Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Clin Pharmacol Ther. 2019 January ; 105(1): 161–167. doi:10.1002/cpt.1178.

Safety Threshold Considerations for Sunscreen Systemic Exposure: A Simulation Study

Jian Wang[1] and **Charles J. Ganley**[1]

[1]Division of Nonprescription Drug Products, Office of Drug Evaluation IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Abstract

Sunscreens are regulated as over-the-counter drugs in the United States. Some sunscreen ingredients are absorbed into the systemic circulation, which raises concerns about the safety of these drugs. There is limited information on the systemic exposure for most sunscreen ingredients. This report estimates the systemic absorption of two sunscreen active ingredients, oxybenzone and enzacamene, by developing a pharmacokinetic model from published sunscreen absorption data and compares the results with safety thresholds proposed by the US Food and Drug Administration and in the literature. Our analysis indicates that systemic absorption can be substantial, and evaluation of the systemic exposure of sunscreen ingredients is warranted to better assess any long-term risks of use.

Sunscreen products are regulated as over-the-counter drug products in the United States because they affect the structure or function of the body by absorbing, reflecting, or scattering the harmful burning rays of the sun, thereby altering the normal physiological response to solar radiation.[1–5] Sunscreen products contain active ingredients and inactive ingredients. Most sunscreen active ingredients are organic chemicals, and some have been shown to be absorbed through human skin, with detectable levels in the blood or urine.[6–12] Some inactive ingredients in a sunscreen formulation may affect the absorption of the active ingredients. As part of the assessment of safety of a drug, the US Food and Drug Administration (FDA) requests an assessment of systemic absorption of the active ingredients in humans. If testing establishes that the sunscreen is not absorbed through the skin into the body, some aspects of toxicology testing may not be needed.[1] If there is systemic absorption, then blood levels from the clinical study can be compared with exposure levels associated with findings, if any, from long-term nonclinical toxicology studies.

Correspondence: Charles J. Ganley (charles.ganley@fda.hhs.gov).

AUTHOR CONTRIBUTIONS

J. Wang and C.J. Ganley wrote the manuscript; J. Wang and C.J. Ganley designed the research; J. Wang and C.J. Ganley performed the research; J. Wang and C.J. Ganley analyzed the data.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

Publisher's Disclaimer: DISCLAIMER

The article reflects the views of the authors and should not be construed to represent the views or policies of the US Food and Drug Administration.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Sunscreen products have a wide range of extent of use, including some individuals who have sunscreen applied daily, and over many years, starting as early as 6 months of age. The amount of sunscreen ingredients in sunscreen products varies, but for some organic ingredients, permitted levels are as high as 15%. Even when not extensively applied to the skin, this can represent gram quantities a day. With this amount of drug applied to the skin, absorption as low as only 0.1% can lead to milligrams of drug being systemically absorbed. For a hypothetical sunscreen product with a sun-screen ingredient present in a 5% concentration, Table 1 shows the amount of a sunscreen product and sunscreen ingredient applied to the body and relates it to the calculated amount of ingredient absorbed on the basis of a range of bioavailability (*F*). With the application of a product containing a 5% concentration of the sunscreen ingredient, 30 g (1 ounce) provides 1,500 mg of the sunscreen ingredient (5% of 30 g); and, in turn, if the bioavailability is 2%, then 30 mg may be absorbed with each application. Because sunscreen may be applied daily, exposure to these systemically absorbed doses may be sustained. Such prolonged exposure underlies the importance of obtaining safety data from long-term nonclinical toxicity studies for sunscreen ingredients that are absorbed into the body.

In November 2016, the FDA finalized the guidance entitled “Guidance for Industry: Nonprescription Sunscreen Drug Products–Safety and Effectiveness Data” (sunscreen guidance).[1] The guidance recommends assessment of the human systemic absorption of sunscreen active ingredients, with a pharmacokinetic (PK) trial performed under conditions of maximal use as defined in the product label, referred to as a Maximum Usage Trial (MUsT).[13,14] The FDA sunscreen guidance notes that some non-clinical toxicity studies may be waived if an adequately conducted human PK MUsT results in a steady-state blood level of <0.5 ng/ml. However, the Public Access for Sunscreens Coalition[15] proposes 20–200 fold (10–100 ng/ml) higher concentration as a safety threshold. Similarly, Sargent and Travers[16] suggest a higher threshold, up to 100-fold increase. For an ingredient known to be absorbed through the skin, an MUsT can assess the level of systemic exposure for comparison to the systemic exposure observed in animal toxicity studies. However, it alone cannot quantify the absolute amount of the ingredient systemically absorbed. It also is not able to prove unequivocally that a sunscreen ingredient is not absorbed if none is detected in blood samples.

This study evaluates the safety threshold in the context of total absorbed amount vs. steady-state blood concentrations of the sun-screen active ingredients. We estimated the systemic absorption of two sunscreen active ingredients, oxybenzone and enzacamene, that are known to be absorbed, by developing a PK model from published data. We compare the estimates with safety thresholds proposed by the FDA and explain how the limitations identified are accounted for by recommendations for the conduct of an MUsT in the FDA sunscreen guidance.

RESULTS

PK characterization

PK models describing the concentration–time profiles for oxyben-zone, enzacamene, and octinoxate were developed on the basis of the observed data from the study by Janjua *et al.*[8]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The formulation studied by Janjua *et al.*[8] contains 10% of each ingredient. The PK parameter estimates from the model are summarized in Table 2.

The model predicted plasma concentration–time curves fit well with the actual concentrations, except for the octinoxate levels in males (Figure 1). The latter was likely caused by the quality of the median concentration data from the limited number of subjects, because the data were only available in less than half of males at time points 1 and 24 hours. Therefore, we excluded octinoxate from further evaluation, and simulations were only conducted on oxybenzone and enzacamene for the subsequent analysis. Overall, Figure 1 indicated that significant accumulation could happen after once-daily application of enzacamene and octinoxate, and the concentrations plateau after 2–4 days of continuous use.

Estimating absorbed amount in the study by Janjua *et al.*[8]

To assess the absorbed amounts given the estimates of apparent clearance and apparent volume of distribution by the model, we first calculated the theoretical F ranges of oxybenzone and enzacamene for this sunscreen formulation by making assumptions about the minimum volume of distribution and the maximum clearance. Theoretically, the minimum volume of distribution should be >3 l, the average volume of plasma in adults; the total clearance should be smaller than the sum of hepatic blood flow and renal blood flow, which is 144 l/hour, assuming there are no other elimination pathways (i.e., lung).[17] On the basis of these principles, the estimated F in this sunscreen formulation from the study by Janjua *et al.*[8] should be within the ranges of 0.1–13.7% for oxybenzone and 0.01–2.5% for enzacamene, as shown in **Table 3.** The European Commission (EC), the agency that regulates sun-screens for the European Union, reported that the mean estimate of oxybenzone systemic absorption is 3.7% (range, 1.2–8.7%), and the estimate for enzacamene systemic absorption is 0.9%.[9,11,12,18] The EC estimate for oxybenzone was based on urine excretion data in 25 volunteers after application of a commercially available sunscreen containing 4% oxybenzone twice a day for 5 days. The EC estimate for enzacamene was based on the recovery of radioactivity in the urine and feces in a radiolabeled mass balance study with six healthy male volunteers in an oil-in-water formulation at a concentration of 5% enzacamene.

On the basis of the ranges of the estimated F, we can calculate the range of the amount absorbed by multiplying the estimated F times the amount of sunscreen ingredient applied to the skin. The daily systemically absorbed amounts in this study can be in the range of 3.5–548 mg/day for oxybenzone and 0.35–100 mg/day for enzacamene after daily sunscreen applications of 35 and 40 g for females and males, respectively. The 7.5-fold difference of steady-state blood concentrations observed between oxybenzone and enzacamene were partially attributed by the authors to the differences in absorption, in addition to drug clearance.[8]

Estimating maximal concentration after four times daily application

What blood level will be achieved if ≥1.5 μg of oxybenzone and enzacamene are systemically absorbed with the formulation of Janjua *et al.*[8]? The directions on sunscreen products instruct the user to apply every 2 hours. The PK model was used to simulate the

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

concentration–time profiles after the daily systemic absorption of 1.5 or 150 μg of oxybenzone and enzacamene, with application every 2 hours four times per day. To simulate the concentration–time profile at steady state for the absorption of 1.5 and 150 μg, we need to know the amount of ingredient applied to the skin. We can calculate the amount applied using the equation: Amount of Ingredient Applied to Skin = Amount of Ingredient Absorbed/Bioavailability. We assume that the mean F values for oxybenzone and enzacamene are 3.7% and 0.9%, respectively, as reported by the EC.[11,12] Table 4 shows the amount of ingredient applied to the skin calculated for 1.5 and 150 μg absorbed using F of 3.7% and 0.9% for oxybenzone and enzacamene, respectively.

After calculating the amount applied to the skin, we simulate the concentration–time profiles from the PK model for the formulation of Janjua *et al.*[8] Figure 2 shows the full concentration–time profiles after daily absorption of 1.5 and 150 μg/day of each ingredient. For oxybenzone, the daily absorption of 1.5 and 150 μg/day yields steady-state maximal concentration (C_{max}) of 0.0022 and 0.2224 ng/ml, respectively. For enzacamene, the daily absorption of 1.5 and 150 μg/day yields steady-state C_{max} of 0.0014 and 0.1387 ng/ml, respectively. These C_{max} estimates are markedly below the FDA proposed limit of 0.5 ng/ml.

Estimating absorbed amount for different C_{max}

Because the PK model relates the steady-state concentration to the amount of ingredient applied to the skin, using the model we can calculate the amount of sunscreen ingredient applied to the skin for steady-state concentrations of 0.5, 10, and 50 ng/ml. Table 5 shows the amount of oxybenzone and enzacamene applied to achieve each steady-state level. Inserting these values into the following equation (Amount of Ingredient Absorbed = Amount of Ingredient Applied to Skin × F) and using the F range estimated from PK parameters and listed in Table 3, we are able to calculate a range of the amount of ingredient absorbed for each steady-state level of oxybenzone and enzacamene. Table 5 illustrates the predicted amounts of ingredient absorbed to achieve targeted steady-state C_{max} of 0.5, 10, and 50 ng/ml. For the formulation of Janjua *et al.*,[8] the estimated range of oxybenzone bioavailability is 0.1–13.7%, which calculates to a daily absorption of anywhere from 8 to 1,155 μg of oxybenzone for a steady-state C_{max} of 0.5 ng/ml. Likewise, for enzacamene, the bioavailability of this formulation is between 0.01–2.5%, which calculates to a daily absorption of 6–1,503 μg/day for a steady-state C_{max} of 0.5 ng/ml. For a steady-state level limit of ≥10 ng/ml, the lower limit of the calculated absorption of sunscreen is >100 μg/day, an amount well above the threshold of toxicological concern (TTC).

DISCUSSION

In some countries, sunscreen products are regulated as cosmetics and by regulation require less data than drug products to support their safety. In the United States, however, sunscreen products are regulated as over-the-counter drugs, and the FDA has established specific requirements to support their safety and effectiveness.[1] For the safety assessment of a sunscreen ingredient, it is important to determine whether systemic absorption occurs and, if so, to what extent. Most sunscreen active ingredients are organic chemicals. For some, there is evidence of systemic absorption leading to detectable levels in the blood or urine,[6–12]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

whereas for many others, the systemic absorption has not been adequately characterized. Absorption will vary depending on many factors, including physicochemical attributes of the active ingredient, vehicle/formulation properties, and the thickness and composition of the stratum corneum (which depends on the body site).[19–21] If a drug is systemically absorbed, long-term exposure raises safety concerns that should be evaluated. For drugs, human PK studies to assess the extent of systemic absorption are typically needed to fulfill the requirements of 21 CFR part 320. This has been a standard for the safety assessment of dermally active topical drugs in the United States for many years. The potential risks of repeated, long-term, regular systemic exposure to sunscreen active ingredients cannot be detected or evaluated on the basis of commercial marketing experience alone.[6,22,23]

The study by Janjua *et al.*[8] demonstrated measurable blood concentrations for three different sunscreen active ingredients. Using the blood concentration–time data for two of the ingredients in the study by Janjua *et al.*,[8] we developed a PK model that described the measured blood concentrations of oxybenzone and enzacamene applied to the skin. Because absorption can depend on the formulation, the model is only applicable for the formulation of Janjua *et al.*[8] but illustrates the potential for substantial absorption. Another limitation of our analysis is that the individual-level PK data were not available, so the modeling was based on the median values for males and females at each timepoint. A simulation of 1,000 virtual subjects was performed on the basis of the range and median values of concentrations reported, and the simulated median PK profiles were similar to those estimated by using median values reported by Janjua *et al.*[8] In addition, our analysis was conducted under the assumption that bioavailability and the absorption rate were independent of the dose.

The model-derived parameters of apparent clearance and apparent volume of distribution enabled an estimation of the range of the absolute bioavailability for both ingredients. With the application of 40 g of sunscreen to men (containing 10% oxybenzone and 10% enzacamene), the daily amount absorbed into the body was estimated to range from 4–448 mg for oxybenzone and from 0.4− 100 mg for enzacamene. For women, with application of 35 g of sunscreen, the daily amount absorbed into the body was estimated to range from 3.5–480 mg for oxybenzone and from 0.35–87.5 mg for enzacamene. These findings demonstrated that systemic absorption supports the need for appropriate risk assessment, including the use of long-term nonclinical toxicology studies.

When evaluating safety, a detection limit threshold for systemic exposure needs to be established on the basis of the analytical capability to measure drug exposure. For exposure under this threshold, the risk would be assumed to be low. The FDA sunscreen safety and efficacy guidance[1] justified the choice of 0.5 ng/ml as the regulatory threshold, as follows: (i) A TTC-based acceptable intake of a mutagenic impurity of 1.5 μg per person per day is considered to be associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure) present in pharmaceuticals for long-term treatment (>10 years) and where no carcinogenicity data are available.[13] (ii) The 0.5 ng/ml limit uses the generous assumption that all of the 1.5 μg is restricted to the plasma compartment of 3 l in an adult and that the entire 1.5 μg is absorbed instantaneously. Because absorption is not instantaneous, we recognize that the limit is higher than we would expect for the detection of 1.5 μg.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

For the formulation of Janjua *et al.*,[8] we estimated the steady-state C_{max} from our model to be <0.5 ng/ml for the daily absorption of 1.5 and 150 μg of oxybenzone and enzacamene. To achieve a blood level of 0.5 ng/ml, we estimated that the upper range of the amount absorbed is >1 mg/day for both ingredients. The results show that the absorbed amount of sunscreen could be greater than the TTC or 100-fold the TTC and not be detectable at the 0.5 ng/ml level. For sunscreen ingredients that are readily absorbed, such as oxybenzone or enzacamene, this does not present a problem. However, there may be sunscreen ingredients with low absorption with amounts at ≥1.5 μg and not be detected at the 0.5 ng/ml level.

It can be argued that a 0.5 ng/ml threshold limit is not sufficiently sensitive to waive long-term nonclinical systemic carcinogenicity and reproductive studies. A limit <0.5 ng/ml may be justified but there are likely to be technical difficulties with developing an assay with greater analytical sensitivity. The FDA currently does not have, as a matter of policy, an established safety threshold for all drug substances below which there is, by default without data, no risk for carcinogenicity or reproductive toxicity. There is, however, no simple definition of “no absorption,” and it is difficult to establish physicochemical thresholds beyond which absorption is limited without exception. For sunscreens, processes have been recommended that maximize the effort to detect systemic absorption:

1. Conduct an MUsT that incorporates dosing every 2 hours (as per sunscreen label instructions), four times a day, with sufficient duration to attain steady state.
2. Test multiple different formulations in an MUsT.
3. Identify the formulations to include in the MUsT by testing *in vitro* absorption using validated assays.
4. Apply a standard amount with each application.
5. Enroll a variety of subjects with different skin types.
6. Enroll a sufficient number of subjects of varying demographic characteristics.

If an adequately conducted human MUsT results in a steady-state blood level of <0.5 ng/ml, to waive a systemic carcinogenicity and reproductive study for a generally recognized as safe and effective determination, one must provide an adequately conducted toxicology program that does not reveal any other safety signals for the ingredient or for any known structurally similar compound, indicating the potential for adverse effects at lower levels.[1]

In summary, our case study using oxybenzone and enzacamene data demonstrated that applying a little more than 1 ounce of a 10% sunscreen per day can result in substantial systemic absorption of sunscreen ingredients. The FDA’s proposed safety threshold of a 0.5 ng/ml steady-state concentration for a sunscreen active ingredient may not detect the absorption of milligram quantities of a sun-screen ingredient under certain circumstances. It is clear from our analysis that higher thresholds proposed by others are not justified.

METHODS

Our exercise was based on the sunscreen study in humans with repeated whole-body topical application published by Janjua *et al.*[8] In this study, 32 healthy volunteers, consisting of 15

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

young males and 17 postmenopausal females, were exposed to a daily whole-body topical application of 2 mg/cm^2 of a sunscreen formulation containing 10% (w/w) of each active ingredient for 4 days. The average daily sunscreen applications are 35 and 40 g for females and males, respectively. Blood concentrations of oxybenzone, enzacamene, and octinoxate were measured at 0, 1, 2, 3, 4, 24, and 96 hours postdose. Because the individual-level PK data were not available, the modeling was based on the median values for males and females at each timepoint.

On the basis of the observed PK data, we developed a one compartment linear model with first-order absorption and elimination to estimate the PK parameters for each ingredient. When developed, the model was evaluated by visual diagnostic plots.

On the basis of the PK characteristics of the three sunscreen active ingredients, we conducted simulations to illustrate the relationship between daily applied amount, daily absorbed amount, and predicted steady-state maximal blood concentration. First, we estimated the amount absorbed using a theoretical range of bioavailability, as described in Results. Second, we estimated the steady-state maximal concentrations after daily absorption of prespecified amounts of ingredients: 1.5 and 150 μg of oxybenzone and enzacamene. Octinoxate was excluded from modeling estimates because of limited data. The prespecified amounts (1.5 and 150 μg/day) were chosen on the basis of the following rationales: (i) 1.5 μg/day is the threshold value of the TTC in the “ICH Guidance for Industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk”[24]; and (ii) 150 μg/day, which represents an amount 100-fold higher than the TTC threshold, as suggested by Sargent and Travers.[16] Third, we assessed the applied and absorbed amounts of sunscreen ingredients to achieve targeted steady-state C_{max} at 0.5 and 10 ng/ml, the latter amount proposed as a safety threshold by the Public Access for Sunscreens Coalition.[15] To take consideration of the real-world scenario, our steady-state simulations were based on daily topical application of sunscreens at every 2 hours for four times a day, following dosing instruction for sunscreens in the United States.

All modeling and simulations were conducted using the nonlinear mixed-effects modeling software Program NONMEM (v7.3; ICON Development Solutions, Ellicott City, MD). The first-order method was used to estimate the parameters. The data are modeled as a single average subject without considering between subject variability. Figures were generated with SAS (Version 9.3; SAS Institute, Cary, NC) or R (Version 2.15.1; R Development Core Team, Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

ACKNOWLEDGMENTS

The authors thank Drs. Peter Stein, Theresa Michele, Lesley-Anne Furlong, Steve Adah, and Shiew-Mei Huang for valuable comments and critical review of the manuscript.

FUNDING

No funding was received for this work.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Abbreviations:

FDA	Food and Drug Administration
OTC	over-the-counter
MUsT	Maximum Usage Trial
TTC	Threshold of Toxicological Concern
PK	pharmacokinetics
C_{max}	maximal concentration
Oxybenzone	benzophenone-3 (BP-3)
4-MBC	3-(4-methylbenzylidene) camphor
OMC	octyl-methoxycinnamate
CL/F	apparent clearance
V/F	apparent volume of distribution
Ka	absorption constant
$T_{1/2}$	terminal half-life
T_{max}	The amount of time that a drug is present at the maximum blood concentration
F	bioavailability

References

1. US Food and Drug Administration (FDA). Guidance for industry: nonprescription sunscreen drug products–safety and effectiveness data 11 2016 <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473464.pdf>. Accessed 27 December 2016.
2. Food and Drug Administration, HHS. Labeling and effectiveness testing: sunscreen drug products for over-the-counter human use: final rule. Fed. Regist 76, 35620–35665 (2011). [PubMed: 21682059]
3. Nash JF Human safety and efficacy of ultraviolet filters and sunscreen products. Dermatol. Clin 24, 35–51 (2006). [PubMed: 16311166]
4. Jansen R, Wang SQ, Burnett M, Osterwalder U & Lim HW Photoprotection, part I: photoprotection by naturally occurring, physical, and systemic agents. J. Am. Acad. *Dermatol.* 69, 853. e1–853.e12; quiz 65–6 (2013). [PubMed: 24238179]
5. 21 C.F.R. § 700.35.
6. Benson HA Assessment and clinical implications of absorption of sunscreens across skin. Am. J. Clin. Dermatol 1, 217–224 (2000). [PubMed: 11702366]
7. Klimová Z, Hojerová J & Beránková M Skin absorption and human exposure estimation of three widely discussed UV filters in sunscreens: *in vitro* study mimicking real-life consumer habits. Food Chem. Toxicol 83, 237–250 (2015). [PubMed: 26151237]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

8. Janjua NR, Kongshoj B, Andersson AM & Wulf HC Sunscreens in human plasma and urine after repeated whole-body topical application. J. Eur. Acad. Dermatol. Venereol 22, 456–461 (2008). [PubMed: 18221342]
9. Gonzalez H, Farbrot A, Larko O & Wennberg AM Percutaneous absorption of the sunscreen benzophenone-3 after repeated whole-body applications, with and without ultraviolet irradiation. Br. J. Dermatol 154, 337–340 (2006). [PubMed: 16433806]
10. Benech-Kieffer F, Meuling WJ, Leclerc C, Roza L, Leclaire J & Nohynek G Percutaneous absorption of Mexoryl SX in human volunteers: comparison with *in vitro* data. Skin Pharmacol. Appl. Skin Physiol 16, 343–355 (2003). [PubMed: 14528058]
11. European Commission (EC). Opinion of the Scientific Committee on Consumer Products on benzophenone-3, SCCP/1201/08 <https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_159.pdf>. Accessed 18 January 2017.
12. European Commission (EC). Opinion of the Scientific Committee on Consumer Products on 4-methylbenzylidene camphor, SCCP/1042/06 <https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_075.pdf>. Accessed 18 January 2017.
13. Bashaw ED, Tran DC, Shukla CG & Liu X Maximal usage trial: an overview of the design of systemic bioavailability trial for topical dermatological products. Ther. Innov. Regul. Sci 49, 108–115 (2015). [PubMed: 26634191]
14. US Food and Drug Administration (FDA). Draft guidance for industry: maximal usage trials for topical active ingredients being considered for inclusion in an over-the-counter monograph: study elements and considerations <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM608356.pdf>. Accessed 27 June 2018.
15. Public Access to SunScreens (PASS). Coalition, public comments on draft guidance “over-the-counter sunscreens: safety and effectiveness data draft guidance for industry” [Docket No. FDA-2015-D-4021] <https://www.pharmamedtechbi.com/~/media/Supporting%20Documents/The%20Rose%20Sheet/37/PASS%20 Sunscreen%20Data%20Guidance%20Comment.pdf>. Accessed 12 October, 2017.
16. Sargent EV & Travers JB Examining the differences in current regulatory processes for sunscreens and proposed safety assessment paradigm. Regul. Toxicol. Pharmacol 79, 125–141 (2016). [PubMed: 27016397]
17. Carlisle KM, Halliwell M, Read AE & Wells PN Estimation of total hepatic blood flow by duplex ultrasound. Gut 33, 92–97 (1992). [PubMed: 1740284]
18. Gustavsson Gonzalez H, Farbrot A & Larko O Percutaneous absorption of benzophenone-3, a common component of topical sunscreens. Clin. Exp. Dermatol 27, 691–694 (2002). [PubMed: 12472548]
19. Ates G, Steinmetz FP, Doktorova TY, Madden JC & Rogiers V Linking existing *in vitro* dermal absorption data to physicochemical properties: contribution to the design of a weight-of-evidence approach for the safety evaluation of cosmetic ingredients with low dermal bioavailability. Regul. Toxicol. Pharmacol 76, 74–78 (2016). [PubMed: 26807814]
20. Touitou E & Godin B Skin nonpenetrating sunscreens for cosmetic and pharmaceutical formulations. Clin. Dermatol 26, 375–379 (2008). [PubMed: 18691518]
21. European Commission (EC). The SCCS notes of guidance for testing of cosmetic ingredients and their safety evaluation, SCCS/1564/15, Version of 3 2016 <http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf>. Accessed 18 January 2017.
22. Ruszkiewicz JA, Pinkas A, Ferrer B, Peres TV, Tsatsakis A & Aschner M Neurotoxic effect of active ingredients in sunscreen products, a contemporary review. Toxicol. Rep 4, 245–259 (2017). [PubMed: 28959646]
23. Wang J et al. Recent advances on endocrine disrupting effects of UV filters. Int. J. Environ. Res. Public Health 13, pii: E782 (2016). [PubMed: 27527194]
24. International Conference on Harmonization (ICH). Guidance for industry: M7 (R1) assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, version of 3 2018 <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm347725.pdf>. Accessed 15 June 2018.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sunscreens are regulated as over-the-counter drugs in the United States. Some sunscreen ingredients are absorbed into the systemic circulation, which raises concerns about the safety of these drugs.

WHAT QUESTION DID THIS STUDY ADDRESS?

What is the reasonable blood level below which the risk is low enough such that some nonclinical studies may not be needed to characterize the risk of systemic absorption of sun-screen ingredients?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The US Food and Drug Administration's recommended safety threshold of a 0.5 ng/ml steady-state concentration for a sunscreen active ingredient is reasonable. Our analysis does not support a higher threshold, as proposed by others. In some situations, sunscreen ingredients may be systemically absorbed in amounts >150 μg/day but not achieve a blood level of 0.5 ng/ml.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Systemic absorption of sunscreen ingredients can be substantial, and evaluation of the systemic exposure is warranted to better assess any long-term risks of use of sunscreen products.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

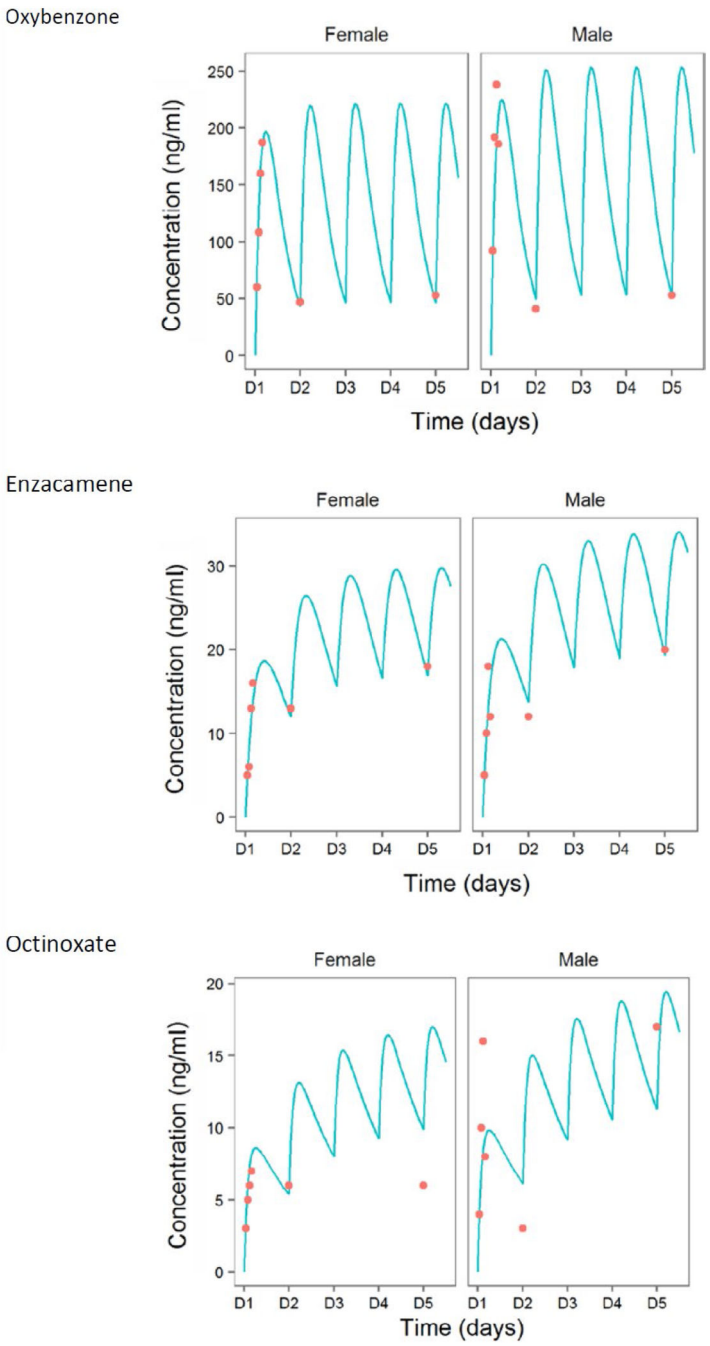

Figure 1.

Observed vs. simulated concentration–time plot after once-daily application of 40 or 35 g of a sunscreen product containing 10% each of oxybenzone, enzacamene, and octinoxate. The points represent the observed median concentrations, and the lines present predicted concentrations, for the three ingredients.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

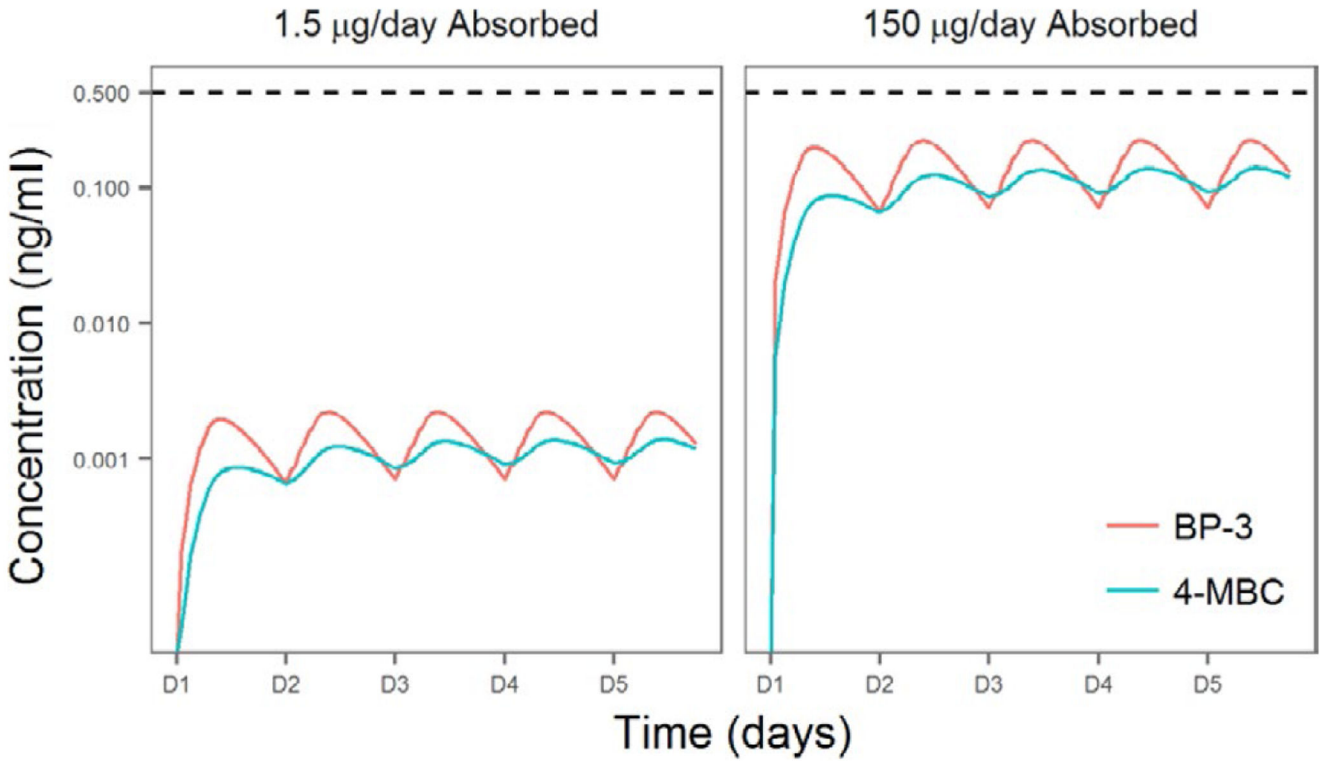

Figure 2.

4-MBC, 3-(4-methylbenzylidene) camphor; BP-3, oxybenzonebenzophenone-3. Steady-state concentration–time plot after daily absorption of 1.5 and 150 µg of oxybenzone and enzacamene. Simulation was performed with sunscreen applied every 2 hours for four times per day. The US Food and Drug Administration's safety threshold of 0.5 ng/ml is marked by a dashed line.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Calculated amount of sunscreen ingredient absorbed at varying bioavailability from a sunscreen product containing 5% of the sunscreen active ingredient

Amount of sunscreen product applied (ounce)	Amount of sunscreen ingredient applied (mg)	Bioavailability of the sunscreen active ingredient			
		0.001%	0.1%	2.0%	4.0%
		Calculated amount of systemic absorption of sunscreen ingredient (mg)			
0.5	750	0.0075	0.75	15.0	30.0
1	1,500	0.015	1.5	30.0	60.0
1.5	2,250	0.0225	2.25	45.0	90.0
2	3,000	0.030	3.0	60.0	120.0

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Pharmacokinetic parameter estimates for oxybenzone, enzacamene, and octinoxate

Parameter	Oxybenzone	Enzacamene	Octinoxate
V/F (1)	4,250	33,750	21,250
CL/F (l/hour)	1,050	5,875	10,150
Ka (hour^{-1})	0.115	0.053	0.03
$T_{1/2}$ (hour)	2.81	3.98	1.45
T_{max}(hour)	5.79	9.85	6.18

CL/F, apparent clearance; Ka, absorption constant; $T_{1/2}$, terminal half-life; T_{max}, amount of time that a drug is present at the maximum blood concentration; *V/F*, apparent volume of distribution.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3

Systemic absorption of oxybenzone and enzacamene for the formulation of Janjua *et al.*[8]

Drug	Sunscreen product applied (g/day)[a]	Ingredient applied (g/day)	C_{max}(ng/ml)		Estimated *F* range (%)	Range of absorbed amount (mg)
			Day 1	Day 5		
Oxybenzone	35 (Females)	3.5	196	224	0.1–13.7	3.5–480
	40 (Males)	4	224	253		4–548
Enzacamene	35 (Females)	3.5	18	29	0.01–2.5	0.35–87.5
	40 (Males)	4	21	34		0.4–100

C_{max}, maximal concentration; *F*, bioavailability.

aApplied once daily.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

Calculation of applied amount of ingredients for targeted amount of absorption

	Absorbed	
Bioavailability	**1.5 μg**	**150 μg**
Oxybenzone 3.7%[a]	40.5 μg	4,054 μg
Enzacamene 0.9%[a]	167 μg	16,700 μg

Data are given as the applied amount.

aEuropean Commission mean estimate of bioavailability.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 5

Systemic absorption of oxybenzone and enzacamene for the formulation of Janjua *et al.*[8]

Ingredient	$C_{max,ss}$(ng/ml)	Ingredient applied (mg/day)[a]	Estimated F range (%)	Range of amount of ingredient absorbed (μg/day)
Oxybenzone	0.5	8	0.1–13.7	8–1,155
	10	168	0.1–13.7	168–23,104
	50	843	0.1–13.7	843–115,185
Enzacamene	0.5	6	0.01–2.5	6–1,503
	10	120	0.01–2.5	120–30,050
	50	601	0.01–2.5	601–150,250

$C_{max,ss}$,maximal concentration at steady-state; *F*, bioavailability.

aSunscreen applied every 2 hours four times per day.