugs to support determinations of safety and effectiveness in the U.S.[11] This process should permit FDA to conserve resources and not engage in an unnecessarily extensive review of ingredients that have a long-standing safety record abroad.

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[10] 21 U.S.C. § 321(s) (permitting use of food generally recognized as safe prior to January 1, 1958 solely based on "common use").

[11] 67 Fed. Reg. 3060 (Jan. 23, 2002); also Fmail Herb, Inc. v. Heckler, 715 F.2d 1385, 1390-91 (9th Cir. 1983).

Sunscreens Work on the Surface of the Skin.

FDA has stated that their approach to sunscreen safety and effectiveness testing is most analogous to the approach for dermal drugs. However, Industry views sunscreens as topical dermal drugs, with the unique aspect of their efficacy being predicated on not absorbing into or through the skin. In other words, to be effective, these topically applied products must be formulated to remain on the surface of the skin, with minimal absorption beyond the stratum corneum. This is a very important consideration when performing a toxicological risk assessment.

Overview of Industry Comments

In the Draft Guidance, the Agency has proposed a detailed list of recommended studies to provide data sufficient for obtaining GRASE status for Time and Extent Application (TEA) sunscreen active ingredients, new to the US market. In this document, we present concerns, suggestions and specific comments on areas of agreement and disagreement with the Guidance Document, within the following major topics:

- **Acceptance criteria for safety data and calculation of Margin of Safety (MOS);**
- **Inclusion of updated risk assessment approaches and flexibility in data requirements;**
- **Application of the risk assessment process to TEA sunscreen active ingredients;**
- **Comments and concerns regarding specific sections of the Draft Guidance; and**
- **Need for further dialogue in a scientific forum to discuss broadening the Guidance to include newer risk assessment approaches and greater flexibility.**

The Draft Guidance should provide clarity and sufficient detail as to how an MOS is determined, and what margin is considered acceptable.

The Draft Guidance is clear in terms of the Agency's proposed study requirements for TEA sunscreen active ingredients. However, we strongly disagree regarding which studies are actually necessary and the absence of clearly articulated "success criteria" based on such data requirements is problematic.

To explain why some of these toxicological endpoint studies are needed, the Agency should communicate the methodology to be used to determine from the toxicology studies that a TEA sunscreen active ingredient is Generally Recognized As Safe (GRAS)e. Clarity is provided in other regions of the world for the process and methods whereby human safety and market acceptability are determined from toxicological endpoints. In the absence of such clarity, the guidance serves only as a checklist without perspective or judgment applied to interpretation of the data.

Guidance on success criteria and the interpretation of results will permit meaningful discussion of data requirements. The notion that the studies presented in the guidance are needed to make a safety judgment is, in our view, inconsistent with the direction being taken by toxicological communities today. The comments that follow will illustrate the need to significantly revise this guidance in order to draft a modern version based on advances in toxicological risk assessment, a.k.a. "21st Century Toxicology".

The Draft Guidelines do not sufficiently consider current approaches in toxicological risk assessment that are appropriate and applicable for *all* chemical exposures, whether from food, drugs, cosmetics or environmental contaminants.

The discipline of toxicology is experiencing an exciting evolution from an observational discipline to a mechanistic-based science combining *in silico, in vitro* and *in*

vivo data to quantitate risk and assess safety.[12] This transformational change is driven by many factors including the overwhelming need to toxicologically evaluate the universe of chemicals using limited resources and in many cases doing away with animal tests that may not be predictive of human toxicity. Quoting from Hartung[13] in reference to regulatory toxicology, "There is almost no other scientific field in which the core experimental protocols have remained nearly unchanged for more than 40 years".

While changes in toxicology will take time and verification, there is one constant that has been used in product safety assessments for this length of time: quantitative risk assessment (QRA). This approach would clearly describe the criteria used to define safety of TEA sunscreen active ingredients or finished product.

The input of experts who have led new developments in the practice of toxicologic risk assessment should be brought to bear on the Draft Guidance. The Nonprescription Drugs Advisory Committee (NDAC) meeting in September 2014 where safety was discussed provided only a narrow view of safety assessment, as sufficient input from experts in the field of toxicological risk assessment was not obtained. The panel did not include members or input from toxicologists with specific expertise in emerging areas relevant to safety assessment such as pharmacokinetics and toxicogenomics. Additional input from such individuals is needed to provide current thinking in these important areas. This would include scientists from academia, other regulatory agencies, other offices within the FDA and from industry. The need for the Agency to look broadly for expertise that is specific to the questions at hand was noted in the PCPC-CHPA Sunscreen Task Force comments on "Guidance for Industry: Sunscreen Innovation Act: Section 586C(c) Advisory Committee Process", submitted January 19, 2016.

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12 National Research Council. (2007) Toxicity Testing in the 21st Century: A Vision and a Strategy. Washington, DC: The National Academies Press. doi:10.17226/11970.

13 Hartung T. (2009) Toxicology for the twenty-first century. Nature 460, 208-212.

As part of any discussion going forward, the Agency should include toxicologists versed in the practice of risk assessment using modern approaches that are members of The Society for Toxicology (SOT). The SOT is ". . .a professional and scholarly organization of scientists from academic institutions, government, and industry representing the great variety of scientists who practice toxicology in the US and abroad. The Society's mission is to create a safer and healthier world by advancing the science and increasing the impact of toxicology."[14] It seems obvious that any discussion of human health assessment would include individuals who are practicing toxicologists. Engaging leaders in the profession could allow for meaningful discussions in the practice of human safety evaluations. Later in this document, it is recommended that a scientific forum under the auspices of the SOT could be used to discuss current best approach for assessing the topical application of UV filters/sunscreen products.

Another alternative might be a session within the Toxicology Forum.[15] The Toxicology Forum ". . . is an international, nonprofit organization that is devoted to conducting open dialogues among various segments of society concerned with problems in toxicology." At such meetings, ". . . views are exchanged among experts from domestic and international government regulatory and health agencies, industry, academia, 'political policymakers', and public interest groups." This venue would likewise present an opportunity for discussion of advances in toxicology and risk assessment practices with top individuals in the profession.

Regardless of the organization or venue, it is critical to obtain the opinions of key leaders in the field of toxicology to best address the question of human safety of TEA sunscreen active ingredients.

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14 http://www.toxicology.org/
15 http://toxforum.org/

The risk assessment process is applicable to TEA sunscreen active ingredients.

Risk assessment involves the comparison of a "safe" dose determined in toxicological studies to human exposure and to quantitatively estimate risk. This is mentioned in the guidance but seemingly as an afterthought rather than THE process wherein data requirements to determine such a "safe" dose could be discussed. While QRA may be considered by some as applicable only to environmental toxicants or food additives or cosmetic ingredients rather than "drugs", it is, in fact, the approach used for assessment of safety for any chemical where human exposure occurs. A chemical is a chemical regardless if it has medicinal properties or is a food additive or environmental pollutant. Human exposure and consequences thereof need to be evaluated and "judged". Risk assessment approaches are embraced globally amongst regulatory authorities, e.g., the U.S. Environmental Protection Agency,[16] the European Commission's Scientific Committee on Consumer Safety (SCCS),[17] Health Canada,[18] and others. Most health authorities are incorporating new/better methods that also take into account the desire to eliminate unnecessary and often non-predictive animal studies.

The principal question in QRA is "what data are needed to determine a safe human exposure?" In this regard, judgment will play a role since risk assessment will always involve areas of extrapolation and uncertainty no matter how many toxicological studies are conducted. As outlined further below, all of the available data for a chemical are evaluated collectively to determine their sufficiency to support the derivation of a safe exposure level. In the case of data gaps, a variety of studies may be conducted to inform this judgment provided they are scientifically reliable and robust. If a risk assessment, with

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16 http://www.epa.gov/risk

17 Scientific Committee on Consumer Safety. The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 9th revision. SCCS/1564/15. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf

18 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000 http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_tc-tm-eng.php

areas of uncertainty appropriately addressed, provides an adequate MOS, there is no need to conduct a long list of studies that may not add real value to the determination of "safe" human exposure.

A discussion regarding the steps of a risk assessment as applied to the evaluation of TEA sunscreen active ingredients.

We acknowledge that FDA scientists are familiar with the steps and criteria used in risk assessment. Our intention is to illustrate where there are advancements in this process and how these may be considered in the assessment of TEA sunscreen active ingredients.

1. Hazard identification:

Hazard identification is the process of determining whether a chemical can cause or increase the frequency or severity of an adverse health effect, i.e., inherent or intrinsic toxicity. The first step is to determine what data exist for a given chemical, whether in the open literature or from closed or unpublished sources. In the determination of a UV filter intrinsic hazard profile, it is critical to evaluate all of the available data before deciding to generate new data. Local tolerability is determined early in the process of hazard assessment, including a basic set of data addressing acute and topical toxicity of the UV filter such as skin/eye irritation, skin sensitization, and photo-induced toxicities. Genotoxicity tests provide the basis for an assessment of a potential mutagenic or cytogenetic effect of the UV filter. It is important in the Guidance document that the Agency incorporate flexibility in the methods used to generate these data, as methodology has and continues to evolve and improve.

In silico tools such as structure-activity comparisons, *in vitro* tests, laboratory animal studies, and epidemiology data, are all considered in the hazard

identification step.[19] Importantly, hazard identification has changed dramatically in the past decade. Much of the change is driven by the acknowledgment that the universe of chemicals, existing and new, will never undergo full animal-based toxicological studies. Moreover, the usefulness of such animal studies to humans continues to be challenged[20] leading to fundamental shifts in the approach toward chemical hazard identification. Thus, there is continuing acceptance of alternatives to traditional toxicological studies in evaluating the intrinsic toxicity of chemicals.

Structure Activity Relationship (SAR)-based read-across is an increasingly common alternative method to testing and was used extensively in the Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) program and European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation. A variety of *in silico* tools (e.g., OECD Toolbox) are now available to help identify structural analogs for data deficient chemicals. Thus, SAR is used ever increasingly in the initial stages of a toxicological assessment to understand the toxicological profile of the chemical of interest based on structure analysis.[21] For example, an analysis of the chemical structure for structural alerts for genotoxicity is done routinely using programs/databases such as Leadscope (http://www.leadscope.com/), DEREK (http://www.lhasalimited.org/) and TOPKAT (www.accelrys.com/products/topkat). DEREK is quite comprehensive although

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19 Casarett & Doull's Toxicology: The Basic Science of Poisons, Eighth Edition. 2013. Curtis Klassen, ed. McGraw Hill.

20 Knight A et al. (2006) Animal carcinogenicity studies. I. Poor human predictivity. ATLA Alternatives to Laboratory Animals 34:19-27; Knight, A et al. (2006) Animal carcinogenicity studies: 2. Obstacles to extrapolation of data to humans. ATLA Alternatives to Laboratory Animals 34: 29-38. Knight A (2006) Animal carcinogenicity studies: 3. Alternatives to the bioassay. ATLA Alternatives to Laboratory Animals 34: 39-48.

21 Organisation for Economic Co-operation and Development. (2014). Guidance on Grouping of Chemicals Second Edition; European Centre for Ecotoxicology and Toxicology of Chemicals, (2012) Category Approaches, Read-Across, (Q)SAR. Technical Report No. 116; European Food Safety Authority, (2014) Modern methodologies and tools for human hazard assessment of chemicals. EFSA Journal 12(4): 3638.

there is the possibility that a finding of no alerts could reflect the absence of chemical information for the endpoints since DEREK is a knowledge database. Nevertheless, the expert chemical evaluation in combination with the SAR analysis should adequately identify a chemical that may be outside the "rules" established in a specific database (i.e., outside respective applicability domain).

In vitro studies as a standard battery for TEA sunscreen active ingredients can address genotoxicity, skin/eye irritation and phototoxicity. Further, the science is progressing to enable evaluation of "adverse outcomes pathways" for such ingredients in development. A recent publication has highlighted the utility of genomic approaches in characterizing endocrine toxicity.[22] Using such approaches, endocrine pathways can be evaluated to determine the activity and potency *versus* established benchmarks. In the absence of endocrine activation there is no reason to suspect such a pathway is operative *in vivo*. A careful and methodical elimination of possible toxicological pathways for these materials could reduce the need for observational animal studies.

There is, however, an understanding that animal testing may be required to establish a No-Observable-Adverse-Effect-Level (NOAEL) based on the information that has been established or to reduce uncertainty in the MOS determination. The number and types of such studies depend on the totality of data that exist for a given TEA sunscreen active ingredient and the integration of all toxicological endpoints needs to be ensured.

For a thorough assessment of potential systemic / organ toxicity, repeated dose toxicity studies (i.e., subacute or subchronic toxicity studies) after oral (worst case) or dermal administration combined with reproductive and/or developmental

[22] Naciff J and Daston G. (2011) Genomics in Characterizing Endocrine Toxicity, in Applications of Toxicogenomics in Safety Evaluation and Risk Assessment. D. Boverhof and B. Gollapudi, eds. John Wiley and Sons.

toxicity (DART) studies allow a robust determination for a NOAEL, taking into account all potential adverse effects observed. Based on the outcome of these studies, chronic toxicity studies are to be considered, if 1) serious/severe toxicity effects were observed in subacute or subchronic studies for which the available evidence is inadequate for risk characterization; 2) molecular structure shows a clear relationship to effects that were not detected in a subacute or subchronic toxicity study; or 3) the substance may have a hazardous property that cannot be detected in a subacute or subchronic toxicity study.

The assessment of carcinogenicity is to be performed based on all TEA sunscreen active ingredient-specific data with focus on genotoxicity, repeated dose toxicity and absorption, distribution, metabolism and excretion (ADME) data. A full carcinogenicity study may be required, if the substance is determined by well-accepted methods to be genotoxic or if there is evidence from repeated dose studies that the substance is able to induce pre-neoplastic lesions. It is noted here that it is highly unlikely that a clearly genotoxic chemical with carcinogenicity alerts would be recommended for an application as a TEA sunscreen active ingredient.

2. Dose-response assessment:

The dose-response assessment entails identification of a critical effect and a point of departure (POD), often a NOAEL. In general, the POD is used to derive a "safe dose" by adjustment with appropriate uncertainty factors (UFs) to address areas of extrapolation or uncertainty, including potential inter- and intra-species differences and duration of exposure during an animal toxicity study. The uncertainty factors typically used have been well substantiated.[23,24] Newer methods have been utilized

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[23] Kaberlah et al. (2003) Uncertainty in toxicological risk assessment for non-carcinogenic health effects. Regul. Toxicol Pharmacol. 37: 92-104.

[24] Renwick AG and Lazarus NR. (1998) Human Variability and Noncancer Risk Assessment—An Analysis of the Default Uncertainty Factor. Regul. Toxicol. Pharmacol 27: 3-20.

in recent years to help refine the dose-response evaluation, including the use of biologically-based dose-response models, SAR and toxicogenomics.[25] Such approaches are relevant to TEA sunscreen active ingredient evaluation, where they may be used to help address emerging questions such as endocrine disruption.

If a NOAEL can be determined from adequate systemic toxicity studies such as repeated dose, reproductive toxicity or carcinogenicity studies, the next step would be an exposure assessment in order to conduct a risk characterization. If no NOAEL can be established, more data may be needed; however this may also depend upon the estimate of exposure. Thus before proceeding to additional data collection, an exposure assessment would be conducted.

3. Exposure assessment:

Estimating exposure is the process of identifying the dose of a compound and/or mixture that an individual applies and extrapolating this to a population. It includes the routes, magnitude, duration, and frequency of exposure. Much of the data for applied dose is determined empirically and derived from studies of use. The data include quantity and frequency of use as well as body surfaces covered. For sunscreen active ingredients there are published values for applied dose used by the SCCS.[26]

In addition to empirically determined applied dose, estimates of the systemic exposure or internal dose for humans require TEA sunscreen active ingredient-specific dermal penetration data. Dermal penetration is an integral part for determination of an internal dose, since it links the substance specific

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[25] Baskerville-Abraham et al. (2011) Introduction to Human Health Risk Assessment, in Applications of Toxicogenomics in Safety Evaluation and Risk Assessment. D. Boverhof and B. Gollapudi, eds. John Wiley and Sons.

[26] Scientific Committee on Consumer Safety. Notes of Guidance. 9th revision SCCS/1564/15

characteristics with the most relevant human exposure route for sunscreen use. As part of an evaluation and for comparative purposes, there exist methods to estimate internal dose using *in vitro* and *in silico* approaches. *In vitro* penetration studies provide parameters such as flux rates that are useful in estimating an internal dose or for comparison of penetration of a TEA sunscreen active ingredient from different formulations.[27] In general, models of dermal penetration are conservative in the risk assessment sense (i.e., protective of health by tending to overestimate exposure), and use resources effectively. This is in part because the *in vitro* design does not take into account elimination processes occurring *in vivo*. Although repeated dosing is not easily performed using *in vitro* skin penetration setups and does not reflect the variations in skin types of different body parts, such studies provide a robust determination of skin penetration of a compound in light of a sufficiently high margin of safety. Such approaches should be considered before progressing to the extensive clinical testing recommended in the Draft Guidance, given the increasingly sophisticated capability to predict blood levels of an ingredient under a variety of scenarios.

A detailed discussion of a physiologically-based pharmacokinetics (PBPK) modeling approach useful for estimating systemic exposure of TEA sunscreen active ingredients is provided in Appendix I. The outcome of the modeling would be compared to an internal exposure estimate based on clinical data or measured/estimated from animal data.

In cases where there might be insufficient data for this approach, we believe there are alternative ways to develop the necessary data to the MUsT studies proposed by FDA in the draft Guidance, as discussed later in this document.

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[27] Organization for Economic Cooperation and Development (OECD). 92004) Guideline for the Testing of Chemicals. Test Guideline 428: Skin absorption: In Vitro method. Paris. http://www. oecd-ilibrary.org/environment/test-no-428-skin-absorption-in-vitro-method_9789264071087-en

Exposure data as described above could conceivably allow an internal dose Threshold of Toxicological Concern (TTC) to be applied. The Draft Guidance provides a threshold blood concentration below which no additional systemic toxicological data generation would be needed (0.5 ng/ml) and we infer that this corresponds to the TTC of 1.5 μg/day. However, TTC levels that are tiered according to chemical groups have been widely accepted[28, 29] and there now are efforts underway to develop such tiered TTCs based on internal dose. We believe that the Guidance should be written to enable incorporation of advances in the science including tiered thresholds below which additional testing would not be necessary.

4. **Risk Characterization**:

Risk characterization or assessment is the overall integration of the three steps listed above, i.e. hazard profile assessment with respective dose response and exposure, to develop a qualitative and/or quantitative risk assessment to estimate the likelihood that any hazard associated with the chemical of concern will be realized in humans for the exposure scenario being assessed. The quantitative part of the risk assessment is to provide a means of comparing doses that produce no toxicity to human exposure to understand the degree of separation between these and, based on the strength of the data, build some conservative assessment factors for higher certainty into the calculation. The MOS is the ratio of a NOAEL based on the most sensitive toxicological test results, divided by the appropriate uncertainty factor (UF), compared to human exposure dose: MOS = (NOAEL/UF) ÷ human dose.

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28 Kroes R et al. (2004) Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Food Chem. Toxicol. 42: 65–83.

29 Munro IC et al. (1996) Correlation of Structural Class with No-Observed-Effect Levels: A Proposal for Establishing a Threshold of Concern. Food Chem Toxicol 34: 829-867.

Following steps 1-3, an evaluation of the data is made. If the TEA sunscreen active ingredient is used at a concentration where exposure is "safe" because the MOS is considered sufficient, i.e., greater than 1, then additional hazard data requirements may be unwarranted.

On the other hand, if there are deficiencies in the data or the QRA is not supportive of human exposure, then additional data would be needed to address such gaps. This may include experimental data or alternative approaches to reduce uncertainty in the QRA calculation or better define the NOAEL.

Flexibility in data needs for GRASE status is appropriate and necessary.

It is our position that the Agency should be flexible in consideration of the dataset required to demonstrate GRASE status for a TEA sunscreen active ingredient. While we recognize that *in vitro* alternatives do not exist for all toxicological endpoints, there is growing recognition that incomplete data sets can be supplemented with *in vitro* data or *in silico* predictions. With the application of appropriate uncertainty factors, a level of confidence in the final risk assessment comparable to that from traditional animal studies can be achieved. A quantitative risk assessment approach, that incorporates up to date *in vitro* and *in silico* approaches such as PBPK modeling as well as mechanistic and mode of action data, would reduce unnecessary testing that does not truly add a public health benefit.

We provide the following comments on specific sections of the Guidance:

1. **Nonclinical Safety Testing (Carcinogenicity, DART Studies)**

The need for oral and dermal carcinogenicity testing, as outlined in the FDA draft guidance may be academic and unnecessary. In general, the absence of carcinogenicity alerts such as genotoxic effects, histopathological changes seen in

repeated dose toxicity studies and evident systemic exposure, can be included in a weight of evidence approach to exclude a carcinogenic potential and establish safe use of the TEA sunscreen active ingredient assessed without performing two-year animal bioassays. While a NOAEL can be obtained in such studies, the requirement for two carcinogenicity studies and even the necessity of a single one if other data are sufficient is questionable. A subchronic repeat dose toxicity study, coupled with evidence of non-genotoxicity and additional data to demonstrate lack of hormonal perturbation, can rule out carcinogenicity by low-dose-linear modes of action.[30] High dose only tumorigenic effects are addressed in the threshold-based risk assessment of pre-neoplastic lesions.

In the presence of a carcinogenicity alert and evidence of dermal penetration, only one relevant route of exposure for a carcinogenicity study needs to be considered. Dependent on the available hazard data, a decision between a dermal carcinogenicity study (i.e., the relevant exposure conditions during human use) or an oral carcinogenicity study (i.e., the potential worst case, dependent on substance specific ADME data) needs to be made instead of requesting studies for both routes.

For Developmental and Reproductive Toxicity (DART) endpoints, a combination of *in vivo* and *in vitro/in silico* data may also be utilized in a safety assessment as described earlier in these comments. A recent publication demonstrates that for chemicals within a given domain, repeat dose toxicity data, coupled with extensive structural comparison with known developmental and reproductive toxicants, can be used to determine an appropriate uncertainty factor for use in QRA, with the result that new DART studies may be not be needed.[31]

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30 Luijten et al., (2012) Prediction of carcinogenic potential of substances using repeated dose toxicity data. RIVM Report 340700006/2012

31 Blackburn KL et al. (2015) A strategy for safety assessment of chemicals with data gaps for developmental and/or reproductive toxicity. Regul Toxicol Pharmacol. 72(2): 202-15.

2. Human Absorption Studies/Maximal Use Trial (MUsT)

We recognize that the extent of systemic exposure of TEA sunscreen active ingredients is an important safety consideration. This could be addressed in several ways. We describe simplified, yet rational and scientifically supportable approaches in Appendix 1, using *in vitro/in silico* data. In cases where more refined or additional exposure data are needed to verify that the MOS value will remain protective if dermal penetration is increased, human pharmacokinetic studies, such as MUsT studies as recommended in the Draft Guidance, could be conducted. In this case, we do not believe it is necessary to test four formulations as is currently specified in the Draft Guidance. We believe *in vitro* penetration data could be used to identify, for example, one or two formulations that are more prone to dermal absorption to be used in further clinical PK testing.

FDA identifies in the Draft Guidance a steady state blood level less than 0.5 ng/mL in a Maximal Usage Trial as the level below which a systemic carcinogenicity study and studies to assess fertility and pre- or postnatal toxicity would not be needed. While we strongly support the threshold construct, rather than a single, absolute blood level for all TEA sunscreen actives, we propose that the allowable systemic bioavailability of a TEA sunscreen active ingredient be predicated on the hazard profile of that specific molecule. Applying the TTC principles described earlier, an ingredient with sufficient evidence of non-genotoxicity, and lacking structural alerts for other toxicities of concern and/or with additional toxicological data, should be assigned a higher steady state threshold.

We consider it unnecessary to conduct MUsT or other studies in young children for TEA sunscreen active ingredients. While full skin development continues through the first year of life, the stratum corneum barrier is sufficient at birth.[32] In addition, biotransformation and excretory systems in general develop rapidly after birth and

[32] http://www.cir-safety.org/supplementaldoc/infant-skin-resource-document

most are considered to be fully competent by about 6 months of age.[33] Several reviews have addressed the differences in toxicokinetics and toxicodynamics between children and adults with respect to the sufficiency of current uncertainty factors used in QRA.[34,35] These analyses indicate that for exposures to infants greater than 6 months of age, the standard 10X uncertainty factor effectively accounts for human variability including surface area to volume ratio changes with age.

3. Anticipated Final Formulation Testing

It is our position that *in vitro* penetration studies for each formulation containing TEA sunscreen active ingredients as described in the Draft Guidance are not necessary to assess the safety of a finished product. Such testing of every formulation would not be needed if ranges of penetration with different types of vehicles are established or reliably predicted through modeling and a sufficiently wide margin of safety exists to encompass such variations in predicted internal exposures. Through this approach, changes in dermal penetration would not affect the safety determination. This would return the focus to developing sunscreen products with greater acceptability, with a goal of motivating more consumers to use sunscreens appropriately.

4. Pharmaceutical Quality/Manufacturing Data

We agree with the Agency on the importance of following Good Manufacturing

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33 Felter S et al. (2015) Assessment of health risks resulting from early-life exposures: Are current chemical toxicity testing protocols and risk assessment methods adequate? Crit. Rev. Toxicol. 45: 1-26.

34 Renwick A et al. (2000) An Analysis of the Need for an Additional Uncertainty Factor for Infants and Children. Regul. Toxicol. Pharmacol. 31: 286–296.

35 Felter S et al. (2015) Crit. Rev. Toxicol. 45: 1-26.

Practices (GMPs) for sunscreen products. In the United States, products that meet the legal definition for Over-The-Counter (OTC) drugs must follow the FDA GMP regulations that are described in 21 CFR Parts 210 and 211. In addition, the Personal Care Products Council developed Quality Assurance Guidelines to promote best practices in GMPs for cosmetics and OTC products. We also agree with the Agency that following United States Pharmacopoeia (USP) – National Formulary compendial standards, official or proposed, and specifications are important to ensure quality of these products. In addition, we agree that sponsors should describe aspects of formulation, if any, needed to assure and enhance photostability, efficacy, or safety of the active ingredient to establish its GRASE status.

5. Postmarketing Safety Data

We support performing in the market comprehensive and continuous pharmacovigilance to measure safety performance of products-in-use. We believe this is critical to ensure overall product safety for all non-prescription drug products available to consumers in the US and other markets worldwide. While national requirements may vary, pharmacovigilance efforts typically include:

a. Collection of all adverse events
b. Regular trending and analysis to identify any new potential safety signal
c. Investigation and assessment of each serious individual case report and every potential safety signal by medically-trained professionals
d. Maintenance of a periodic summary of safety information on each marketed product, which will be provided to health authorities upon request, as may occur during inspections

More specifically, we agree that companies marketing sunscreen products in the U.S. must notify the Agency of any known serious and unexpected adverse event as a result of the use of any of its sunscreen products in the United States. "Serious" and

"Unexpected" are defined in accordance with the Agency's definition in 21 CFR 314.80(a). Such information should be made available for inspection by the Agency following the Guidance for Industry Postmarketing Adverse Event Reporting for Nonprescription Human Drug Products Marketed Without an Approved Application.[36]

While we recognize the limitations and challenges of spontaneous reporting of in-market consumer product experiences, including underreporting, we do consider post-market surveillance data to be relevant to monitor for safety signals not otherwise observed in clinical or nonclinical testing.

Further, we support consumer education regarding FDA's Medwatch program to enable consumers to report adverse events directly to FDA. An example is available on the home page of CHPA's consumer-facing website: www.knowyourotcs.org.

We encourage FDA to work via Memoranda of Understanding with ex-US health authorities to better understand postmarket safety reports that are available on potential TEA ingredients. These data are not likely available directly to a US sponsor, but could be shared directly with FDA.

Summary

In conclusion, we believe the Draft Guidance proposes a framework that is not reflective of the current state-of-art in ingredient safety assessment. There now exist scientifically sound approaches that enable a robust evaluation of substances without an expansive set of animal studies as a default position. While in some cases additional data may need to be generated in traditional animal toxicological studies for a TEA sunscreen active ingredient, the default approach should include a holistic review of all available data of sufficient quality, and consideration of *in vitro* and *in silico* mechanistic or mode of action

36 http://www.fda.gov/downloads/Drugs/.../Guidances/ucm171672.pdf

data to evaluate consumer exposure and to inform the safety assessment. Further we support the proposal to establish a threshold internal dose below which systemic toxicity data are not needed; however, we strongly believe that the Guidance should be written to enable incorporation of tiered thresholds based on the hazard profile of the TEA sunscreen active ingredient.

Recommendation

Both FDA and industry alike recognize that skin cancer prevention is a public health priority; and that sunscreens have a demonstrated ability to reduce the risk of this often deadly disease. Thus, it is critical that manufacturers have a broad variety of sunscreen active ingredients available to formulate products that the public will accept and use as well as a broad variety of tools to substantiate safety. With this in mind, **we ask that the Agency engage with us in a scientific forum to determine how the Sunscreen Guidance can incorporate flexibility appropriate to 21st century toxicology.**

We appreciate the opportunity to provide comments and look forward to continuing our dialogue.

Should you have any questions or comment, please feel free to contact Farah K. Ahmed, Chair, PCPC-CHPA Joint Sunscreen Task Force at ahmedf@personalcarecouncil.org or 202-331-1770.

Sincerely,

Farah K. Ahmed
Chair, PCPC—CHPA Joint Sunscreen Task Force
Personal Care Products Council
Association

Barbara Kochanowski, Ph.D.
VP, Scientific and Regulatory Affairs
Consumer Healthcare Products

APPENDIX I

Approach for *in vitro/in silico* estimation of internal dose

It is possible to predict the steady state chemical concentration in blood following exposure via any route by taking into account hepatic blood flow, hepatic activity of the overall elimination process (intrinsic clearance), chemical binding in the blood and renal clearance.[37,38,39,40,41,42]

There have been several derivations of a pharmacokinetic equation to predict steady state concentration in blood depending on route of exposure (see References cited above). When considering dermal exposure, the below derivation of the equation can be used to estimate systemic concentration in blood:

$$C_{ss} = \frac{J_{max} \times SA \times Duration}{(GFR \times F_{ub}) + \left[\frac{(Q_l \times F_{ub} \times Cl_{int})}{(Q_l + F_{ub} \times Cl_{int})}\right]} \quad \textbf{Equation 1}$$

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37 Wetmore BA et al. (2012) Integration of dosimetry, exposure, and high-throughput screening data in chemical toxicity assessment. Toxicol. Sci. 125: 157–174.

38 Wetmore BA et al. (2013) Relative Impact of Incorporating Pharmacokinetics on Predicting In vivo Hazard and Mode of Action from High-Throughput In vitro Toxicity Assays. Toxicol. Sci. 132: 327 – 346.

39 Wetmore BA et al. (2014) Incorporating Population Variability and Susceptible Subpopulations into Dosimetry for High-Throughput Toxicity Testing. Toxicol. Sci. 142: 210-224.

40 Wetmore BA et al. (2015) Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In vitro Bioactivity to Inform Chemical Toxicity Testing. Toxicol. Sci. 148: 121-136.

41 Wetmore BA (2015) Quantitative in vitro-to-in vivo extrapolation in a high throughput environment Toxicology 332: 94-101.

42 Wilkinson GR and Shand (1975) A physiological approach to hepatic drug clearance. Clin. Pharmacol. Ther. 18: 377-389.

Table 2. Comments on Parameters and PK Approach

Parameter	PK Approach - Perspective on Parameters
C_{ss}	Steady state concentration in blood and can be used to relate internal concentrations between humans or between animals and humans.
J_{max}	Maximum dermal penetration rate through skin may be obtained from appropriate *in vitro* assays, performed at a relevant dose and duration. This will impact the amount of UV filter transferred from the skin to the systemic circulation.
SA	Surface area of exposure to UV filter may be adjusted depending on context of use. Systemic exposure is directly proportional to surface area (Equation 1), i.e., increasing the surface area of application will result in an increase in the amount of UV filter reaching systemic circulation.
Duration	Duration of exposure to UV filter may be adjusted depending on context of use. Systemic exposure is directly proportional to duration of exposure (Equation 1), i.e., increasing the duration of application will result in an increase in the amount of UV filter reaching systemic circulation.
F_{ub}	The amount of chemical that remains unbound to plasma proteins represents the fraction of chemical available for metabolism, distribution, and excretion. The fraction unbound can be reliably measured using well accepted and frequently employed *in vitro* methods.
GFR	In the absence of alternative methods for prediction of renal clearance, the GFR is used to represent the basal rate of elimination via the kidneys. GFR is a passive diffusion process and typical GFRs in adults, elderly, and children are available in the published literature. Use of

<table>
<tr><td></td><td>GFR for chemicals that are actively excreted would result in a lower estimated renal clearance rate (as compared to passive diffusion) and therefore a higher systemic exposure, which is conservative for a risk assessment.</td></tr>
<tr><td>Q_l</td><td>The rate of blood flow through the liver determines the rate at which the chemical reaches liver tissue and becomes available for hepatic metabolism. Typical hepatic blood flow rates are available for adults, elderly, and children in the published literature.</td></tr>
<tr><td>Cl_{int}</td><td>Hepatic intrinsic metabolic clearance is routinely measured through well accepted in vitro assays (e.g. Hepatocytes, Microsomes, Cytochrome P450 enzymes). This provides a means for estimating chemical metabolism using 21st century approaches.

Equation 1 limits metabolism to liver tissue, and does not incorporate metabolism in extrahepatic tissues, which underrepresents total metabolism within the body and therefore is generally conservative for a risk assessment.

An example calculation for how to scale in vitro hepatocyte clearance rate to in vivo hepatic clearance rate is presented below:

Equation for scaling liver metabolism: $\mathbf{Cl_{int}\ (L/hr) = Cl_{invitro} * HPGL * V_{Liver}}$

<table>
<tr><th>Parameter</th><th>Definition (unit)</th><th>Comment</th></tr>
<tr><td>$Cl_{invitro}$</td><td>Clearance by hepatocytes ($L/hr/10^6$ cells)</td><td>Empirically-derived, chemical-specific value</td></tr>
<tr><td>HPGL</td><td>Number of</td><td>Standard values</td></tr>
</table>
</td></tr>
</table>

		hepatocytes per gram of liver (10^6 cells/g liver)	available in literature
	V_{Liver}	Volume of liver (g)	Standard values available in literature

When using Equation 1 it is possible to estimate the internal steady state concentration for a sunscreen used in different scenarios (See Table 3)

Table 3. Different usage scenarios of possible interest and the parameters that affect the systemic exposure estimates

Potential Questions of Interest (Exposure Scenario)	C_{ss} Parameter(s) That Influence Systemic Exposure	Comment
Vehicle Effect	J_{max}	Jmax values obtained from *in vitro* studies utilizing different vehicles.
Product Application	SA , Duration	Change to represent a specific product exposure scenario based on consumer Habits & Practices, or theoretical dosing scenarios, age-specific body surface area, etc.
Age	GFR , Q_l , Cl_{int}	Change to represent a specific age group. Values reported in literature.
Disease State	J_{max} , GFR , Q_l , Cl_{int}	Change to represent a specific disease state. Values reported in literature.

- Several recent studies (Wetmore et al., 2012, 2013, 2014, 2015) have compared human C_{ss} estimates for oral exposure to *in vivo* PK data by utilizing a derivation of Equation 1 (see Table 4 for data comparisons). Overall, there was good concordance between the estimated C_{ss} and the *in vivo* PK data, with the C_{ss} estimates generally resulting in a higher (more conservative) human systemic exposure.

Table 4. Comparing Results of PK Approach with Published Human *in vivo* PK Data (Modified from Wetmore (2015) and Wetmore et al. (2015))

Drug	C_{ss} Values (µM) [a]	
	in vivo	PK Approach [b]
Diphenhydramine HCl	0.11–0.16	3.18
Triamcinolone	0.05–0.29	0.22
Lindane	0.46	1.27

[a] Css concentration at steady state after equivalent dose of 1 mg/kg/day

[b] PK approach results in overestimate of systemic exposure to these drugs, which is conservative for risk assessment.

- The advantage of using Equation 1 to predict systemic exposure is that it allows for estimation of internal exposure to a chemical in a relatively simple and straightforward manner. The data (i.e. dermal penetration rate, hepatic clearance and protein binding) needed for C_{ss} estimations can all be collected through modern *in vitro* toxicology approaches. Additionally, once the *in vitro* data are generated, Equation 1 can be modified to account for different

experimental designs as outlined in Table 3. This approach helps enable fast decision making while maintaining assurance of chemical safety.

- One of the limitations of Equation 1 is that it does not account for all biological processes within a person. As such, some processes that can affect systemic exposure are not accounted for, such as pre-systemic metabolism, non-hepatic metabolism active renal clearance or uptake. However, the approach remains conservative for risk assessment since these additional clearance mechanisms would serve to reduce the internal exposure.

- If route to route comparisons are of interest, additional refinements are also possible, such as: incorporation of data from CaCo2 cell assays, to measure gastric absorption rates *in vitro*.

- Equation 1 can also estimate the C_{ss} achieved during existing *in vivo* preclinical studies, by incorporating species-specific PK parameters. This avoids the need to conduct additional preclinical studies to collect internal concentrations, when there are existing data that suggest a lack of related systemic effects.