June 27, 2019

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments Submitted to Docket No. 1978N-0018 (Formerly Docket No. FDA–1978–N–0038) for "Sunscreen Drug Products for Over-the-Counter Human Use," Regulatory Information No. 0910-AF43

DSM Nutritional Products LLC ("DSM") is pleased to provide the following comments in response to the Food and Drug Administration's (FDA's) Tentative Final Monograph ("TFM") for Sunscreen Drug Products Over-the-Counter (OTC) Human Use, published at 84 Fed. Reg. 6204 (February 26, 2019).

As a global science-based company active in Nutrition, Health and Sustainable Living, DSM is a world leading supplier of vitamins, feed, food, pharmaceutical, cosmetic, personal care and aroma ingredients. In sunscreens, DSM is a leading world-wide provider of numerous UV filters, including Avobenzone. DSM takes human health and safety very seriously and believes that sunscreens are proven and effective interventions that help provide consumer protection against skin cancers and skin damage caused by the sun's rays. DSM is committed to proactively supporting the safety and availability of existing and new sunscreen active ingredients that help protect public health.

DSM requests that FDA modify its proposed rule taking into consideration the comments provided herein.

1. Background and Action Requested

Skin cancer is a significant, and largely preventable, public health concern. Sunscreens have been widely and safely used by the general public for their photoprotective properties, including prevention of photocarcinogenesis and photoaging and management of photodermatoses for more than 40 years.

FDA's Sunscreen Monograph rule has identified the permitted active ingredients (UV-filters) for sunscreens since 1978. As such, there are decades of human exposure from use of the active ingredients in recreational and daily sunscreen products. Importantly, these active ingredients do not represent

"new chemical entities" and have existing data supporting their safe use. Moreover, at present these UV filters are not considered "unsafe" as there are no human health risks identified from existing toxicological data or medical literature (e.g., case reports or credible scientific journal articles) necessitating immediate action to remove such materials from the market.

Under the current proposed TFM, FDA has asked industry and other interested parties for additional safety data to support the GRASE status of the sunscreen active ingredients currently available in marketed products. In general, we do not believe the safety testing requirements that FDA has set forth in the TFM are the only mechanisms by which the safety of these active ingredients can be demonstrated.

Furthermore, FDA's proposed rule is requiring extensive testing similar to what is required under an NDA for what are basically "older commodity chemicals" that are globally manufactured, sold and distributed at discount prices. Many of FDA's proposed changes will result in tremendous economic consequences for sunscreen manufacturers, testing laboratories, and ultimately the consumer. As such, FDA's regulatory impact analysis does not adequately address the negative benefits if the final rule results in reduced sunscreen use or if the "willingness to pay" analysis does reflect current sunscreen market realities. In particular, we note two particular areas of concerns:

1. The costs of changes and of the proposed safety studies are significantly underestimated, particularly given the strain on testing lab capacity and under-estimates on the costs of a MUsT study. Table 1 provides a cost estimate for the range of safety studies required per active ingredient. The MUsT and DART study estimate provided are based on an actual study quotes received from Contract Research Organizations (CROs) in the US for conducting the pilot and pivotal MUsT and DART studies required. As shown, there is a large disparity between FDA's estimates and those related to the MuST and DART studies. Furthermore, it is anticipated that carcinogenicity study costs will also be modestly higher due to a number of additional safety testing and direct associated administrative costs which do not appear or have been factored into FDA's economic impact analysis. In general, these include:

    - Development costs associated with identifying, evaluating and preparing appropriate formulations for each of the tests required;
    - Preliminary dose-ranging studies and assessments for toxicological studies;
    - Analytical method development and validation of methods required for each study;
    - Company and CRO study monitoring and quality assurance costs;
    - Recruiting costs associated with clinical studies;
    - Meeting and travel costs associated with lab qualification and study design and protocol development, etc.; and
    - Electronic data reporting and formatting costs which typically require the use of specialized companies to prepare and submit.

Table 1. Safety Study Costs – Actual Versus FDA Estimated Costs

Total Cost Estimates (in $ thousands)	MUsT	Pediatric	Carcinogenicity (Dermal and Systemic)	DART	Toxico-kinetic	Total
FDA	**$201**	**$201**	**$4,087**	**$1,006**	**$107**	**$5,602**
CRO Quotes	**$1,433**	**Not available**	**$4,505**	**$1,600**	**$165**	**$7,703**

2. Costs will be disproportionately borne by a limited number of firms marketing or manufacturing sunscreens or their active pharmaceutical ingredients. A significant number of globally located low-cost active ingredient producers and domestic consumer sunscreen product companies are simply not participating or contributing to the testing costs and are unfairly benefiting from those ethical and responsible companies that are. Moreover, since these are OTC active ingredients and not NDA products, there are no exclusivity provisions afforded to for those companies who contribute to the test costs under established industry consortiums.

Therefore, given that these OTC active ingredients are not "new chemical entities", but rather "older commodity chemicals" that have existing scientific and extensive human use data which has supported their safe use for more than four decades, the use of alternative studies, risk assessment tools and Toxicology in the 21st Century (Tox21)[1,2] toxicity assessment methods may be more suitable or appropriate for quickly and more efficiently assessing whether these compounds have the potential to disrupt processes in the human body that may lead to negative health effects. Additionally, this approach would also help advance FDA's, as well as industry's, long sought goal of refining, reducing, and replacing testing on animals. Clearly, this approach would also be in line with the evaluation processes that FDA has proposed in its "Predictive Toxicology Roadmap", "Drug Safety Priorities 2018"[3,4], and "Real World Evidence" approach for monitoring postmarket safety and adverse events to make regulatory decisions.[5]

Furthermore, FDA should not discount other potential categories of valid scientific and global epidemiological evidence, including real world evidence and post-market surveillance data. Use of such information would meaningfully reduce the time that it will take for the agency to issue a final rule on the sunscreen ingredients for which further data are provided or deferrals are requested and provide more certainty to the public around safe sun practices. Finally, the use of Real-World Evidence and Real-

[1] http://dels.nas.edu/resources/static-assets/materials-based-on-reports/reports-in-brief/Toxicity_Testing_final.pdf (accessed June 20, 2019)
[2] https://tox21.gov/overview/ (accessed June 20, 2019)
[3] https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2018/05-fdaroadmap.pdf (accessed June 20, 2019)
[4] https://thehill.com/opinion/healthcare/364262-fdas-new-predictive-toxicology-roadmap-will-improve-human-safety (accessed June 20, 2019)
[5] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (accessed June 20, 2019)

World Data from safety surveillance advanced by many experts must be part of this effort. With regard to this point, it is important to note that other regulatory bodies, both at the domestic and international level, are either currently evaluating or have conducted safety evaluations of many of these same ingredients. To our knowledge, these groups have not indicated a concern as to the active ingredients currently proposed to be Category III by FDA.

Herein, we propose an alternative scientific approach which demonstrates that the use of avobenzone in sunscreens at concentrations of up to 5% should be considered safe for repeated human use. This approach addresses FDA's stated concerns regarding the need to evaluate the GRASE status of sunscreen active ingredients in light of increased sunscreen usage and exposure risks associated with chronic use.

2. Statement of Grounds

2.1. Classify Avobenzone as Category I, GRASE Under Current TFM (at Use Levels Up to 3 or 5 Percent)

Avobenzone is a critical ingredient for UVA protection. It has the highest UVA absorbance and is the only dedicated UVA absorber approved in the U.S., making its use necessary to achieve well formulated products with high UVA protection. Therefore, it is important that formulators are able to use sufficient levels of this UVA absorber to create sunscreens which protect from both UVB and UVA radiation in balanced amounts and thereby protecting the consumer from the associated skin damage.

Overall, it is our assessment that the available non-clinical data, in silico assessments, and PK profiles, are consistent with the very high Margin of Safety estimations for avobenzone in sunscreens, even under chronic and excessive dermal application amounts.

Based on the results of our quantitative risk assessment (section 6), DSM concludes that the use of 3% avobenzone in sunscreens should be considered as safe (GRASE) for repeated human use. In addition, based on the very high Margin of Safety (MoS) obtained (i.e., systemic MoS is 2 to 5 x 10^6), we also conclude that our analysis also substantiates it safe use at a level of 5%, an increase of about 65% that could be expected to remain a safe exposure for all age categories as indicated by the very high MoS estimations. Furthermore, from an efficacy perspective, DSM agrees with FDA's finding that sufficient information exists to satisfy the effectiveness prong of the GRASE standard for sunscreens containing avobenzone at concentrations up to 5 percent.[6] Our previous sunscreen monograph comments submitted to Docket number 1978N-0038 on December 21, 2007 also contains a substantial amount of safety, efficacy and human exposure information supporting avobenzone's safety at a maximum use level of 5%.[7] As such, we request that the FDA grant Category I GRASE status to Avobenzone 3% and consider to allow an increase in the maximum use level of avobenzone up to 5% under the current TFM.

[6] 84 Fed. Reg. 6227

[7] DSM Sunscreen Monograph Comments, December 21, 2007, FDA Comment Number EC2726, https://www.regulations.gov/document?D=FDA-1978-N-0018-0833 (accessed on June 27, 2019)

2.2. Allow Combinations of Avobenzone and Proposed Category I GRASE Ingredients (Zinc Oxide and Titanium Dioxide) Under Current TFM

An extensive amount of information has been submitted to the OTC Docket supporting the safety and efficacy of the combination of avobenzone with other sunscreen active ingredients (e.g., zinc oxide and titanium dioxide).[8] DSM fully supports FDA's proposal to finalize a monograph that would permit all listed active ingredients to be combined without limitation.[9] However, as indicated herein, we believe that sufficient information currently exists to make a positive GRASE determination for avobenzone under the current monograph. As such, we request that FDA allow avobenzone to be used in sunscreens either alone or in combination with all other GRASE sunscreen active ingredients (i.e., zinc oxide and titanium dioxide) without limitation under the current sunscreen monograph.

Allowing the combination of avobenzone with other TFM Category I ingredients such as titanium dioxide and zinc oxide will provide formulators greater flexibility to achieve balanced broad-spectrum sunscreen products to better protect the consumer. Furthermore, the combination of avobenzone with other GRASE Category I ingredients would provide the ability to achieve higher UVA protection in sunscreens. It would also allow for the formulation of mild sunscreens with sufficient UVA protection. It is especially important for babies (over 6-months old), children, and adults with skin disorders to fully protect their skin from both UVB and UVA radiation as their delicate skin is even more susceptible to damage.

3. Avobenzone Description and Identity

Avobenzone has the empirical formula $C_{20}H_{22}O_3$ and a molecular weight of 310.39 g/mol. It is a yellow powder with a weak characteristic odor. While it is soluble in a variety of polar and non-polar solvents, it exhibits low solubility in water; i.e., 0.01 mg/L at 20°C. Further chemical identity information is presented below.

IUPAC Name: 1-(4-tert-butylphenyl)-3-(4-methoxyphenyl)-propane-1,3-dione

CAS No.: 70356-09-1

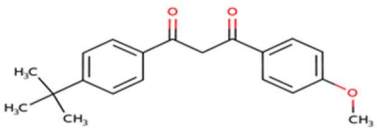
INCI Name: Butyl Methoxydibenzoylmethane (BMDBM)

USAN: Avobenzone

FDA/USP Unique Ingredient Identifier (UNII): G63QQF2NOX

Structure:

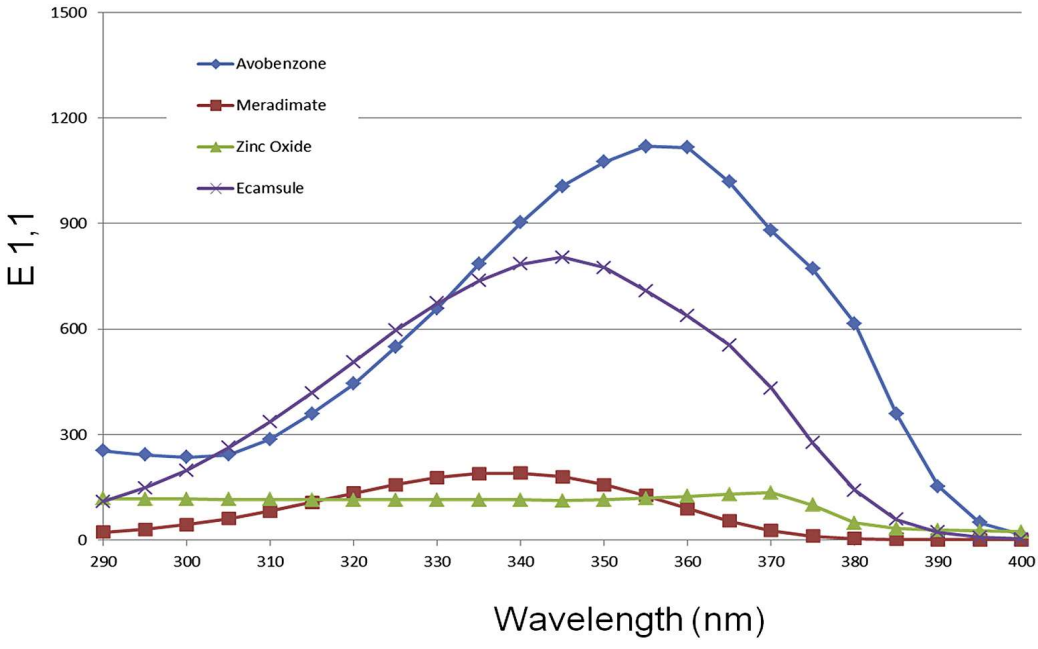
[8] IBID
[9] 84 Fed. Reg. 6209



3.1. UV Absorption Spectra

Avobenzone is one of the most effective absorbers in the UVA range (320–400 nm) of the electromagnetic spectrum and therefore is a critical ingredient for UVA protection. Avobenzone is currently the only dedicated UVA absorber listed on the OTC Sunscreen Drug Monograph. Avobenzone is essential for making well-formulated and broad-spectrum sunscreen products with high UVA protection. Such products help protect consumers from UVA induced skin damage including premature skin aging, aging skin disorders, lowered immunity against infection, DNA damage and cancer. Figure 1 illustrates the UV absorption spectra of avobenzone in comparison to other common UV sunscreen filters.

Figure 1. UV Absorption Spectra of Avobenzone in comparison to other UV Sunscreen Filters[10] (Jansen, Rebecca et al. (2013)



[10] Jansen, Rebecca et al. (2013). Photoprotection: Part II. Sunscreen: Development, efficacy, and controversies. Journal of the American Academy of Dermatology, Volume 69, Issue 6, 867.e1 - 867.e14

3.2. Photostability

With regard to photostability, it is well-known that avobenzone degrades upon exposure to sunlight. To address this issue and increase its stability and duration of action, photostabilizers are typically added to commercial sunscreen products. In the current TFM, FDA has proposed that any future sunscreen monograph including avobenzone as a GRASE active ingredient for use in sunscreen products require that it be photostabilized (via use of a photostabilizing UV filter or other photostabilizing ingredient/mechanism) to prevent its photodegradation. This should not be a problem as current sunscreen formulations already utilize appropriate and safe ingredients to address this issue without impact on safety or efficacy and this should continue in the future as well.

4. Global and US Regulatory Status

Avobenzone has a long history of safe use in sunscreen products in the United States and around the world. Table 2 presents a summary of the levels, countries and regions of the world where avobenzone is currently approved for use in sunscreen products. These permitted levels are based on the review of avobenzone safety, efficacy and post-market surveillance data by numerous regulatory bodies and safety experts around the world. Currently, none of the global regulatory bodies that have approved avobenzone for use in sunscreen products have reported that there are any health or safety concerns related with avobenzone.

Table 2. Global Regulatory Status of Avobenzone

	Maximum Level (Percent - %) Allowed in Sunscreens by Country/Region								
	EU	USA	Canada	MERCOSUR	Japan	Australia	China	Korea	ASEAN
Avobenzone	5	3	3	5	10	5	5	5	5

Under the TFM, FDA has proposed that avobenzone be listed as Category III at concentrations of up to 3% and FDA has requested that industry provide additional data characterizing its absorption and safety in order to support to support a positive GRASE determination for the ingredient. FDA has also indicated that it will defer the rulemaking for avobenzone (as well as other ingredients for which it receives a deferral request) in order to allow the necessary research to be conducted, submitted, and evaluated. Deferred ingredients may continue to be marketed as long as safety study workplans are submitted and progress continues to be made on the development of new data.

From a new drug approval perspective, it important to note that from 1992 to 2009, FDA reviewed and approved five OTC New Drug Applications (NDAs) containing avobenzone at concentrations ranging from 2-3%[11]. As part of the approval process, FDA reviewed the safety of avobenzone (together with other active sunscreen ingredients) at levels of 2-3% in the NDA formulation and various dosage forms.

[11] FDA Orange Book of Approved Drug Products with Therapeutic Equivalence Evaluations, https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm (accessed June 17, 2019)

Given the rigor of the NDA approval process, these NDA approvals should provide a high degree of confidence that avobenzone is safe for sunscreen use. Table 3 provides a summary of the OTC sunscreen NDA products that contain avobenzone.

Table 3. NDAs Containing Avobenzone (2-3%) Approved by FDA

Product Name / NDA # / Approval Date	Active Ingredient Levels Approved and Other Information
ANTHELIOS 20 – N021471 Approval Date: Oct 5, 2006	Active Ingredient: AVOBENZONE (2%); ECAMSULE (2%); OCTOCRYLENE (10%); TITANIUM DIOXIDE (2%) Dosage Form; Route of Administration: CREAM; TOPICAL Applicant Holder: LOREAL USA PRODUCTS INC Marketing Status: Over-the-counter
ANTHELIOS 40 – N022009 Two Product Approval Dates: Mar 31, 2008 and October 29, 2009	Active Ingredient: AVOBENZONE (2%); ECAMSULE (3%); OCTOCRYLENE (10%); TITANIUM DIOXIDE (5%) Dosage Form; Route of Administration: CREAM; TOPICAL Applicant Holder: LOREAL USA PRODUCTS INC Marketing Status: Over-the-counter
ANTHELIOS SX – N021502 Approval Date: Jul 21, 2006	Active Ingredient: AVOBENZONE (2%); ECAMSULE (2%); OCTOCRYLENE (10%): Dosage Form; Route of Administration: CREAM; TOPICAL Applicant Holder: LOREAL USA PRODUCTS INC Marketing Status: Over-the-counter
CAPITAL SOLEIL 15 - N021501 Approval Date: Oct 2, 2006	Active Ingredient: AVOBENZONE (2%); ECAMSULE (3%); OCTOCRYLENE (10%) Dosage Form; Route of Administration: CREAM; TOPICAL Applicant Holder: LOREAL USA PRODUCTS INC Marketing Status: Over-the-counter
SHADE UVAGUARD – N020045 Approval Date: Dec 7, 1992	Active Ingredient: AVOBENZONE (3%); OCTINOXATE (7.5%); OXYBENZONE (3%) Dosage Form; Route of Administration: LOTION; TOPICAL Applicant Holder: BAYER HEALTHCARE LLC Marketing Status: Discontinued

5. Safety of Avobenzone

5.1. Global Safety Reviews

Avobenzone is listed as 1-(4-tert-butylphenyl)-3-(4-methoxyphenyl) propane-1,3-dione in the Cosmetics Directive of the European Union and may be used as a UV filter in cosmetics and personal care products at a maximum concentration of 5% (Annex VI of the Regulation (EC) No 1223/2009).[12] Avobenzone's safety has been reviewed and found to be acceptable for use in sunscreens at levels of 5% by the authoritative regulatory bodies such as the EU Scientific Committee on Cosmetology (SCC) and Scientific

[12] https://data.europa.eu/euodp/data/dataset/cosmetic-ingredient-database-list-of-uv-filters-allowed-in-cosmetic-products (accessed June 18, 2019)

Committee on Consumer Safety (SCCS). [13,14] Moreover, avobenzone has been classified as not having estrogenic effects that could potentially affect human health by the EU Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP).[15] Independent non-governmental organizations such as the Environmental Working Group (EWG) have also reviewed the existing human exposure and toxicity data for avobenzone and have concluded that it has low toxicity concern and there is no evidence of hormone disruption associated with the ingredient.[16]

A summary of the registration dossier supporting the safety of avobenzone is publicly available in the EU. As part of the European Union's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, a current and extensive safety dossier exists for avobenzone at the European Chemicals Agency (ECHA) website that can be used to support its use in sunscreens at a level of 5%.[17] Medically credible institutions such the American Academy of Dermatology (AAD) also indicate that it is safe to apply sunscreens containing avobenzone.[18]

In 2015, the Ministry of Environment and Food, The Danish Environment Protection Agency conducted a Survey and Health Assessment of UV Filters to assess which UV-protective substances may can be considered sufficiently well-described and safe to use in relation to the possible effects on the environment and consumers.[19] Based on a preliminary safety assessment of the publicly available summaries of the confidential substance registrations reports contained in the REACH registration dossier[20], and using a worst-case dermal absorption rate of 10%, the Danish authorities concluded that the use of avobenzone as a UV filter at levels of up to 5% in sunscreen products does not pose a risk to consumers (Margin of Safety (MoS) ≥ 300).

The calculation and assumptions used in the Danish study to ascertain a MoS for 5% avobenzone used in sunscreen applications is presented Table 4.

[13] https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scc_o_9.pdf (accessed June 18, 2019)
[14] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf (accessed June 18, 2019)
[15] http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/sccnfp_opinions_97_04/sccp_out145_en.htm (accessed June 18, 2019)
[16] EWGs 2019 Guide to Sunscreens https://www.ewg.org/sunscreen/ (accessed June 18, 2019)
[17] https://echa.europa.eu/registration-dossier/-/registered-dossier/14835/7/5/2 (accessed June 17, 2019)
[18] https://www.aad.org/practicecenter/managing-a-practice/media-relations-toolkit/dermatology-issues-in-the-news/frequently-asked-questions-about-avobenzone (accessed June 20, 2019)
[19] https://www2.mst.dk/Udgiv/publications/2015/10/978-87-93352-82-7.pdf
[20] https://echa.europa.eu/registration-dossier/-/registered-dossier/14835/7/5/2 (accessed June 17, 2019)

Table 4. Danish Margin of Safety Calculation for Avobenzone

Parameter	Value
Amount of sunscreen applied daily (A)	18,000 mg/day
Concentration of ingredient in finished product (C)	5%
Total amount of active ingredient applied (Qi) = Q x C	900 mg/day
Typical body weight of human (bw)	60 kg
Absorption of active ingredient (DAp)	10%
Total amount absorbed Aabs= Qi x DAp	90 mg/day
Systemic exposure dose (SED) 90/60	15 mg/kg bw/day
No Observed Adverse Effect Level (NOAEL)* * based on subchronic oral repeated dose toxicity study, rats	450 mg/kg bw/day
MoS	**NOAEL/SED = 300**

The Danish EPA also performed a MoS calculation for sunscreens with an amount of 36 g applied daily. In this case, the calculated MoS was 150. Normally, when the MoS of an ingredient is ≥100, it can be considered to be safe. [21,22,23] As such, avobenzone was determined to be acceptable for sunscreen use at a concentration of up to 5%.

5.2. Avobenzone Safety Data

As indicated by FDA, the available nonclinical data for avobenzone include acute oral and dermal toxicity studies in rats; a 13-week oral toxicity study in rats; a 28-day dermal toxicity study in rats; a 21-day dermal toxicity study in rabbits; several in vitro genotoxicity tests; an in vivo micronucleus test in mice, as well as a sensitization test in guinea pigs; a primary skin irritation test in rabbits; an ocular irritation test in rabbits; a phototoxicity study in guinea pigs; a photoallergenicity study in guinea pigs; and embryofetal development studies in rats and rabbits.[24] These studies indicate that avobenzone has a low acute toxicity. Based on 13-week subchronic oral repeated dose toxicity study in rats, the NOAEL of avobenzone is considered to be 450 mg/kg bw/day.

Study results also indicate that the compound does not produce irritation of mucous membranes at concentrations up to 20% and caused slight irritation in rabbit skin by repeated applications (up to 18%) under occlusion. However, in human in-vivo studies, a repeated patch test was negative, as was a rechallenge after 10 days. Tests in the guinea pig for sensitization, phototoxicity, and photoallergenicity were negative. There was no evidence of mutagenicity or of photomutagenicity. Tests for genotoxicity as well as for teratogenic activity in the rat and the rabbit were negative. Clinical experience has shown the compound to be a rare allergen and photoallergen.

[21] http://www.sesec.eu/app/uploads/2015/12/CFDA-cosmetic-safety-evaluation-guideline_English.pdf (accessed June 18, 2019)
[22] http://ec.europa.eu/health/scientific_committees/environmental_risks/opinions/sctee/sct_out110_en.htm (accessed June 18, 2019)
[23] https://toxtutor.nlm.nih.gov/02-005.html (accessed June 17, 2019)
[24] 84 Fed. Reg. 6227

5.2.1. FDA Review of Avobenzone Safety Data

FDA proposes to find that avobenzone is Category III as it has identified several data gaps that are needed to be filled to support a finding that avobenzone (at up to either 3 percent or 5 percent) is GRASE for use in sunscreens.

The most critical data gap identified by FDA relates to the absorption of avobenzone *in-vivo* (under maximal use conditions). According to FDA these data are needed to assess the potential absorption of avobenzone from formulated sunscreen products and thereby determine if the carcinogenic risk of the ingredient is acceptable (i.e., less than 1 in 100,000 after single dose). As such, FDA expects that a MUsT clinical study[25] be conducted with sunscreen formulations containing avobenzone to assess if plasma concentrations exceed a threshold value of 0.5 ng/mL (which corresponds to determination of less than 1 in 100,000 carcinogenic risk after single dose), which together with the non-clinical and clinical safety data, will allow FDA to make a determination for supporting a positive GRASE finding for avobenzone use in sunscreens. Moreover, FDA indicates that the sunscreen formulations used in the MUsT designs must include a photostabilizer to ensure that the potential transdermal absorption of intact avobenzone from avobenzone-containing sunscreens is accurately assessed. The MUsT design should also be adequate to support the maximum level of avobenzone desired to be GRASE (i.e., either 3% or 5%).

Furthermore, FDA also indicates that if MUsT results show that there is significant systemic absorption of avobenzone, additional fertility and early embryonic development and prenatal and postnatal development studies in rats will be needed to support a positive GRASE finding. Depending on the results of the MUsT, systemic carcinogenicity studies may also be needed. However, it is important to note that the available embryofetal development studies in rats and rabbits did not reveal any findings of concern for its use during critical phases of pregnancy and postnatal development. With regards to pediatric studies, FDA has indicated that if the calculated safety margin for an active ingredient (based on nonclinical results and human MUsT) is relatively small, FDA will exercise its scientific judgment to determine whether a sunscreen active ingredient MUsT in young children or other studies are warranted to ensure that the safety margin for marketed products containing the ingredient is within an acceptable range for this population. From a chronic use perspective, dermal carcinogenicity and toxicokinetic data may also be needed to support to support a positive GRASE finding for sunscreens containing avobenzone. All studies should be designed to support the maximum level of avobenzone desired to be GRASE (i.e., either 3% or 5%). These considerations are addressed in the risk assessment (Section 6) below.

From a dermal safety perspective, FDA finds that the clinical dermal studies submitted to the monograph on avobenzone demonstrate that avobenzone, at a concentration of up to 5% has a favorable safety profile, is well tolerated for topical use and is essentially non-allergenic, non-irritating, and non-sensitizing, with mild to moderate reactions occurring only rarely. As such, no further dermal photosafety, irritation, or sensitization clinical studies are required to support the safety of avobenzone use at up to 5%.[26]

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[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/maximal-usage-trials-topically-applied-active-ingredients-being-considered-inclusion-over-counter (accessed June 19, 2019)

[26] 84 Fed. Reg. 6227

Table 5 summarizes the studies that FDA is recommending to support a positive GRASE determination for avobenzone.

Table 5. Summary of FDA Recommended Studies for Avobenzone Up to 3 (or 5) Percent

Safety studies FDA proposes are necessary to support a GRASE determination	Additional studies or data necessary?
harmacological Studies:	
Human absorption (MUsT) (including metabolite study in humans)	Yes.
lonclinical Safety Studies:	
Toxicokinetics	Yes.
Dermal Carcinogenicity	Yes.
Systemic Carcinogenicity	Dependent on results of the MUsT.
ART:	
Fertility and early embryonic development	Dependent on results of the MUsT.
Embryofetal development in two species (rodent and non-rodent)	No.
Prenatal and postnatal development	Dependent on results of the MUsT.
linical Safety Testing:	
Skin irritation and sensitization	No.
Skin photoallergenicity and phototoxicity	No.
Pediatric studies	Pediatric studies may be required depending on the outcome of the MUsT.

5.2.2. FDA MUsT Study Results

FDA recently published the results of Part 1 of their Maximum Usage Trials (MUsT) to determine whether the active ingredients (avobenzone, oxybenzone, octocrylene, and ecamsule) are absorbed into systemic circulation at plasma concentrations above 0.5 ng/mL.[27] As indicated in the study, the 0.5-ng/mL threshold is based on the principle that the level would approximate the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100 000 after a single dose.

Under the study, commercially available sunscreen products containing avobenzone (3% max.) and representing different product dosage forms (sprays, lotions and creams), were utilized under maximal use conditions (2 mg of sunscreen per 1 cm^2 applied to 75% of body surface area 4 times per day for 4 days) to ascertain avobenzone and other sunscreen ingredient plasma levels. For avobenzone, the geometric mean maximum plasma concentrations observed were 4.0 ng/mL, with different dosage forms having different mean plasma concentrations ranging from 1.8 ng/mL to 4.3 ng/mL. The commercial products tested, together with a listing of active and inactive ingredients were provided in the study protocol and supplemental summary tables in the FDA study.[28]

Review of the commercial formulations used in the study indicate that the products tested contained a photostabilizer to prevent the photodegradation avobenzone. In general, the inclusion of a photostabilizer protects avobenzone from photodegradation and provides a more accurate assessment of the absorption levels of avobenzone in final formulated sunscreen products as required by FDA for avobenzone to be considered GRASE.

[27] Matta MK, Zusterzeel R, Pilli NR, et al. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. JAMA. Published online May 06, 2019. doi:10.1001/jama.2019.5586; https://jamanetwork.com/journals/jama/article-abstract/2733085 (accessed June 17, 2019)

[28] IBID

Furthermore, with regard to the MUsT findings, it should be noted that the measurable avobenzone plasma concentrations attained are not expected to translate into any toxicological consequences based on its long history of safe use by consumers. More importantly, as discussed in the hazard and risk assessment section below, these human pharmacokinetic study results are recast as the key systemic exposure parameters to estimate more representative safety margins based on representative non-clinical study results.

Therefore, from a practical perspective, the results of FDA's MUsT study already provide a reasonable estimate of what the transdermal absorption of avobenzone is in humans under maximum use conditions, using commercially available products. Data that will again be repeated as required by FDA under a second pilot and broader pivotal MUsT study for all active ingredients deferred under the TFM. From a scientific perspective, it is important to realize that data generated under FDA's current MUsT study protocol, including the in-progress study Part 2, can be used to extrapolate and obtain a general estimate of what the general population transdermal absorption levels are for avobenzone. This exposure information can then be coupled with the existing safety (toxicity) data on avobenzone to conduct a toxicological risk assessment that can be utilized to:

- Characterize the nature and magnitude of the potential health risks associated with dermal absorption of avobenzone (using marketed sunscreen formulations);
- Assess whether adequate safety margins (MoS) exist for it use in sunscreens under maximal use and real-world formulation conditions;
- Assess whether the carcinogenic risk associated with chronic use is less than 1 in 100 000 after a single dose; and most importantly,
- Provide FDA with a more efficient mechanism for informing, evaluating and supporting a positive GRASE determination for avobenzone (or any other sunscreen active ingredient) from a scientific perspective.

It should also be noted that combining the results of this alternative risk assessment approach together with an evaluation of the real-world evidence and post-market surveillance data associated with avobenzone (or any other UV-filers) would have the added benefit of helping eliminate unnecessary animal testing.

We have conducted such a risk assessment for avobenzone (below) using FDA's current MUsT findings as a sufficiently representative to allow estimating the transdermal absorption potential of avobenzone in humans. The results of our assessment show that a sufficiently large margin of safety currently exists supporting avobenzone's designation as GRASE in sunscreens at a level of 3% and 5%. As such, we request that FDA make a positive GRASE determination for avobenzone under the current TFM.

6. AVOBENZONE DATA OVERVIEW AND RISK ASSESSMENT

Avobenzone, an OTC Sunscreen Monograph (TFM) Category III UV filter, as noted above was recently reviewed by FDA for adequacy of its safety data and continuation of it listing on the Monograph. Using a checklist approach, FDA identified the additional safety data needed to support the FDA GRASE evaluation. It is our objective to focus attention on the safety data that are available for avobenzone and rather than use the data gaps checklist approach, build an informed framework of available data and

information that will support avobenzone safety as sufficiently defensible for a GRASE evaluation without further non-clinical animal testing. Below, Tables 6 and 7 respectively provide a summary of the avobenzone's chemical characteristics and associated non-clinical and clinical safety data.

Table 6. Identifiers and General Characteristics of Avobenzone[29]

Chemical-IUPAC Name	4-tert-Butyl-4'-methoxydibenzoylmethane
INCI name	Butyl methoxydibenzoylmethane (BMDBM)
CAS Reg Number	70356-09-1
EINECS	274-581-6
Molecular wt (Daltons)	310.38
Melting point	81 – 84 °C (reported experimental range)
Log P_{ow} Log K_{ow}	6.1 (measured) 4.51 (KOWIN v1.67 estimate)
Solubility	Water 0.01 mg/L; DMSO 0.062 mg/L
Vapor pressure	1.36E-006 mm Hg, 25 °C (EPISuite)

Table 7. Summary of Avobenzone Non-Clinical and Clinical Safety Data

Results of Safety Testing with AVOBENZONE[30]	
Study (related Test Guideline)	**Study Results /Conclusions**
Acute Oral LD_{50} (OECD TG 401) **Acute Dermal LD_{50} (OECD TG 402)**	>16,000 mg/kg bwt (rat) > 1,000 mg/kg bwt (rat)
Skin irritation (OECD TG 404)	NZ White rabbit, 6/group; 10% AVOBENZONE, occluded on intact & abraded skin, scored at 4hrs: very slight irritation potential
Eye irritation (OECD TG 405)	NZ White rabbit, 3/group; avobenzone at 5, 10, or 20%. Reversible Conjunctival irritation scores: 0, 0.44, 0.67, respectively; other effects did not occur. Not eye irritant
Skin Sensitization (OECD TG 406)	Guinea pig Maximization test: induction using 5% intradermally then 20% under occlusion for 2d; challenge with 20% and 6% for 24h. Not sensitizing
Skin Photosensitization	Guinea pigs, 10 in each of four groups: 2 for test item dosed at 10% or 1%, negative acetone control and positive control; induction by adjuvant intradermally then 5 topical doses followed by UVA irradiation given over 2-weeks period. Challenge dose

[29] https://pubchem.ncbi.nlm.nih.gov/compound/Avobenzone (accessed June 21, 2019)

[30] Data from DSM Archive (legacy Givaudan-Roure Docket No. FDA-1978-N-0018-0751), EU SCC Opinion 1992, or from European Chemical Agency (ECHA) published database (https://echa.europa.eu/registration-dossier/-/registered-dossier/14835) and also as reported by Danish EPA 2015 (Survey and health assessment of UV filters, No. 142)

Results of Safety Testing with AVOBENZONE[30]	
	with 10% solution and UVA on each of days 21 and 35. Photoallergenicity did not occur.
Bacterial reverse mutation (OECD TG 471)	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100, TA102 up to 5000 μg/plate, with & without activation: Not mutagenic
Mammalian cell in vitro mutation (OECD TG 476)	V79 (Chinese hamster lung fibroblasts) up to 20 μg/ml with and without metabolic activation assessed for activity at HGPRT locus. Not mutagenic
Photomutagenicity	Separate tests with Saccrharomyces cerevisiae and Chinese hamster ovary cells exposed to the test item and UVA and UVB irradiation did not show mutagenic effects. Not photomutagenic
Micronucleus test, mice in vivo (OECD TG 474)	Bone marrow polychromatic erythrocytes of mice dosed once orally 100, 2500 or 5000 mg/kg wt. were evaluated. Not genotoxic
13-Wk repeat dose test (OECD TG 408)	Dosed feed at 0, 200, 450, or 1000 gm/kg bwt/d to 12 rats/sex/dose for 91-94 days and a 30d non-dosed recovery period with 6/sex from control & high dose groups, did not show effects on mortality, body wts, food consumption, urinalysis parameters, gross pathology or microscopic neoplastic changes. High dosed females showed dose-related reduced RBC and hemoglobin (Hb) & in high dosed males and each female dosed group a reversibly increased ($p<0.05$) liver relative wts, with hypertrophic hepatic parenchyma cells persisting at the high dose. The LOAEL= 1000 mg/kg/d and the NOAEL= 450 mg/kg/d
28-day Dermal daily dosing (OECD TG 410)	Rats in four groups each with 5 male and 5 females dosed 5 h/d under occlusion on abraded and intact skin for 28-days did not show test item related adverse changes systemically or to skin at dosages up to 230 mg/kg/d. NZ White rabbits, 10/sex/group, half with abraded and half intact skin exposed under occlusion 6-h/day for 21d with 0, 30 (1.5% w/v), 100 (5%) or 360 (18%) mg avobenzone at the highest soluble amount in Carbitol/ kg bwt/d did not show mortality or test item-related adverse effects in any dosed group based on standard study parameters including body wt, organ wts, hematology, clinical chemistry, gross- and histopathology; dose-related local dermal effects included erythema and edema. The systemic NOAEL is 360 mg/kg/d, and the topical local effects indicate a LOAEL of 100 mg/kg/d and a NOAEL of 30 mg/kg/d.
Developmental Toxicity (OECD TG 414)	Rabbits given single oral gavage doses up to 500 mg/kg/d on each of gestation days 7-19 did not show test item related effects or teratogenicity. Rats dosed once daily by oral gavage at 0, 250, 500, or 1000 mg/kg bwt/d on each gestation day 6-17 (12 days); 18 dams per group sacrificed & examined on GD 21, 18 dams/group allowed delivery and litters retained until weaning. Examination of dams, embryos, fetuses & neonates did not reveal dose-related adverse effects. Maternal NOAEL = 1000 mg/kg/d; Developmental NOAEL = 1000 mg/kg/d
Endocrine activity	Estrogen receptor-alpha in vitro only slightly induced, not corroborated by in vivo zebra fish assay. Reporter gene assays showed only weak antagonism of androgen receptor and no influence on progesterone receptor. No Endocrine activity.
Human repeated insult patch test	10% in ethanol/diethylphthalate was not sensitizing (0/50 subjects); 6% in ethanol/diethylphthalate and UV exposure was not photosensitizing (0/25 subjects)
Human phototoxicity	6% in ethanol/diethylphthalate and UV exposure was not phototoxic (0/25 subjects)

6.1. Hazard Assessment

Based on the available non-clinical and limited human clinical safety test results, avobenzone shows a very good safety profile without any clear markers of toxicity or endpoints of concern. This conclusion has been reached and considered to be well supported by all global regulatory authorities as indicated by their registering this substance for use at up to 5% in consumer end-use products, as has been discussed in Section 4 of this document.

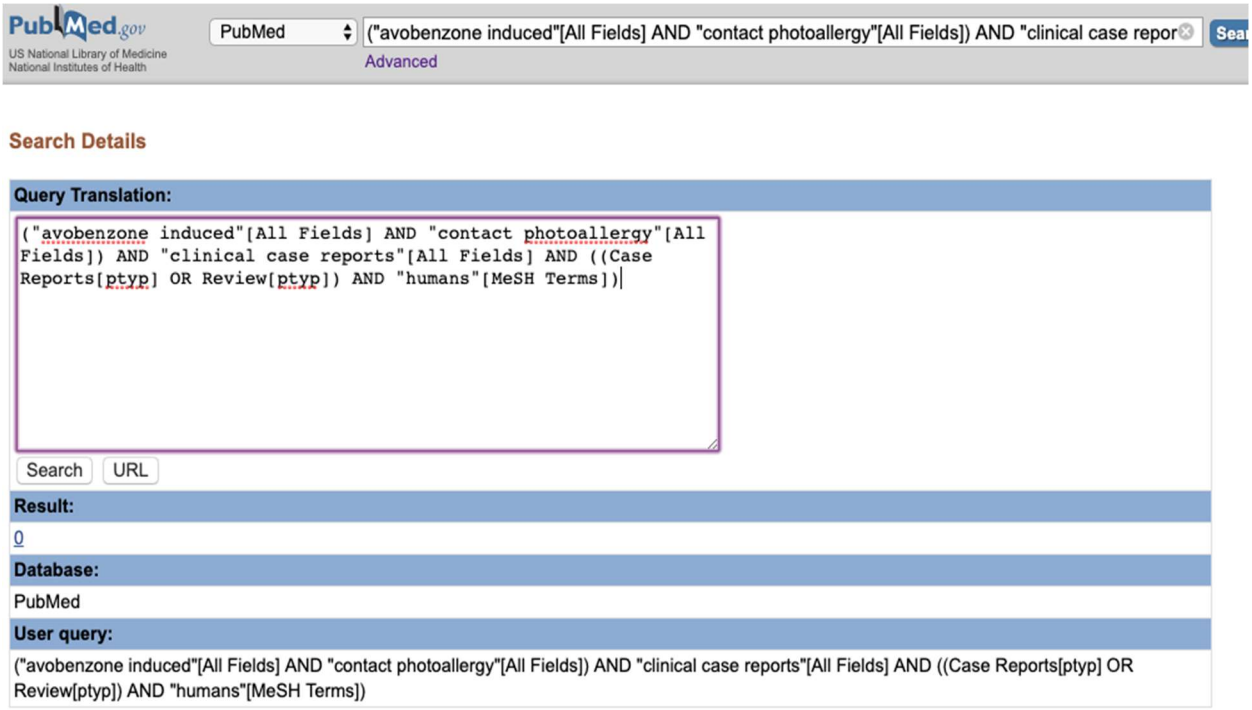
Key indicators for avobenzone safety are that it is not mutagenic or genotoxic in vitro or in vivo, is not photo-genotoxic or photomutagenic, did not indicate adverse interactions with endocrine systems, disrupt developmental or maternal processes in pregnant animals, or induce skin sensitization responses in animals or humans by standard tests either without or with UV irradiation. Repeated dose testing in rats via their diet and in rabbits with topical applications did not reveal signs of systemic toxicity or microscopic changes in tissues and organs that would increase concern for adverse changes or neoplasia with longer term exposures. Reproductive tissues, and the in vivo embryo, fetal, or neonatal stages were not adversely affected or altered under high daily doses of avobenzone from 450 to 1000 mg/kg bwt/day.

The local topical tolerance NOAEL for avobenzone is 30 mg/kg/day from a 28d dermal rabbit test, and the systemic hazard NOAEL is 450 mg/kg/d from the subchronic (90 days) rat dosed feed study.

6.1.1. Adverse Event Reports

As previously noted, FDA finds that avobenzone, at a concentration of up to 5% has a favorable safety profile, is well tolerated for topical use and is essentially non-allergenic, non-irritating, and non-sensitizing, with mild to moderate reactions occurring only rarely. As seen in Figure 2, results from a recent literature search did not reveal any citations for Clinical Adverse Event reports for avobenzone.

Figure 2. Snapshot of recent PubMed Search of Clinical Adverse Event Reports for Avobenzone



6.1.2. In Silico Evaluations

A recently completed in silico assessment of avobenzone for chemical structure-related alerts of toxicity using DEREK Nexus algorithms at a reasoning level of equivocal showed good consistency between the completed guideline-equivalent tests and the DEREK results. [31,32] Derek Nexus is a knowledge-based expert system that predicts the toxicity and metabolism of a chemical, respectively. It provides an effective mechanism for the sharing of data and knowledge on chemical toxicity and metabolism. It also provides a more direct assessment of predictive performance, avoiding the inherent difficulties of reference to published studies, by allowing the user to access information directly on predictive performance. We emphasize that carcinogenicity was not predicted by the system's reference database. The endpoint summary is shown in Table 8.

[31] https://omictools.com/derek-nexus-tool

[32] DSM 2019. DEREK Nexus Prediction Report for 70356-09-1 (BMDBM). Program version Derek Nexus: 6.0.1, Nexus: 2.2.1; Lhasa Ltd. Reported on 24 May 2019.

Table 8. Results of DEREK Nexus Predictions for Avobenzone[1]

Endpoints NOT firing any alerts at DEREK Nexus reasoning level of : Equivocal[a,b]	
5alpha-Reductase inhibition	Kidney function-related toxicity
Adrenal gland toxicity	Lachrymation
alpha-2-mu-Globulin nephropathy	Methaemoglobinaemia
Anaphylaxis	Mitochondrial dysfunction
Androgen receptor modulation	Mutagenicity in vivo
Bladder disorders	Nephrotoxicity
Bladder urothelial hyperplasia	Neurotoxicity
Blood in urine	Non-specific genotoxicity in vitro
Bone marrow toxicity	Non-specific genotoxicity in vivo
Bradycardia	Occupational asthma
Carcinogenicity	Ocular toxicity
Cardiotoxicity	Oestrogen receptor modulation
Cerebral oedema	Oestrogenicity
Chloracne	Peroxisome proliferation
Cholinesterase inhibition	Phospholipidosis
Chromosome damage in vitro	Photo-induced chromosome damage in vitro
Chromosome damage in vivo	Photo-induced non-specific genotoxicity in vitro
Cumulative effect on white cell count and immunology	Photo-induced non-specific genotoxicity in vivo
Cyanide-type effects	Photocarcinogenicity
Developmental toxicity	Photomutagenicity in vitro
Glucocorticoid receptor agonism	Phototoxicity
Hepatotoxicity	Pulmonary toxicity
HERG channel inhibition in vitro	Respiratory sensitisation
High acute toxicity	Splenotoxicity
Irritation (of the eye)	Teratogenicity
Irritation (of the gastrointestinal tract)	Testicular toxicity
Irritation (of the respiratory tract)	Thyroid toxicity
Irritation (of the skin)	Uncoupler of oxidative phosphorylation
Kidney disorders	Urolithiasis

[a.] Report date: 24 May 2019 (Derek Nexus 6.0.1, Nexus: 2.2.1; Lhasa Ltd.)
[b.] Equivocal defined in DEREK Nexus as: There is an equal weight of evidence for and against the proposition.

6.1.3. Photo-allergenicity and Photo-degradation Products

The DEREK Prediction report identified and substantiated the chemical structural components that triggered the alert for mammalian photoallergenicity as probable, citing “715 Diaryl-1,3-propanedione” as the alert match and avobenzone as the exact match example. The rule base used the logic that if the species considered is human then photoallergenicity is certain. Clinical records and case reports have documented the photoallergenicity of avobenzone as presented below.

The UV-light induced degradation of avobenzone is a recognized characteristic of the molecule and has been associated with a number of published clinical case reports documenting allergic contact

dermatitis.[33,34,35,36,37] The mechanism associated with the induction of the photo-contact allergenicity has been related to the formation in the skin of a protein-binding hapten formed after UV-photodegradation of avobenzone to its arylglyoxal form. These haptens have been shown to have direct protein interactions that are the basis for their classification as strong sensitizers.[33,38]

Concurrently, it is well known, and is commonly employed in sunscreen formulations using avobenzone, that including certain UV filters or other specific ingredients in the formulation will prevent the photodegradation of avobenzone and stabilize it in the formulation. Details of the mechanisms associated with these effects have been explored by Lhiaubet-Vallet et al. (2010). [39]

In the TFM FDA, the photoinstability of avobenzone is cited as an issue of concern and requires specifically that a photostabilizer be used in any sunscreen formulations containing avobenzone. While avobenzone can be a cause of photoallergic skin reactions when present in sunscreens, the hazard can be mitigated with judicious use of recognized photostabilizers in the formulation.

[33] Bryden A.M., Moseley H, Ibbotson SH, Chowdhury MMH, et al. 2006. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. Br J Dermatol 155, 737–747. DOI 10.1111/j.1365-2133.2006.07458.x

[34] Neumann NJ, Holzle E, Plewig G, et al. 2000. Photopatch testing: the 12-year experience of the German, Austrian and Swiss photopatch test group. J American Acad Dermatol, 42, 183-192. DOI: 10.1016/S0190-9622(00)90124-5

[35] Journe F, Marguery MC, Rakotondrazafy J, El Sayed F and Bazex J. 1999. Sunscreen sensitization: a 5-year study. Acta Dermato-Venereologica, 79, 211-213.

[36] Schauder S and Ippen H. 1997. Contact and photocontact sensitivity to sunscreens. Review of a 15-year experience and of the literature. Contact Dermatitis, 37, 221-232.
DOI: 10.1111/j.1600-0536.1997.tb02439.x

[37] Karlsson et al. 2009, Photodegradation of Dibenzoylmethanes: Potential Cause of Photocontact Allergy to Sunscreens. Chemical research in toxicology. 22. 1881-92. 10.1021/tx900284e.

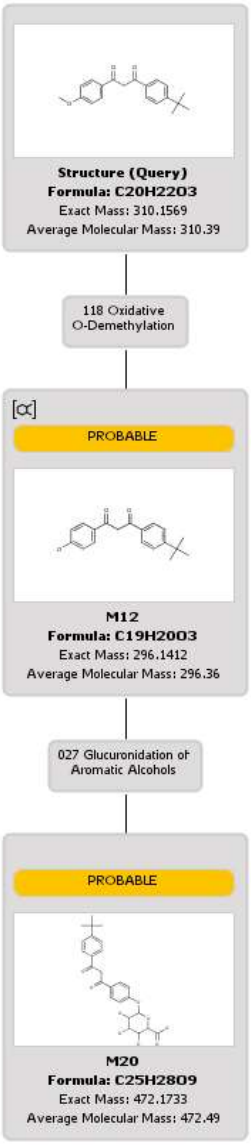
[38] DSM 2019. DEREK Nexus Prediction Report for 70356-09-1 (BMDBM). Program version Derek Nexus: 6.0.1, Nexus: 2.2.1; Lhasa Ltd. Reported on 24 May 2019.

[39] Lhiaubet-Vallet V, Marin M, Jimenez O, et al. 2010. Filter-filter interactions. Photostabilization, triplet quenching and reactivity with singlet oxygen. Photochem & Photobiolog Sci 9, 552-558. DOI: 10.1039/b9pp001158a.

6.1.4. In Silico Metabolism Assessment

In vivo metabolism studies of avobenzone were not available. Therefore, the metabolism prediction tool Meteor Nexus (Lhasa Ltd) was queried with avobenzone to assess the Probable in vivo mammalian metabolic pathways (DSM Meteor Nexus Prediction Report, 24 May 2019. Program version Meteor Nexus: 3.1.0; Nexus: 2.2.1). Results indicated the predominant biotransformation processes to be terminal oxidative o-demethylation and terminal methyl hydroxylation with subsequent glucuronidation or sulfonation (plausible) of aromatic alcohols. These biotransformation steps readily facilitate urinary excretion by the resulting increased water solubility, as summarized in the nearby graphic. This implies that any systemically available avobenzone will be readily eliminated via urine and not accumulate in tissues or fat. Figure 3 depicts the Predicted Probable Metabolic Pathway of Avobenzone. Additionally, metabolic intermediates or formed moieties are not among those chemical structural alignments associated with adverse effects or target organ toxicity.

Figure 3. Predicted Probable Metabolic Pathway of Avobenzone



6.1.5. Toxicokinetics and Exposure Assessment

The uptake and distribution of avobenzone, in the absence of in vivo absorption, distribution, metabolism and elimination or kinetics testing has been inferred from results of the completed in vivo animal studies and the chemical characteristics of avobenzone. The reported liver effects seen in the 13-week rat feeding study can be taken as indirect evidence for the absorption of avobenzone or its metabolites from the GI system.

Dermal absorption of avobenzone after topical application is expected to be low based on its molecular weight being less than 500, its log P_{ow} being above the range favoring skin penetration (log P_{ow} -1 to +4), and its low water solubility (DSM information submitted to ECHA). The absence of systemic adverse effects in the 28-d dermal rat and rabbit studies suggests that these expectations may be relatively consistent with the animal test results.

In the EU SCC opinion for avobenzone[40] are included results for a series of in vitro percutaneous penetration tests using skin preparations from naked rat, minipig and human abdominal cadaver skin exposed to avobenzone at 1% up to 10% in solvent or cosmetic formulations (o/w lotion, o/w cream,

[40] SCC (Scientific Committee on Cosmetology) 1992. Reports of the Scientific Committee on Cosmetology, 9th series. 4-Tert.-butyl-4'-methoxydibenzoylmethane, COLIPA S66. 50th plenary meeting of 2 June 1992. pp 222-227.

w/o cream). Rats showed a comparatively 2- to 3-times higher amount of avobenzone in the skin layers than found in minipig skin (about 3% of an applied 2% test item in a cosmetic formulation) or in the human skin test system; none of the test systems showed measurable avobenzone amounts in the receptor fluid chamber. In the human skin in vitro test system dosed with ^{14}C-labelled avobenzone, up to 2.7% of the applied radioactivity was observed in the epidermis, 7.3% in the dermis 18-hour post dose but no activity was found in the collection fluid at any time and the lower dermis contained only 0.34% of the applied radioactivity. The in vitro test results indicated that the dose concentration did not have an apparent effect on increasing the skin penetration amounts, whereas, increasing durations of exposure resulted in higher amounts in the skin upper layers. A skin penetration amount of approximately 10% of the applied avobenzone would be a conservative (worst case) estimator based on in vitro data.

An in vivo human skin absorption study used 4 subjects each treated with 200 µl of a 10% solution of ^{14}C-labelled avobenzone in carbitol applied at 2 mg/cm^2; dose sites for three subjects were non-occluded and occluded for one subject, over an 8-hour exposure. The amounts of avobenzone found in the skin stripping samples were 0.48% and 0.17% and in urine 0.08 and 0.013% for the occluded and non-occluded experiments, respectively. No radioactivity was found in the blood or feces in any subject. These data suggest that after a single topical application that only a very low level of systemic penetration of avobenzone or its metabolites would be expected (SCC 1992, ECHA 2019). Using these in vivo data could support a 1% skin penetration amount of the applied avobenzone as a conservative estimator for systemic exposure used for risk assessments.

6.1.6. Human Pharmacokinetic Systemic Results

FDA recently published the results of their MUsT test to determine whether the active ingredients (avobenzone, oxybenzone, octocrylene, and ecamsule) are absorbed into systemic circulation at plasma concentrations above 0.5 ng/mL.[41] As indicated above, the 0.5-ng/mL threshold becomes a demarcation line approximating the highest plasma level below which the carcinogenic risk of any unknown compound would be less than 1 in 100,000 after a single dose in the absence of other hazard data.

Under the study, commercially available sunscreen products containing avobenzone (3% max.) and representing different product dosage forms (sprays, lotions and creams), were utilized under maximal use conditions (2 mg of sunscreen per 1 cm^2 applied to 75% of body surface area 4 times per day for 4 days) and plasma samples collected to ascertain avobenzone concentrations over the 4 dosing days and then on study days 5, 6, and 7 to show the avobenzone elimination profile. This application regimen resulted in a daily use of 105 grams of sunscreen formulation containing 3.15 g of avobenzone (3% in products) applied topically.

The commercial products tested, together with a listing of active and inactive ingredients were provided in the study protocol and supplemental summary tables in the FDA study.[42] Review of the commercial formulations tested in the study indicate that the products contained a photostabilizer to prevent

[41]Matta MK, Zusterzeel R, Pilli NR, et al. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. JAMA. Published online May 06, 2019. doi:10.1001/jama.2019.5586; https://jamanetwork.com/journals/jama/article-abstract/2733085 (last accessed June 17, 2019)

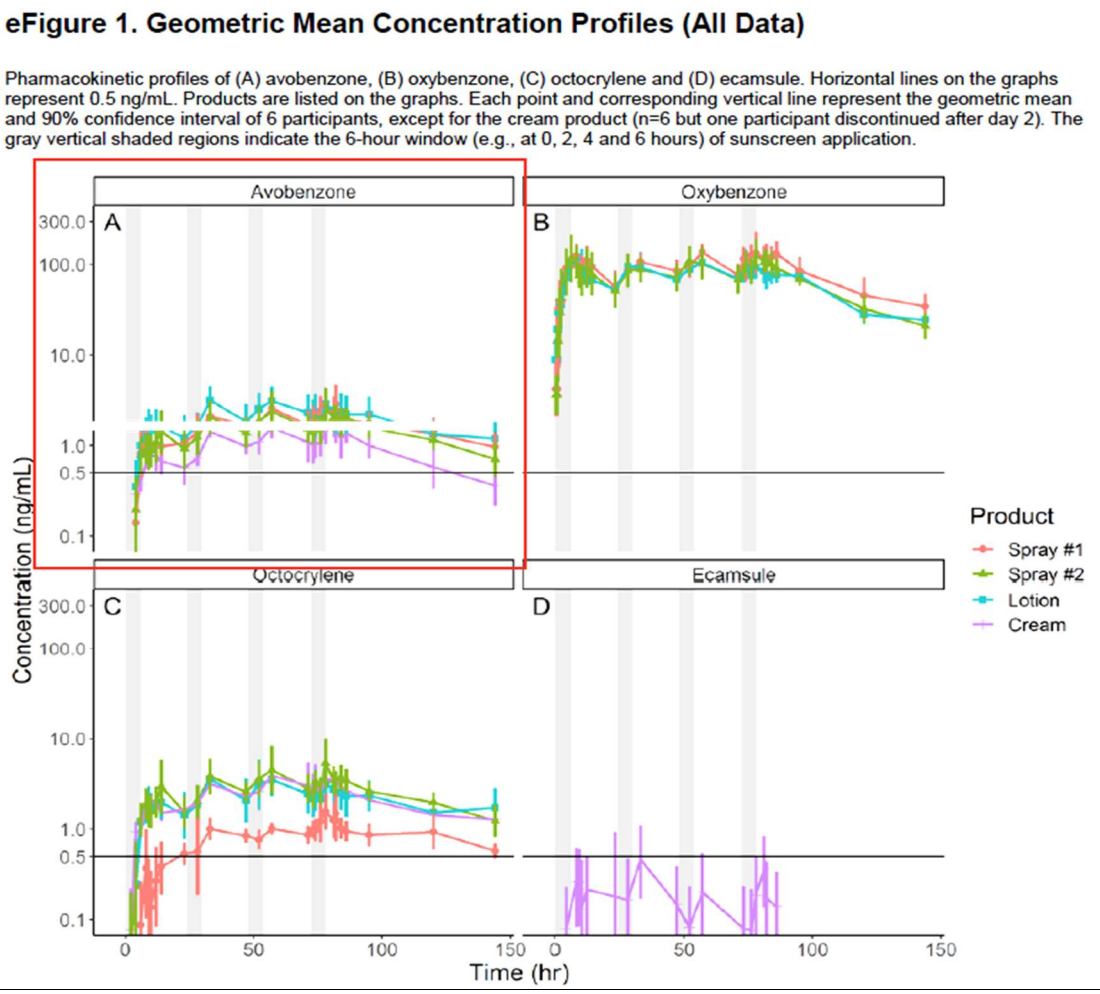
[42] IBID

photodegradation of avobenzone. In general, the inclusion of a photostabilizer protects avobenzone from photodegradation and provides a more accurate assessment of the absorption levels of avobenzone in final formulated sunscreen products as required by FDA for avobenzone to be considered GRASE.

Over the four days of sunscreen applications, the avobenzone geometric mean maximum plasma concentrations (C_{max}) observed were 4.0 ng/mL (T_{max} 77h), with different dosage forms having different mean plasma concentrations ranging from 1.8 ng/mL to 4.3 ng/mL (T_{max} 69h to 67.5h). The results from samples taken before the next day's applications (trough concentrations) indicated the daily elimination of about 75% of the C_{max} amounts in each study group; the C_{max} concentrations on Day 4 were about twice the Day 1 amounts (geometric mean ratios of Day 4 to Day 1 were 2.38 to 1.47). The geometric mean ratios of the AUC values (ng/mL*h) for Day 4 to Day 1 showed a similar range of 2.77 to 2.00 (report supplement 2).

A plasma steady state of about 3 to 5 ng/mL may have been reached based on a visual estimation from the graphical presentation of the plasma profile over the study (Figure 4). The residual avobenzone concentrations at Day 7 were 1.2 to 0.3 ng/mL and indicated a Terminal half-life of 54.6 to 33 hours.

Figure 4. Avobenzone plasma kinetic profiles augmented for Steady state estimation.
(Original Figure taken from Matta et al. 2019[43]; Estimation line was set by visual approximation)



Overall, even with small panel sizes of 6 volunteers per formulation (24 subjects), the study results indicated a slow dermal absorption rate, a daily elimination pattern suggesting avobenzone was not accumulating, although a steady state appeared to be established, and a clear elimination profile for the UV filter at the end of exposures. These results are consistent with those predicted from the substance kinetics assessment discussed above.

In this initial human PK study using exposure to extreme amounts of avobenzone in sunscreen formulations, the various calculated PK parameters showed wide ranges for interindividual results (Coefficient of Variation % values in Table 9 below and in the Supplement Data eTables of Matta et al. 2019).[44] We suggest that results of FDA's current MUsT study with avobenzone and other active

[43] Ibid
[44] https://jamanetwork.com/journals/jama/article-abstract/2733085 (accessed June 17, 2019)

sunscreen formulations (Matta et al. 2019, Data Supplement 1) provides sufficient information to appropriately characterize the human PK results for avobenzone.

6.2. RISK ASSESSMENT

As documented in the hazard assessment section the local topical tolerance NOAEL is 30 mg/kg/day from a 28d dermal rabbit test, and the systemic hazard NOAEL is 450 mg/kg/d from the subchronic (90 days) rat dosed feed study.

As summarized above, a number of safety characterizations have been made by other regulatory agencies and show good Margin of Safety (MoS) values (>100) for avobenzone at 3% or 5% in sunscreens. The exposure estimations were based on standard cosmetic formulation usage amounts, skin surface area treated, and application frequencies: 1 mg formulation/cm^2 to 17,500 cm^2 of skin and 18 g of finished cosmetic product. While sunscreens are recommended to be applied at 2 mg/cm^2 and with repeated applications during sun-exposure events, it is known that sunscreens and personal care cosmetic applications generally are at the lower application rate[45].

In contrast, the Maximum Usage Trial (MUsT) is designed to use an estimated maximum highest likely application rate of the dermal therapeutic in order to estimate the human pharmacokinetic profile (FDA 2019 MUsT guidance). For UV filters, maximal use conditions are considered to be 2 mg of sunscreen/cm^2 applied to 75% of body surface area (13,125 cm^2) 4 times per day. This application regimen results in a daily use of 105 grams of sunscreen formulation containing 3.15 g of avobenzone (3% in products) applied topically. It is recognized that these application amounts are intended to be extreme as they are for experimental design purposes and are not modelling actual human use scenarios.

Systemic exposure estimations for avobenzone from avobenzone use are best represented by human PK parameters determined with a maximal topical exposure to commercial sunscreen formulations and other personal care cosmetics containing 3% avobenzone. The plasma kinetic results and the calculated human systemic dose from the MUsT paradigm are summarized in Table 9 below.

Using the C_{max} geometric mean plasma concentrations over the 4 days of exposure for each of the four formulations, as seen in the table, the calculated systemic avobenzone amounts are 5 to 13 micrograms per person and below 1 microgram/kg/body wt. across the groups. From each exposure compared to the rat NOAEL, **the systemic MoS is 2 to 5x10^6**. Applying an adjustment (uncertainty) factor for extrapolation of the 90d rat to a chronic exposure (factor 10) and for human variability (factor 3), the adjusted MoS values are only 1 or 2 orders of magnitude lower than before adjustments and still well above the values (100 based on non-clinical data or 10 as for clinical results) considered as minimum thresholds for safe human exposures.

Further substantiating avobenzone as safe for sunscreen use in commercial formulations, as shown in the highlighted column of Table 9, the visually estimated higher plasma steady state value of 5 ng/mL has been used to estimate a comparative SED (systemic estimated dose) and the MoS of 6x10^4, which is

[45] SCCS (Scientific Committee on Consumer Safety) 2018. The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation. SCCS/1602/18 Final version October 2018.

also exceedingly high. This estimated SED is only about one order of magnitude higher than the TTC systemic exposure dose.

Table 9. Avobenzone Pharmacokinetic Overview and Safety Characterization (PK Data from Matta et al. 2019).

Parameter	Spray 1	Spray 2	Lotion	Cream	Steady State est.	Comment
Overall Max Plasma Amount (ng /ml)	4	3.4	4.3	1.8	5	Results are the Geometric Mean
CV% (range, ng/mL)	60.9 (1.6-8.3)	77.3 (1.0-7.3)	4.2 (2.8-9.3)	32.1 (1.1-2.7)	Not Avail.	Results for 5-6 subjects/group
Time to Plasma Max conc (h)	77-h	67.5-h	67.5-h	69.0-h	Not avail.	
Systemic a.i. 'Burden' (mg)	0.012	0.010	0.013	0.005	0.0105	Based on 3L approx. plasma volume
SED: Systemic Estimated Dose (mg/kg b.wt)	0.0002	0.0002	0.0002	0.0001	0.0003	Burden / 60 kg body weight
Margin of Safety (NOAEL / SED)	2.25E+06	2.65E+06	2.09E+06	5.00E+06	1.80E+06	Rat NOAEL = 450 mg/kg/d, 90 day oral
Adjusted MOS (MOS / UF=30)	**7.50E+04**	**8.82E+04**	**6.98E+04**	**1.67E+05**	**6.00E+04**	Uncertainty factor=10 (90-day to chronic) x 3 (human variation)
Factor higher than TTC SED	8.00	6.80	8.60	3.60	10.00	SED / TTC-SED
TTC SED	2.50E-05	2.50E-05	2.50E-05	2.50E-05	2.50E-05	0.5 ng/ml x 3L) / 60 kg bwt = 2.5E-05

Thus, it can be concluded from commonly used and recognized risk characterization approaches, the use of 3% avobenzone in sunscreens should be considered as safe for repeated human use. Extending these data for a 5% avobenzone sunscreen concentration, an increase of about 65% and taken together with the lack of a dose-related increase in the in vitro penetration amount, it could be expected to remain a safe exposure under the very high MoS estimations. This together with FDA's finding that sufficient information exists to satisfy the effectiveness prong of the GRASE standard for sunscreens containing avobenzone at concentrations up to 5 percent should allow for a positive GRASE determination under the current TFM.

6.2.1. Rationale for Waiving Additional Non-clinical and Clinical Studies

In the FDA comparison of avobenzone safety data available compared to that deemed necessary for a GRAS assessment shown in Table 4, FDA indicated the need for a number of non-clinical tests that are resource intensive for animal use, cost, and study executions. The results of this comparison is a simple "check the box" approach to identifying data gaps that is not a true evaluation and assessment of the available non-clinical data and does not address the value and relevance of the safety conclusions from these data.

It is our position that the data and conclusions we put forth in this section are adequate to address FDA data requirements without additional non-clinical testing.

We repeat here that avobenzone has the following key indicators for avobenzone safety: it is not mutagenic or genotoxic in vitro or in vivo, is not photo-genotoxic or photomutagenic, did not indicate adverse interactions with endocrine systems, disrupt developmental or maternal processes in pregnant animals, or induce skin sensitization responses in animals or humans by standard tests either without or with UV irradiation. Repeated dose testing in rats via their diet and in rabbits with topical applications did not reveal signs of systemic toxicity or microscopic changes in tissues and organs that would increase concern for adverse changes or neoplasia with longer term exposures. Reproductive tissues, and the in vivo embryo, fetal, or neonatal stages were not adversely affected or altered under high daily doses of avobenzone from 450 to 1000 mg/kg bwt/day.

Additionally, in silico assessments indicated only the structural alert of adverse effects that confirmed the documented human photoallergenicity of the molecule. Carcinogenicity signals are not characteristic of the AVOBENZONE structure. The predicted phase I and phase II metabolism of avobenzone indicates metabolic pathways that do not result in degradants or moieties with known adverse effects but in those that enable excretion and hence the lack of systemic accumulation. Thus, there is no expectation of greater systemic toxicity following longer term exposure. These conclusions are supported by the observed plasma kinetic profiles in the MUsT results summarized above.

A dermal carcinogenicity test with avobenzone is not expected to show topical primary neoplastic effects in that it is not mutagenic or genotoxic; the dermal absorption profile indicates that it could have some intradermal residence time, but it can be expected to be metabolized in the skin, passed to systemic circulation, or otherwise removed from the skin upper layers. As avobenzone in sunscreens is photostabilized by other formulation constituents, photodegradation within the skin is known to be minimized. In the rabbit repeat dose dermal study, local dermal intolerance was seen at doses of 100 mg/kg/d while 30 mg/kg/d did not reveal adverse skin reactions; similarly, low tolerance is expected in rats. Conducting a dermal carcinogenicity study would be compromised by the relatively low dosages possible.

Further, avobenzone does not fit a profile of chemicals with known skin carcinogenic effects, such as petroleum related polycyclic aromatic hydrocarbons (e.g., Roy et al. 1988).[46] As is well known, exposure to UV radiation is recognized as the primary, and preventable, cause of skin carcinogenic maladies. The

[46] Roy TA, Johnson SW, Blackburn, GR, et al., Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content, Fundam Appl Toxicol, Vol 10, Issue 3, 1988, 466-476, ISSN 0272-0590, https://doi.org/10.1016/0272-0590(88)90293-X (accessed June 24, 2019)

available indicators of dermal safety and absence of key markers of dermal carcinogenicity imply that the cost in animals and other resources for conducting a dermal carcinogenicity study will exceed any benefit that could be derived from this study.

Much focus is place on the 0.5 ng substance/mL plasma, the TTC plasma level for mutagenic or other unknown substances in consumer substances and the UV filters currently on the TFM. While the approach is useful for substances with little or no toxicity data available, it can also be a reference point for comparison to existing data. As shown for the MUsT kinetic data in Table 9, the systemic exposures of avobenzone over the course of dosing were above the "bright line" of 0.5 ng/mL but readily decreased after dosing ended. However, even with the excessive dermal applications used, the avobenzone measurable in plasma remained at or less than an order of magnitude (factor of 10) above the noted threshold. We find it instructive that the final version of FDA's MUsT guidance removed this plasma threshold value and thereby placed the proper emphasis on the robustness of the plasma analytical method and, more importantly on the overall safety profile of the topical therapeutic.

Additional clinical MUsT data are not expected to provide significant gains in safety or reduced risk for human health. Specifically, we would not expect that conducting additional testing of avobenzone formulations in more clinical MUsT experiments to give more meaningful or relevant human PK results than those now available from FDA's MUsT Part 1, or to be reported after completion of MUsT Part 2. In a new and separate MUsT trial it can be expected that the PK parameters may differ somewhat from those data now or to be available. But it should be given fair and reasonable consideration that the resource demands of a new MUsT and the already demonstrated very high margins of safety are out of proportion with any small gains from additional geometric means for C_{max}, T_{max}, and AUC results. The risk estimations already indicate avobenzone can be used safely in commercial sunscreen products.

7. Conclusion

Avobenzone is a critical ingredient for UVA protection in sunscreens. Overall, the results of our assessment indicate that the available non-clinical data, in silico assessments, and PK profiles, are consistent with the very high Margin of Safety estimations for avobenzone in sunscreens under chronic and excessive use conditions. We also believe that the data and conclusions contained in this submission adequately demonstrate that sufficient evidence exists for FDA to make a positive determination of GRASE for avobenzone in the current TFM without additional non-clinical testing. Clearly, the public health benefits of retaining avobenzone as a Category I active ingredient on the sunscreen monograph is of paramount importance. We believe that the information provided will allow formulators to continue to use sufficient levels of this UVA absorber to create sunscreens which protect the consumer from the skin damage and adverse health effects associated with sun exposure.

DSM appreciates the opportunity to provide FDA with our comments on the TFM. Please contact Carl D'Ruiz at carl.d-ruiz@dsm.com if you have any further questions regarding this submission.

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