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Response to the Letter by Dr. Christian Surber

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We are delighted to respond to Dr. Surber's letter and are grateful that he raises some critical issues that were not appropriate for inclusion in a data-driven scientific paper. It seems that the primary thesis of his letter is that consumers were responding to our March 2021 publication, and asking industry and physicians about this phenomenon. We think an engaged and educated citizenry and consumer are the quintessence of a sustainable and progressive civilization. Industries have recently seen a large social movement of consumers demanding accountability and improvement regarding their products. Some of this may have arisen as a consequence of the massive number of lawsuits and demand for recalls regarding consumer products, such as Johnson & Johnsons' talcum-based baby powder products, "No More Tears" baby shampoo (allegedly contained 1,4-dioxane), and the recent discovery of sunscreen products contaminated with benzene¹⁻³. Another critical factor that is driving this consumer-engagement includes the self-education and motivation of consumers regarding the kind of ingredients used in the products they consume and their impact on personal well-being, as well as the products' ecological impacts; consumer choice is moving in the direction of authentic ecological sustainability⁴.

We think physician associations have a crucial role to play. There is an expected delay between the discovery of new science and the integration and translation of that science into medical and public health practice and messaging^{5,6}. For too long, the issue of the safety and effectiveness of sunscreens has been irresponsibly assumed and unchallenged: that sunscreens protect against skin cancers. Independent scientists have been questioning this notion since 1973, and the preponderance of both scientific data, as well as the application of logical argumentation (vs propaganda rhetoric), are directly challenging these assumptions⁷⁻¹⁰. The potential outcome of this deeper examination of sunscreens and their role in skin cancer is a paradigm shift for both the public-health community and industry stakeholders. In the historical struggle of tobacco smoking and cancer, the Journal of the

American Medical Association solicited and posted cigarette smoking advertisements until 1954 and even published an editorial that same year in JAMA that was later used as a pedagogical example to illustrate “manufactured doubt”; for decades, much of the medical community was either ambivalent or skeptical that cigarettes could cause lung cancer¹¹. The U.S. Surgeon General’s report on smoking and lung cancer was released 25 years after Ochsner and DeBakey’s 1939 paper arguing for a causal link between smoking and lung pathologies and cancer^{12,13}. The issue of sunscreen, its individual chemical constituents and its associations with skin cancer and other pathologies is following a similar trajectory as that of the history of tobacco and public health. It is crucial that members of the medical community fully engage in this issue so as to reduce the time curve for the likely outcome regarding sunscreens and public health.

Sunscreens are meant to protect the health of the individual and the public demographic. What and how they protect is not straightforward; are sunscreens meant to protect against UV-induced thiamine dimerization of DNA and/or protect against the occurrence of oxidative-stress induced DNA lesions such as 8-oxo-dG?¹⁴ Are they meant to suppress cytokine-axis inflammatory responses in the epidermis, and if so, does this increase the risk of UV-induced carcinogenesis?¹⁵⁻¹⁷ The questions and answers are not simplistic. This issue requires a critically different perspective in formulating a safe and effective sunscreen product, one that can recognize the inherent complexities and intricacies when UV radiation interacts with the skin. As our and Foubert et al (2021)’s scientific works have demonstrated, the problem of sunscreens requires a deeper examination of the individual constituents of a sunscreen formula so that formulators and industry can devise truly effective and safe products that reduce the adverse effects of broad-spectrum UV exposure^{18,19}.

Surber Critique 1) All syntheses of substances produce by-products that may have to be removed by subsequent purification processes. This applies both to active pharmaceutical ingredients and to substances as used elsewhere - e.g., in cosmetics. For this reason, threshold concentrations are defined in specifications of pharmacopoeias, by raw material producers or by the manufacturing company of a substance. Absolutely pure substances are in general non-existent. Indeed, the presence of by- and degradation products (impurities) always raises questions. According to most legislations, it is the responsibility of the “responsible person” (terminus technicus) of the manufacturing company to assure that stipulated and/or defined specifications are met. Threshold concentrations are established following a comprehensive risk assessment of the impurities. In this context, the authors unfortunately missed to discuss in detail the complexity (including some inconsistencies) of setting safe threshold concentrations against the background of an entire toxicological data package and different legislations (not only Proposition 65 (2)) (see section Ad 3).

Response 1) Regardless of whose responsibility it may be, the continual degradation “in a time-and temperature-dependent manner” of a chemical substance to a known carcinogen (ingested or topically applied) represents a significant health concern to all. The “comprehensive risk assessment” noted is unfortunately conducted in a vacuum; meaning the risk is normally reduced when exposure is from only one source. This is exactly what the European Food Safety Authority (EFSA) did when concluding that there is “no safety concern for benzophenone under the current condition of use as a flavouring substance.” This model, used by many if not all responsible manufacturers, is acceptable when ONLY one source of

exposure is justifiably predicted, and no other contributing sources can be demonstrated. Unfortunately, benzophenone is a ubiquitous compound with numerous routes of exposure as noted in IARC's monograph on benzophenone²⁰.

"Benzophenone is used as a flavor ingredient, a fragrance enhancer, a perfume fixative and an additive for plastics, coatings and adhesive formulations; it is also used in the manufacture of insecticides, agricultural chemicals, hypnotic drugs, antihistamines and other pharmaceuticals. Benzophenone is used as an ultraviolet (UV)-curing agent in sunglasses, and to prevent UV light from damaging scents and colours in products such as perfumes and soaps. Moreover, it can be added to plastic packaging as a UV blocker, which allows manufacturers to package their products in clear glass or plastic rather than opaque or dark packaging. It is also used in laundry and household cleaning products.

Benzophenone is widely used as a photoinitiator for inks and varnishes that are cured with UV light. In addition to being a drying catalyst, benzophenone is an excellent wetting agent for pigments; it can also be used in printing to improve the rheological properties and increase the flow of inks by acting as a reactive solvent"²⁰

IARC also notes that benzophenone can be found in natural foods like muscat grapes, in the air via atmospheric oxidation of the chemical diphenylmethane, which is released from residential oil burners and even dentures can contain and release benzophenone. So, when one looks at the "comprehensive" (cumulative) accumulation of benzophenone, it is significantly higher than what a single-source exposure-model would predict. This is perhaps why IARC concluded that benzophenone is "possibly carcinogenic to humans (Group 2B)" and why octocrylene degradation to benzophenone is of critical concern adding a consistent and chronic source of exposure (from beach, fragrances and anti-aging products) of a Group carcinogen to all the other sources of benzophenone exposure.

With respect to "All syntheses of substances produce by-products that may have to be removed by subsequent purification processes" ... industry has continually misrepresented this concept, by stating only small amounts of the material are present, making it appear that the substance has been purified and little to no risk remains. This is simply incorrect; the issue here has nothing to do with the initial benzophenone impurity within octocrylene as raw material.

Whether benzophenone is present or not in the raw ingredient (and it is present in the raw ingredient), benzophenone will continue to be released by octocrylene "in a time- and temperature-dependent manner". This is the conclusion that our paper (evaluating 16 octocrylene products) and, to a lesser extent, Foubert et al (2021) (evaluating 28 octocrylene products) made, that benzophenone is not an impurity of octocrylene manufacturing, but accumulates through the continual release via degradation in products that were purchased directly from stores^{18,19}.

Regarding Proposition 65, there are no safe thresholds for benzophenone in any product. The law specifies that there is no safe-harbor concentration for benzophenone. As some legal opinions propound, this court case and the decision do NOT allow for any

manufacturing contamination, and in fact, is a legally recognized incrimination that octocrylene products from those manufacturers named in the lawsuits (as well as all others) are all contaminated with benzophenone. The only legal consequence is the Prop65 labeling of all octocrylene products because the benzophenone contained therein "causes cancer."¹¹

Surber Critique 2) The physicochemical properties of benzophenone favor its absorption through skin (low molecular weight: 182.22 g/mol, low melting point 47.8°C, "ideal" LogP octanol/water 3.18). Downs et al. point out the high percutaneous absorption of benzophenone (70% of the applied dose) from a dermatological product and refer to a paper by Bronaugh and coworkers (3). This reference is unfortunate. The "dermatological product" was an acetonic solution (4). Acetone, as a solvent for benzophenone, temporarily dissolves the intercellular stratum corneum lipids during/after application to the skin. Following the rapid evaporation of the acetone, the initially dissolved benzophenone subsequently forms a "depot" in the stratum corneum. Percutaneous absorption of benzophenone in rhesus monkeys is reported to be 69% of the applied dose at the occluded application site and 44% at the non-occluded application site. The application of substances dissolved in acetone followed by occlusion is a mode of application under forced testing conditions that is unrealistic and only meaningful when other substances are co-tested under the same conditions and discussed in this particular context. Downs et al. provide incomplete information and do not discuss the importance of either the application procedure or the vehicles. It can be assumed that under realistic conditions, e.g., sunscreen formulation, dermal bioavailability of benzophenone is significantly lower compared to the values cited by the authors. Downs et al. provide incomplete information and do not discuss the importance of either the application procedure or the vehicles nor the exposure/concentration.

Response 2) Toxicology is a science of worse-case scenarios, because calculating total exposure to a substance can be unknown and/or extremely difficult as noted above. With that said, it is not unusual, and is often a justified default position when conducting a hazard or risk assessment, to exaggerate test conditions to understand the maximum absorption potential of a substance between different species and/or to cover the biodiversity among humans^{21,22}. The selection of acetone (or any solvent) as a vehicle under occlusive conditions (with or without dermal abrasion) is paramount to understanding the potential absorption of a substance^{22,23}. Formulations are not controlled or standardized, nor are products used in the same manner by the public. For example, what is the absorption potential of a 70% alcohol aerosolized product containing 10% octocrylene (containing several parts per million of benzophenone) being sprayed multiple times for "X" number of seconds or minutes a few inches away from the abraded skin of a two-year-old? The use of exaggerated conditions is a tool of toxicology that provides adequate safety margins, not a misrepresentation of data to frighten consumers²⁴.

Surber Critique 3) *In vitro/in vivo* investigations are quoted suspecting genotoxicity, carcinogenicity, and endocrine-disrupting effects of benzophenone. According to Downs et al., benzophenone is mutagenic and the authors express concerns about carcinogenicity. In contrast, the European Food Safety Authority (EFSA) (5) classifies benzophenone as not being of genotoxic concern. This assessment is consistent with the 166 substance evaluation of the European Chemicals Agency (ECHA) under REACH (6). In long-term rodent studies, carcinogenic effects on the liver, kidney, and hematopoietic

system were observed after *oral* intake. However, no evidence for carcinogenicity after *dermal* exposure was found, as also indicated by the International Agency for Research on Cancer (IARC) and EFSA (7,5).

In principle, it is conceivable that scientific data can be evaluated differently and subsequently lead to incongruent assessments. However, it is then everyone's duty to point out the inconsistencies and discuss the possible reasons for the different assessments before making a judgment. The difference between EFSA's approval as a flavoring, fragrance enhancer or perfuming agent and a no-safe-harbor substance by Prop65 calls out for a critical side-by-side comparison (comparable to the detailed comparison of sunscreen products in the paper by Downs et al., Table 1). It is not useful to point to unrelated incidents (Ref. 66 in 1) or to the supposedly biased work of industry consultants (Ref. 67, 68 in 1).

Downs et al. mention the possible endocrine-disrupting effects of benzophenone and octocrylene. First of all, the authors failed to carefully distinguish between endocrine activity and endocrine-disrupting effects. Such distinction is particularly important when communicating such data to third parties (e.g., the media). Many exogenous factors to which we are exposed to on a daily basis show endocrine activity (hormonal contraception, nutritional components, day night shift, etc.). Detection of an endocrine activity of a substance in a single test assay is not proof of an endocrine-disrupting effect. On the contrary, different test setups (*in vitro* and *in vivo*) must provide such evidence in a weight of evidence manner. All sunscreen filters used in Europe are approved by the authorities at a maximum use concentration after rigorous evaluation (8). The endocrine activity is a test criterion in all approvals, and new findings are continuously incorporated into the assessment (e.g., Call for data on ingredients with potential endocrine-disrupting properties used in cosmetic products) (9). The Scientific Committee on Consumer Safety (SCCS) of the European Commission has recently (March 2021) published the opinion on Octocrylene (10). The SCCS considers that, whilst there are indications from some *in vivo* studies to suggest that Octocrylene may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment. It can also be argued that the risk assessment conducted by the SCCS covers a potential endocrine activity of octocrylene, meaning that systemic endocrine activity can be excluded considering exposure levels and dermal bioavailability of octocrylene.

The presentation of Downs et al. gives the impression that they did not consider the entire toxicological data package available for benzophenone/octocrylene, but only selected certain studies to draw their own conclusions. With this approach, the authors did not follow the basic principles of risk assessment to weigh all available information. In addition, and this is particularly noteworthy, no safety assessment was performed with respect to potential exposure to benzophenone. This part of the paper is a hazard presentation rather than a risk assessment.

Response 3) The International Agency for Research on Cancer (World Health Organization) 209 concluded that benzophenone is “possibly carcinogenic to humans (Group 2B)”²⁰. The US National Toxicology Program (National Institute of Environmental Health Sciences)

concluded that there is “some evidence of carcinogenic activity”²⁵. Neither study identifies how the dose administered relates to the “total exposure” humans receive – which is an “unknown” because the substance is ubiquitous. Both studies administered benzophenone orally, which is the preferred route of administration for animal carcinogenicity studies, which is not without its significant caveats as the intestinal microbiome can metabolize the parent product into more or less toxic metabolites. Regardless of the route of administration, benzophenone exposure in humans occurs via ingestion, topically and by inhalation. To understand the “actual” human carcinogenic potential of the chemical the dose from all exposures must be taken into consideration.

An example of how governmental agencies under-estimate chemical exposure can be found in previous publications^{26,27}. Using the 70% absorption level (allows for a safety margin), the lowest level of benzophenone observed for the samples tested was 98 times the FDA level of safe use and 7 times the EFSA levels of safe use. The highest level determined for samples was 6,765 times and 507 times the FDA and EFSA level of banned/safe use, respectively. More concerning would be the pediatric considerations associated with these findings, which demonstrated that 2 Kg or 10 Kg children are exposed to hundreds to thousands of times the FDA and EFSA banned/safe levels. These values were based on using an octocrylene containing product - as directed - for “one” full day at the beach/pool. Even if one were to significantly lower the absorption level, octocrylene would still contribute a significant burden of benzophenone to the body.

With respect to the “no-safe-harbor” level noted about California Proposition 65 above, this is how industry avoids being legally restricted by the concentration(s) of carcinogenic chemicals in a product. The levels that specific companies within industry (and the legal finding does not encompass the contamination of products from other manufacturers) agreed to (currently < 35 ppm of benzophenone) was done so with “opposing” legal counsel during numerous lawsuits¹⁹. Industry argued that they could control the benzophenone “impurity” level^{19,20}. Unfortunately, whoever negotiated the level for industry did not know or understand that benzophenone is not just an impurity, but it is also a degradation by-product of octocrylene – meaning that the starting concentration at the time of manufacturing is not reflective of what accumulates in a product over time²¹. A 60-Day Notice of Violation was filed against a large segment of the global cosmetic industry to label all SPF-products containing octocrylene with a Proposition 65 label that these products contain a carcinogen²².

With respect to the SCCS Final Opinion on octocrylene, the Opinion was released immediately after our paper and Foubert et al (2021) paper were published, and it does mention that “The SCCS is aware that Octocrylene generates benzophenone (CAS 119-61-9, EC 204-249 337-6) through a retro-aldol condensation and also that benzophenone was detected in the pure Octocrylene manufactured ingredient (Dawns et al. 2020). Benzophenone is a hazardous impurity and degradation product of Octocrylene and it should be monitored and kept at trace levels”³¹. What defines “trace levels?” Are “trace levels” convenient to the manufacturer with no relevancy to its hazard from the total exposure and toxicity to the individual/public? Or are “trace levels” defined by honestly intentioned toxicological risk assessment? For the past 60 years, industry and its operatives have argued for the allowance of “trace levels” of a contaminant in single product lines. This

disingenuous argument has met some vigorous resistance lately with other contaminants, such as bisphenols, phthalates, neonicotinoids, heavy metals, polyfluoroalkyl substances (PFAS), etc and are being countered with the argument that there is “no safe level of exposure” from individual contaminated products³²⁻³⁵. This is because cumulative exposure from various sources can pose a palpable and detectable threat, especially at low concentrations regarding non-monotonic dose/response toxicants that affect neurological processes or act as endocrine disruptors.

The hazard of exposure becomes even more perilous with propaganda pushing for the use of sunscreen in front of a computer, driving in your car, etc. - for the whole day, every day. Cumulative and chronic (perpetual) exposure requires a wholly different set of risk and hazard assessments, as it tries to integrate non-monotonic and temporal-differential toxicities and complex and complicated disease etiologies. In 1999, 60 years after the Ochsner and Debaquey 1939 paper, the U.S. Department of Justice sued several tobacco companies for fraudulent and unlawful conduct regarding their misrepresentation and manipulation of the toxicology and hazards of tobacco products. In 2006, and again in 2009, the U.S. judicial system found these industry representatives guilty of RICO³⁶. Industry spent more than 70 years challenging the validity of the adverse effects of daily and long-term exposure. Instead of being doomed to repeat the debacles of history, we as a community of scientists and public health clinicians can circumvent these errors and, in conjunction with industry stakeholders, pivot from this highly flawed corporate mentality and adopt a paradigm where innovation and toxicological assessment can merge to produce products that can be highly effective in protecting against UV damage and its associated diseases, as well as being truly safe with prolonged and daily use/exposure.

Surber Critique 4) Proposition 65 is a regulation that primarily applies to the state of California. Other American states have adopted individual regulations. Although three of the five authors work for European institutions, it is very surprising that no comparisons and evaluations with other regulations, e.g., the EU, are made.

Response 4) A good example of how industry manipulates Proposition 65 regulations and 287 perhaps the SCCS to their advantage is noted above. The European Chemicals Agency (ECHA), like the US Food & Drug Administration, relies on industry supplying data to substantiate product safety – which is in general a questionable practice similar to “the fox guarding the hen house.” A good example of this would be on February 26, 2019 the US Food and Drug Administration removed octocrylene, along with 11 other organic UV-filters, from the Generally Recognized As Safe & Effective for human use in sunscreen products because the scientific literature did not demonstrate its safety³⁷. Industry has been requested to provide data for carcinogenicity, developmental and reproductive toxicity, and toxicokinetics among other things; to date industry has not provided such data. The correspondence between BASF and the U.S. FDA regarding their petition for Tinosorb S and Tinosorb M is a perfect example of industry not rising to the challenge and exhibiting transparency and responsibility in both demonstrating and advocating the safety for these two chemicals^{32,33}.

We focus on California Proposition 65 because if California were a sovereign nation, it would rank as the fifth largest economy of the world³⁸. All products containing benzophenone,

meaning all octocrylene-containing products, would need to be labeled at the Point of Sale as containing benzophenone “because it can cause cancer”³⁹. To varying degrees, the entire global industry will be affected by this requirement.

Surber Critique 5) The paper by Downs et al. has received considerable media attention in the German-speaking Europe. Headlines like “Sunscreen from last year may cause cancer” are making the news in print and online media. The French co-authors were quoted as saying “If benzophenone gets on the skin, it can trigger rashes, inflammation or hypersensitivity, but also liver cancer or lymphoma. This has been the case in animal studies. The molecule affects the thyroid and reproductive organs”. They also call for a ban on the two substances benzophenone and octocrylene.

Inaccurate or poorly reported interviews with scientists and the media's reappraisal of unbalanced scientific data unsettle rather than inform consumers.

Response 5) You are correct to say that the quality and scientific accuracy of news media on the subject is variable. The media has been misquoting what people say to the point that it has become a cultural expectation. Making a story controversial to consumers is what sells newspapers and magazines, and the standard for scientific accuracy is the original peer-reviewed articles. However, much of what was reported appears to be accurate and reflects the actual risk of being exposed to these two chemicals when the “total” exposure is taken into account. No one knows what level of exposure will actually cause significant health consequences since no one knows the actual exposure levels consumers are experiencing. The first rule of toxicology is that it is the dose (total exposure) not the poison (benzophenone) that matters. This is because benzophenone is a ubiquitous chemical abundantly found in foods, personal care products, packaging, air, etc., and is not controlled to minimize exposure in any way shape or form³⁶. Consumers should be concerned, and regulatory bodies should consider banning benzophenone, octocrylene and other ubiquitous substances to avoid environmental and human health issues. The flood of questions posed by consumers are the result of an informed citizenry demanding accountability and responsibility. It is the mandate of non-profit professional bodies and cancer leagues to educate the public, and do a better job in educating themselves regarding the scientific literature and resisting the temptations of industry to promote product propaganda that is not supported by the available scientific data^{40,41}.

As a final conclusion in addressing Dr. Surber’s letter, we would like to promote the idea of a precautionary approach to not just the overall safety of commercial products, but in the innovation and informed formulation of sunscreen technologies. One of the best historical examples of a precautionary regulatory approach in providing for the safety of commercial products is the U.S. Federal Food, Drug and Cosmetic Act of 1938, which requires that a drug product be tested and proved safe before it can be commercialized⁴². More recently, the European Commission has announced the adoption of a European Union regulatory framework for endocrine disruptors that is based on the Precautionary Principle and aims “to create a toxic-free environment”⁴³. Application of the field of toxicology will be essential in examining all the chemical components of a sunscreen product, and whose results will be paramount in directing formulators, regulators, physicians, legislators and consumers in

making informed decisions for what is best for public health, as well as for a prosperous future for the personal care product industry.

References

- 1) Lawyers Connect. <https://www.excite.com/education/lawyers/johnson-and-johnson-recall> Accessed June 7, 2021
- 2) Sherman, M. (2021) Justices reject Johnson & Johnson appeal of \$2B talc verdict. <https://www.excite.com/education/lawyers/johnson-and-johnson-recall>
- 3) Petronelli, M. (2021) Detectable levels of benzene noted in some sunscreen batches. *Dermatol. Times*. <https://www.dermatologytimes.com/view/carcinogen-found-in-multiple-sunscreens>
- 4) Close, C. (2021) The global eco-wakening: how consumers are driving sustainability. *World Economic Forum*. May 18, 2021. <https://www.weforum.org/agenda/2021/05/eco-wakening-consumers-driving-sustainability/>
- 5) Brownson, R.C., Kreuter, M.W., Arrington, B., True, W.R. (2006) Translating scientific discoveries into public health action: how can schools of public health move us forward? *Public Health Rep.* 121, 97-103. doi: 10.1177/003335490612100118
- 6) Brownson, R.C., Jones, E. (2009) Bridging the gap: translating research into policy and practice. *Prev. Med.* 49,313-315. DOI: 10.1016/j.ypmed.2009.06.008
- 7) Emmett, E, A. (1973) Ultraviolet radiation as a cause of skin tumors. *CRC Crit. Rev. Toxicol.* 2, 211-55.
- 8) Huncharek, M., Kupelnick, B. (2002) Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case-control studies. *Am. J. Public Health* 92, 1173–7. doi: 10.2105/ajph.92.7.1173
- 9) Gorham, E.D., Mohr, S.B., Garland, C.F., Chaplin, G., Garland, F.C. (2007) Do sunscreens increase risk of melanoma in populations residing at higher latitudes? *Ann. Epidemiol.* 17, 956–63. DOI: 10.1016/j.annepidem.2007.06.008
- 10) Autier, P., Bonil, M., Dore, J-F. (2011) Is sunscreen use for melanoma prevention valid for all sun exposures circumstances? *J. Clin. Oncol.* 29, e425-e426. DOI:10.1200/JCO.2010.34.4275
- 11) 2000 U.S. Surgeon General's Report: Complete Report (2000) Chapter 2. A historical review of efforts to reduce smoking in the United States. https://www.cdc.gov/tobacco/data_statistics/sgr/2000/complete_report/index.htm
- 12) Ochsner, A., DeBakey, M. (1939) Primary pulmonary malignancy: Treatment by total pneumonectomy; analysis of 79 collected cases and presentation of 7 personal cases. *Surg. Gynecol. Obstet.* 68, 435–451.
- 13) Ochsner, A. (1999) Carcinoma of the lung and tobacco smoking: a historical perspective. *Ochsner J.* 1, 106-108.
- 14) Duale, N., Olsen A-K, Christensen, T., Butt, S, T., Brunborg, G. (2010) Octyl methoxycinnamate modulates gene expression and prevents cyclobutane pyrimidine dimer formation but not oxidative DNA damage in UV-exposed human cell lines. *Toxicol. Sci.* 114, 272-278. DOI: 10.1093/toxsci/kfq005
- 15) Couteau, C., Couteau, O., Chauvet, C., Paparis, E., Coiffard, L.J.M. (2013) The effect of ultraviolet radiation on the anti-inflammatory effect of filters. *Int. J. Pharm.* 452, 124-127. DOI:10.1016/j.ijpharm.2013.04.067

- 16) Couteau, C., Chauvet, C., Paparis, E., Coiffard, L.J.M. (2014) Study of the persistence of the anti-inflammatory effect observed after application of preparations containing organic ultraviolet filters. *Int. J. Pharm.* 476, 160-163. DOI: 10.1016/j.ijpharm.2014.09.024
- 17) Ao, J., Yuan, T., Gao, L., Yu, X., Zhao, X., Tian, Y., Ding, W., Ma, Y., Shen, Z. (2018) Organic UV filters exposure induces the production of inflammatory cytokines in human macrophages. *Sci. Total. Environ.* 635, 926-935. DOI: 10.1016/j.scitotenv.2018.04.217
- 18) Foubert, K., Dendooven, E., Theunis, M., Naessens, T., Ivanova, B., Pieters, L., Gilissen, L., Huygens, S., De Borggraeve, W., Lambert, J., Goossens, A., Aerts, O. (2021) The presence of benzophenone in sunscreens and cosmetics containing the organic UV- filter octocrylene: a laboratory study. *Contact Dermatitis* Mar 25. DOI: 10.1111/cod.13845
- 19) SHEFA LMV, LLC vs. Concept 2 Cosmetics, LLC et al. (Sept. 10, 2015) Superior Court of California, County of Marin, Unlimited Civil Jurisdiction. Case No. CIV 1503341.
- 20) Rodan+Fields (2016) FAQ: Benzophenone & octocrylene California Prop 65 ingredients. https://www.rodanandfields.com/images/Archives/FAQs_Benzophenone.pdf Accessed July 17, 2021.
- 21) Downs, C.A., DiNardo, J.C., Stien, D., Rodrigues, A.M.S., Lebaron, P. (2021) Benzophenone accumulates over time from the degradation of octocrylene in commercial sunscreen products. *Chem. Res. Toxicol.* 34, 1046-1054. DOI:10.1021/acs.chemrestox.0c00461
- 22) State of California Proposition 65 60-Day Notice of Violation, Octocrylene SPF products. <https://www.chanler.com/blog/posts/held-issues-notices-dozens-sunscreen-manufacturers-and-retailers>
- 23) International Agency for Research on Cancer (WHO): Monograph 101- Benzophenone. Available at <https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono101-007.pdf>
- 24) Frash, H.F., Dotson, G.S., Bunge A.L., Chen C-P., Cherrie, J.W., Kasting G.B., Kissel, J.C., Sahmel J., Semple, S., Wilkinson, S. (2014) Analysis of finite dose dermal absorption data: implications for dermal exposure assessment. *J. Expo. Sci. Environmntl. Epidemiol.* 24, 65-73. DOI: 10.1038/jes.2013.23
- 25) OECD (2011, amended draft, 2019) No. 156. Guidance notes on Dermal Absorption. <https://www.oecd.org/chemicalsafety/testing/48532204.pdf>
- 26) Dick, I.P., Blain, P.G., Williams, F.M. (1997). The percutaneous absorption and skin distribution of lindane in man. II. In vitro studies. *Hum. Exp. Toxicol.* 16, 652–657. DOI:10.1177/096032719701601104
- 27) Lehman-McKeeman, L.D. (2013) Chapter 5: Absorption, distribution, and excretion of toxicants. In: Casarett & Doull's Toxicology: The Basic Science of Poisons. 8th Ed. Klaassen, C.D. (ed) McGraw-Hill Education.
- 28) National Toxicology Program (NIEHS): Technical report on the toxicology and carcinogenesis. Studies of benzophenone. Available at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr533.pdf
- 29) DiNardo, J.C., Downs, C.A. (2019) Should we use products containing chemical UV absorbing sunscreen actives on children? *Clin. Dermatol. Res. J.* 4, 1. DOI: 10.4172/2576-1439.1000130
- 30) DiNardo, J.C., Downs, C.A. (2021) Fall from GRASE: The Sunset of the Sunscreen Innovation Act. *American J. Dermatol. Res. Rev.* 4, 39. <https://escipub.com/Articles/AJODRR/AJODRR-2020-12-2805.pdf>

- 31) SCCS Opinion on Octocrylene (March 31, 2021) SCCS/1627/2. Opinion of the Scientific Committee on Consumer Safety on Octocrylene (europa.eu)
- 32) Hammer G.D. (2020) Comment submitted by Gary D. Hammer, President, Endocrine Society. Regulations.gov. <https://www.regulations.gov/document/EPA-HQ-OPP-2012-0329-0102>
- 33) Lentz, T.J., Dotson, G.S., Williams, P.R.D., Maier, A., Gadabgui B., Pandalai, S.P., Lamba, A., Heari, F., Mumtaz, M. (2015) Aggregate exposure and cumulative risk assessment-integrating occupational and non-occupational risk factors. *J. Occup Environ. Hyg.* 12, S112-S126. DOI: 10.1080/15459624.2015.1060326
- 34) Clewell, R. A., Leonard, J. A., Nicolas, C. I., Campbell, J. L., Yoon, M., Efremenko, A. Y., McMullen, P. D., Andersen, M. E., Clewell, H. J., 3rd, Phillips, K. A., & Tan, Y. M. (2020). Application of a combined aggregate exposure pathway and adverse outcome pathway (AEP-AOP) approach to inform a cumulative risk assessment: A case study with phthalates. *Toxicology in vitro*. 66, 104855. DOI: 10.1016/j.tiv.2020.104855
- 35) Karrer, C., Andreassen, M., von Goetz, N., Sonnet, F., Sakhi, A. K., Hungerbühler, K., Dirven, H., & Husøy, T. (2020). The EuroMix human biomonitoring study: Source-to-dose modeling of cumulative and aggregate exposure for the bisphenols BPA, BPS, and BPF and comparison with measured urinary levels. *Environment International* 136, 105397. DOI:/10.1016/j.envint.2019.105397
- 36) Eubanks, S. (2010) United States v. Philip Morris (D.O.J. Lawsuit). Public Health Law Center. <https://www.publichealthlawcenter.org/topics/commercial-tobacco-control/commercial-tobacco-control-litigation/united-states-v-philip>
- 37) Food & Drug Administration: Sunscreen Drug Products for Over-the-Counter Human Use. Federal Register/Vol. 84, No. 38/Tuesday, February 26, 2019/Proposed Rules. Available at <https://www.govinfo.gov/content/pkg/FR-2019-02-26/pdf/2019-03019.pdf>.
- 38) U.S. Department of Commerce (2020) Gross domestic product by State, 4th quarter and annual 2019. Bureau of Economic Analysis. <https://www.bea.gov/system/files/2020-04/qgdpstate0420.pdf>
- 39) Office of Environmental Health Hazard Assessment (2021) Benzophenone. https://www.p65warnings.ca.gov/sites/default/files/downloads/factsheets/benzophenone_fact_sheet.pdf
- 40) DiNardo, J.C., Downs, C.A. (2021) Failure to protect: do sunscreens prevent skin cancer in humans? *Toxicol. Open Access* 7, 3. <https://www.omicsonline.org/open-access/failure-to-protect-do-sunscreens-prevent-skin-cancer-in-humans.pdf>
- 41) U.S. National Academies of Sciences, Engineering, and Medicine. <https://www.nationalacademies.org/based-on-science/sunscreen-does-not-cause-skin-cancer>
- 42) Meadows, M. *FDA Consumer Magazine* (2006). <https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years>. Accessed 16 October 2016.
- 43) European Commission. Chemical strategy for sustainability towards a toxic-free environment (2020) <https://ec.europa.eu/environment/pdf/chemicals/2020/10/Strategy.pdf> Accessed 15 October 2020.