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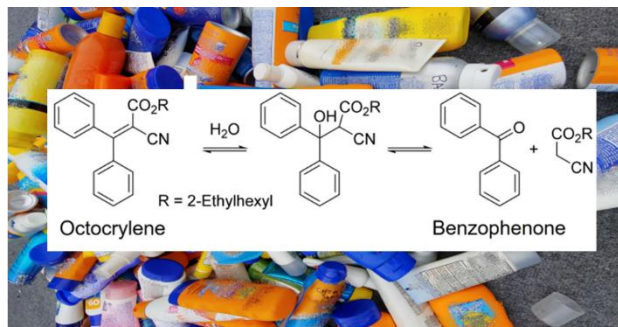


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**Benzophenone accumulates over time from the degradation of octocrylene in commercial sunscreen products.**

C.A. Downs, Joseph DiNardo, Didier Stien, Alice M.S. Rodrigues, Philippe Lebaron

## For Table of Contents Only



## Abstract

Benzophenone is a mutagen, carcinogen, and endocrine disruptor. Its presence in food products or food packaging is banned in the United States. Under California Proposition 65, there is no safe harbor for benzophenone in any personal care products, including sunscreens, anti-aging creams, and moisturizers. The purpose of this study was to determine if (a) benzophenone was present in a wide variety of commercial SPF/sunscreen products and (b) whether benzophenone concentration in the product increased over time, and (c) the degradation of octocrylene was the likely source for benzophenone contamination. Benzophenone concentration was assayed in 9 commercial sunscreen products from the European Union and 8 from the United States (in triplicate), including two single ingredient sources of octocrylene. These same SPF items were subject to FDA-accelerated stability aging protocol for 6 weeks. Benzophenone was measured in the accelerated-aged products. Sixteen octocrylene-containing product lines that were recently purchased had an average concentration of 39 mg/kg benzophenone, ranging from 6 mg/kg to 186 mg/kg. Benzophenone was not detectable in the product that did not contain octocrylene. After subjecting the 17 products to the FDA-accelerated stability method, the 16 octocrylene-containing products had an average concentration of 75 mg/kg, ranging from 9.8 mg/kg to 435 mg/kg. Benzophenone was not detectable in the product that did not contain octocrylene. Benzophenone was detected in the pure octocrylene manufactured ingredient. Octocrylene generates benzophenone through a retro-aldol condensation. *In vivo*, up to 70% of the benzophenone in these sunscreen products may be absorbed through the skin. U.S. FDA has established a zero-tolerance for benzophenone as a food additive. In the United States, there were 2,999 SPF products containing octocrylene in 2019. The safety of octocrylene as a benzophenone-generator in SPF or any consumer products should be expeditiously reviewed by regulatory agencies.

## Introduction

Octocrylene (CAS# 6197-30-4) is one of 14 U.S. Food and Drug Administration active ingredients approved for use in SPF (sun-protection factor) over-the-counter drugs which include sunscreens, moisturizers, lip-balms, and anti-aging products. In March of 2019, 2,999 SPF products that were registered for sale in the United States contained octocrylene<sup>1</sup>. Octocrylene is also used in non-SPF labeled personal care products such as shampoos, hair sprays, tanning oils, and conditioners.

The personal care product industry has known for some time that octocrylene is contaminated with benzophenone (CAS# 119-61-9). When purchasing raw octocrylene for sunscreen or personal care product manufacturing, industry admits that benzophenone is a contaminant found in octocrylene, and for some reason, “cannot be removed by its entirety when octocrylene is being processed...”<sup>2,3</sup>. Furthermore, industry members have also stated that the concentration of benzophenone in octocrylene manufactured-ingredients and consumer products is “negligible”<sup>2</sup>.

Benzophenone is associated with a wide range of toxicities, including genotoxicity, carcinogenicity, and endocrine disruption. Benzophenone and its common metabolites, benzhydrol and *p*-hydroxybenzophenone, were positive mutagens in the Ames Test platforms (strain TA102) in the SOS/Umu mutagenicity platform<sup>4-7</sup>. Benzophenone was also demonstrated to induce thymine dimerization and double-stranded DNA break formation in the presence of UV light<sup>8</sup>.

Benzophenone is an established carcinogen<sup>9-11</sup>. Signs of this pathology induced by benzophenone were first observed in the liver of Guinea pig<sup>12</sup>. In mice, oral ingestion of benzophenone resulted in significant manifestations of hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma (male mice) and histiocytic sarcoma (female mice). Benzophenone also induced the incidence of mononuclear-cell leukemia and renal tubule adenoma in male rats, while female rats saw an increase in histiocytic sarcoma<sup>10,11</sup>.

A preponderance of evidence indicates that benzophenone and its metabolites are potential endocrine disruptors with diverse axis impacts<sup>13-15</sup>. Recent evidence indicated that benzophenone could alter thyroid-hormone balances. In an *in vitro* rat thyroid follicular cell line, benzophenone up-regulated the sodium/iodide symporter and thyroid globulin genes, while down-regulating thyroid peroxidase gene<sup>16</sup>. In an *in vitro* pituitary cell line, benzophenone down-regulated the thyroid stimulation hormone  $\beta$ -subunit gene, the thyrotropin releasing hormone receptor gene, and the thyroid receptor  $\beta$ -subunit gene<sup>16</sup>.

*para*-Hydroxybenzophenone, a metabolite of benzophenone, exhibits estrogenic activity both *in vitro* and *in vivo*, as demonstrated by uterotrophic assays<sup>13,17,18</sup>. *p*-Hydroxybenzophenone was also shown *in vitro* to induce anti-androgenic activity<sup>13,15</sup>. Subcutaneous injection into female, juvenile rats with *p*-hydroxybenzophenone resulted in the proliferation of uterine luminal epithelium cells and cornified vaginal epithelium cells, as well as increased uterine weight<sup>14</sup>. Besides direct interaction with hormone receptors, benzophenone was demonstrated to induce the expression of a number of cytochrome P450 isoforms in male rat livers. This cytochrome P450 induction seems to be elicited by activating both the pregnane X receptor and the steroid receptor coactivator 1<sup>19</sup>. There is some evidence, though not rigorously studied, that benzophenone-exposure resulted in a gross-morphological pathology; mature male rats exhibited

small seminal vesicles which were at an immature stage of development, as well as testicular hypoplasia<sup>10</sup>.

Based on litigation and MSDS/literature provide by manufacturers of octocrylene, it could easily be perceived that benzophenone is a contaminant from the manufacturing synthesis of octocrylene, and that current manufacturing clean-up processes are unable to purify octocrylene to less than 1 mg/kg<sup>2,3</sup>. Another possibility is that benzophenone is created from the degradation of octocrylene. If this possibility is true, then octocrylene products potentially pose a serious health hazard because benzophenone concentration would increase over time in that product. Under the State of California Proposition 65, there is no “safe harbor” or allowable level of benzophenone contamination in a product<sup>20</sup>. This lack of forbearance is consistent with the danger of dermal absorption of benzophenone; 70% of the benzophenone in a dermatological product would be absorbed through skin and into the body<sup>21</sup>. Dermal absorption of other benzophenones (e.g., oxybenzone) and octocrylene are a serious public health conundrum, finally recognized by the U.S. FDA<sup>22,23</sup>.

Octocrylene is quickly becoming the dominant UV-sunscreen environmental contaminant, found in coastlines, rivers, and lakes all over the world<sup>24-26</sup>. Most environmental surveys look for this common sunscreen compound, but few environmental or biomonitoring studies examine metabolites or degradation products<sup>27, 28</sup>. Benzophenone has been seen in some surveys, but its inclusion into methodical target-analyte surveys has largely been ignored because its presence was assumed to be negligible or non-existent. If octocrylene does give rise to benzophenone, then environmental and public health surveys should actively include benzophenone as a targeted analyte<sup>29</sup>.

To begin to address this issue of the relationship between octocrylene and benzophenone, we sought evidence for whether (a) benzophenone was present in a wide variety of commercial SPF/sunscreen products and (b) whether benzophenone concentration in the product increased over time, and (c) the degradation of octocrylene was the likely source for benzophenone contamination.

## Materials and Methods

### *Sunscreen Product Samples*

The following products were purchased in triplicate from retail stores in both France and the United States. Product names, sunscreen actives/UV absorbers, ingredient labeling, lot numbers and expiration dates, are presented in **Table 1**.

Products purchased in France in December 2019 (**Supplemental Figure S1**): Nivea Sun Protect & Hydrate SPF 50+ (does not contain octocrylene). The remaining products all identified OC in the ingredient labeling - Garnier Ambre Solaire Resisto Enfant FPS 50+; Bioderma Photoderm AR SPF 50+ Teinte Naturelle; Uriage Age Protect Fluide Multi-Actions SPF 30; LaRoche-Posay Sans Traces Blanches SPF 50+; LaRoche-Posay 50+ SPF Brume Invisible/Transparentes Spray; Cosmia Sun BB Creme SPF 50 Haute Protection; Cosmia Sun Haute-High Protection SPF 30; and L'Oreal Age Perfect Soins Rose Re-Fortifiant FPS 20.

Products purchased in the United States of America in January 2020 (**Supplemental Figure S2**): Coppertone Kids Sport SPF 50 Spray; Coppertone Sunscreen Lotion Defend & Care Face Oil Free 50 Lotion; Coppertone Sunscreen Spray Water Babies 50, Coppertone Clear Sunscreen Sport Clear 30; Banana Boat Clear UltraMist Sport Performance 30; Banana Boat Sport Performance Sunscreen Lotion 50+; Neutrogena Beach Defense Sunscreen Spray 100; Neutrogena Beach Defense Sunscreen Lotion 70. All products identified OC at levels between 4.5% and 10% in the active ingredients section of the drug facts labeling.

Testing of benzophenone contamination in manufactured octocrylene for use in commercial formulated products were:

(1) Symrise Neo Heliopan 3030 (Octocrylene), Product # 600154. [www.symrise.com](http://www.symrise.com). Code:0978, Impurities = 200 ppm benzophenone.

(2) TRI-K Galsorb Octocrylene, Lot S/3006.

<http://www.tri-k.com/wp-content/uploads/2016/02/GalSORB-Octocrylene-Specifications-v2.pdf>. Accessed June 1, 2020.

All commercial sunscreens were sampled for testing after being purchased directly from stores and represent products stored under normal conditions of use.

The same products were retested after being stored for six weeks in a 40°C incubator (Cincinnati Sub-Zero Model STH-24.25-H/AC StableClimate II Temperature/humidity Stability Chamber; U.S.A) with 75% relative humidity and represents accelerated aging of one-year at room temperature. These test conditions are commonly used to evaluate the stability of product formulations for over-the-counter drug stability in the United States of America<sup>30</sup>.

### *Chemical Analysis*

A set of four standard solutions of acetonitrile containing known benzophenone concentrations of 0, 1, 5, and 25 µg/mL was prepared by successive dilutions from a stock solution at 233 µg/mL benzophenone. Sunscreens were analyzed in a random order. Four samples of each sunscreen were weighed in four 2-mL Eppendorf tubes (≈ 100 mg per each, measured accurately with a 0.1 mg accuracy Mettler Toledo XP204 balance). The different acetonitrile

solutions (1 mL) were added, each one in one Eppendorf tube. The mixtures were sonicated for 30 min in the sweep mode, and then centrifuged at 23,000  $g$  for 10 min<sup>31</sup>. For each tube, the supernatant (20  $\mu$ L) was collected and diluted in acetonitrile (980  $\mu$ L) in an HPLC vial. For every seven sunscreens, a control analysis (no sunscreen in the Eppendorf tubes) was conducted similarly.

The HPLC/MS instrument and method were described by Stien et al. (2019) with modifications<sup>27</sup>. Here the gradient was 5 % B 3 min before injection, then from one to 12 min, a linear gradient increase of B up to 100 %, followed by 100 % B for 6 min in which A was water with 0.1 % formic acid and B was acetonitrile with 0.1 % formic acid. The column was a Phenomenex Kinetex F5 150 $\times$ 2.1 mm, 1.7  $\mu$ m. The flow was diverted (not injected into the mass spectrometer) before injection, up to 1 min after injection. With this method, benzophenone was eluted at  $\approx$  8.3 min. Eventually, another chromatographic method was also used to shorten the analysis time. In this case, the gradient was 5 % B 3 min before injection, then from 1 to 8 min, a linear gradient increase of B up to 100 %, followed by 100 % B for 5 min. With this method, benzophenone was eluted at  $\approx$  7.5 min.

In ThermoFisher FreeStyle software, the ion at  $m/z$  183.0804 corresponding to the protonated molecular ion of benzophenone was extracted from the UHPLC-MS profiles at 5 ppm mass tolerance. The chromatographic peak was integrated automatically using the Genesis algorithm with the following parameters: percent of highest peak 10.0, minimum peak height 1.0, S/N threshold 1.0, with valley detection disabled. The extracted ion peak was clearly detected for each run, and the integrations were repeatable. In order to assure an optimal quality control, blanks and control samples were analyzed to check carryover, background noise, precision and accuracy of the detection. Selectivity, specificity, accuracy, precision, linearity, range, limit of detection (LOD), limit of quantification (LOQ) for benzophenone are listed in Table S1 (supporting information). The integration values were reported in an Excel sheet for linear regression calculation. The linear regression equation was in the form:

$$\text{Benzophenone (BP) Peak Area} = a \cdot m_{\text{added\_BP}} + b$$

where  $m_{\text{added\_BP}}$  was the mass of benzophenone added to the sunscreen samples with the different solution of benzophenone in acetonitrile (0, 1, 5, and 25  $\mu$ g). The equation provided the mass of benzophenone ( $\mu$ g) in the sunscreen product ( $m_{\text{BP}_0}$ ) as follows:

$$m_{\text{BP}_0} = \left| \frac{-b}{a} \right|$$

This value was corrected by the amount of benzophenone ( $_{\text{BP}}$ ) in the corresponding blank analysis:

$$m_{\text{BP}_{\text{corrected}}} = m_{\text{BP}_0} - m_{\text{BP}_{\text{blank}}}$$

A blank of the same day as the analysis was used for correction. When several blanks were available, the “most advantageous” one (*i.e.*, the highest  $m_{BP_{blank}}$ ) was used for correction. Finally, the concentration of benzophenone (BP) in the sunscreen product was calculated as for being:

$$C_{BP} = \frac{m_{BP_{corrected}}}{\text{Average mass of cream}}$$

, and was expressed in mg/kg. The results are provided in Table 2.

## Results

Benzophenone was detected in all of the octocrylene-containing commercial products, while it was not present in significant or detectable quantities in the only non-octocrylene product that was tested (third column from the left, indicated as “Baseline”, **Table 2**).

Product samples were subjected to a U.S. FDA accelerated-stability testing protocol for six weeks; this duration is supposed to reflect a single year shelf-life. In the E.U. samples, the increase in benzophenone concentrations after the 6-week accelerated stability incubation ranged from a geometric mean of 38.7% to 199.4% (**Table 2**). The lowest concentration of benzophenone in a product was Uriage Age Protect SPF30 (GM of 6.3 mg/kg), but whose concentration increased to a geometric mean of 38.6 mg/kg after the accelerated-stability incubation (GM of 38.6 mg/kg). L’Oreal Age Perfect FPS 20 had the highest concentration of benzophenone for both the starting material (GM of 64.6 mg/kg) and accelerated-stability incubated (GM of 193.4 mg/kg). It should be noted that the E.U. and France do not require the concentrations of octocrylene or other sunscreen active ingredients on their label, so starting concentration of octocrylene is unknown.

In the U.S. Samples, benzophenone concentrations at the end of the 6-week accelerated-stability incubation ranged from a geometric mean of 14.5% to 134.4% (**Table 2**). The lowest concentration of benzophenone in a product was Banana Boat Clear UltraMist SPF30 (GM of 11.1 mg/kg), but whose concentration increased to a geometric mean of 17.7 mg/kg after the accelerated-stability incubated. It should be noted that Banana Boat Clear UltraMist contained only 5% octocrylene, one of the lowest octocrylene concentration formulations. Coppertone Sport Clear SPF30 had the highest concentration of benzophenone for both the starting material (GM of 185.45 mg/kg) and accelerated-stability incubated (GM of 434.85 mg/kg). Surprisingly, Coppertone Sport Clear SPF30 only contained 6% octocrylene.

Symrise Neo Heliopan 3030 octocrylene contained 151 mg/kg benzophenone. TRI-K Galsorb Octocrylene contained 47.7 mg/kg benzophenone.

## Discussion

The presence of octocrylene in a commercial product implies a threat of considerable contamination by benzophenone. Octocrylene is a 2-cyano cinnamic ester that can be synthesized by aldol condensation of benzophenone with 2-ethylhexyl 2-cyanoacetate<sup>32</sup>. The aldol condensation is catalyzed either by acidic or basic conditions and whose rate can be accelerated by protic solvents, such as water<sup>33</sup>. The aldol condensation is reversible, and both the aldol and the retro-aldol condensation rates accelerate under these conditions (Figure 1). Our work unambiguously establishes that octocrylene does undergo a slow retro-aldol condensation reaction that gives rise to benzophenone. This process occurred in all commercial sunscreens tested that contain octocrylene, resulting in the concomitant increase of the benzophenone concentration upon aging the product.

The source of benzophenone in a product arises from two main sources: (a) benzophenone contamination in the octocrylene used to manufacture the commercial product and (b) accumulation of benzophenone from the degradation of octocrylene as the product ages. All of the products we tested from the retail stores had benzophenone contamination, violating the State of California Proposition 65. If industry is to continue to use octocrylene in its formulas, it would need to better purify octocrylene from its benzophenone contaminant before selling it to personal care product manufacturers and develop a “safe” stabilizer that prevents the retro-aldol condensation reaction resulting in the formation of benzophenone (Figure 1). Our results did indeed demonstrate that the rate of benzophenone concentration increase depends more on the product formulation than on the initial octocrylene concentration (e.g., Banana Boat Clear UltraMist SPF30 vs. Coppertone Sport Clear SPF30).

Benzophenone and its structurally related compounds (e.g., benzophenone-1, benzophenone-3) are notorious for inducing dermatological pathologies, including contact dermatitis, erythema, urticaria, and photo-induced dermatitis<sup>34-38</sup>. Dermatological pathologies from benzophenone occur not just from personal care product exposure, but also from non-cosmetic products that come into direct and prolonged contact with the skin<sup>39,40</sup>. Benzophenone-induced dermatitis could also arise from prolonged exposure to paper packaging material, plastics, and food that was in contact with these paper packaging materials<sup>41,42</sup>.

Signs of liver morbidity and homeostatic distress when exposed to benzophenone were often recognized in guinea pig, rat, and mouse models, but the risks have been underestimated in both toxicology journal papers and organizational reports<sup>11,43,44</sup>. This is unfortunate because the earliest reports regarding benzophenone toxicology in a whole organism study concluded that a 15-day exposure to benzophenone induced changes resembling chronic hepatitis<sup>45</sup>. Cellular necrosis was “prominent in different parts of the liver” and that histopathological examination in non-necrotizing cells indicated the presence of “double-nucleated cells.” In both guinea pigs and rats, benzophenone-exposure induced significant increases in liver weight<sup>10,43</sup>. Significant increases in alanine aminotransferase level are consistent with hepatotoxic necrosis<sup>10,43</sup>. Furthermore, increased mitotic divisions of biliary epithelial cells with reduced glycogen reserves and increased glycolysis activity in proximate hepatocytes is an environment conducive to potential carcinogenic transformation. This liver pathology is consistent with the conclusion that benzophenone is a carcinogen by creating both mutagenic events, as well as localized unstable cellular/histological environment that could promote carcinogenesis<sup>46</sup>.

Based on the dermal absorption studies of benzophenone and its structurally similar sunscreen active ingredients of oxybenzone and avobenzone, benzophenone that is associated

with octocrylene products suggests that parts per million exposures and absorption of benzophenone could be expected<sup>21-23</sup>. Besides use of sunscreen for sun exposure, sunscreen marketing and advertising claims encourage daily and constant use of sunscreen to protect against the “perceived” dangers of “blue light” induced-dermal damage from LCD displays from computers and other persona devices, as well as from light transmission through building and car windows<sup>47-50</sup>. If dermatologist and marketing propaganda are to be taken seriously, consumers would be using octocrylene-based sunscreens every day, with multiple reapplications through the day, throughout the entire year. Unlike the claims made by various propaganda sources in response to the two studies by Matta and co-workers, that their exposure-design in their two studies were unrealistic, benzophenone exposure concentration may easily exceed the 100 mg/kg/day<sup>51-53</sup>.

As with other chemicals in mass-produced personal care products, benzophenone can be a potential “emerging contaminant of concern.” It can enter environmental systems from at least three routes of contamination: swimmer discharges (sunscreen and fragrances), sewage discharges (sunscreen, cosmetics and fragrances), garbage and debris leachate (personal care products, paper and plastic packaging). Environmental contamination surveys are costly and human resource extensive, requiring ample justification to survey and monitor for a target analyte. This work gives ample justification for launching studies to determine if benzophenone is a significant environmental contaminant, and whether it poses an untenable risk when it contributes to a plume mixture of other contaminants that are known to pose potential ecological threats, such as octocrylene, oxybenzone, avobenzone, and octinoxate.

There are few ecotoxicological studies regarding benzophenone. A marine copepod chronically exposed to benzophenone exhibited decreased egg viability and hatching success, as well as exhibiting significant genomic DNA methylation, raising concerns for potential intra- and trans-generational evolutionary effects<sup>53</sup>. In rainbow trout, benzophenone binds to the trout estrogen receptor and induces vitellogenin mRNA in liver slices<sup>55</sup>. A more fascinating historical examination of benzophenone is that the first patents on benzophenone were for its herbicidal properties. In 1954, the Monsanto Chemical Company patented benzophenone for its “valuable herbicidal compositions and methods of destroying or preventing plant growth<sup>56</sup>.” In 1976, benzophenone and a number of its derivatives were patented by the Rohm and Haas Company as pre-emergent and post-emergent herbicides<sup>57</sup>. In 1978, benzophenone and benzhydrols were patented for their ability to control “undesirable growth of suckers in tobacco plants”<sup>58</sup>. This small amount of information regarding its use and toxicities is a concern for marine and aquatic ecological integrity, from coral reefs and seaweed forests to river and lake systems.

Octocrylene products that contain benzophenone may pose a threat to the public health, and even ecological health<sup>28,29,59</sup>. Safety evaluations done in the past were limited, and in-depth studies need to be conducted to ascertain the full range of toxicity of octocrylene and benzophenone products, so that a more appropriate threat evaluation can be conducted to preserve public health. Mixed xenobiotic exposure-effect studies need to be conducted using chemicals that are commonly found with octocrylene/benzophenone products. Octocrylene by itself is an endocrine disruptor, a developmental toxicant and a metabolic stressor, both to mammal receptor models, but also to various wildlife models, including fish and coral<sup>27,60-63</sup>. Preliminary evidence potentially suggests that octocrylene may have a role in the behavior of tumorigenesis and carcinogenesis<sup>60,64</sup>. What is the danger of being exposed to a product that

simultaneously contains oxybenzone, octinoxate, or homosalate, as well as octocrylene and benzophenone?

Based on the final decision by the E.U. to allow benzophenone as a flavor agent, and the U.S. FDA making no ruling regarding the contamination of over-the-counter SPF drugs, the decisions regarding public health safety regulatory thresholds can be argued to be unjustified and irresponsibly reckless<sup>3,65-66</sup>. Both examples, when examined closely, can be argued to be reminiscent of the debacle of beryllium and the U.S. Occupational Safety and Health Administration<sup>67</sup>. Whether benzophenone and octocrylene products should be allowed for public consumption should not be decided “in the back seat of a taxi by industry consultants” (toxicab standard), but by careful and meticulous review of the literature and publicly available data<sup>64,68</sup>.

There is enough scientific literature to make an argument that octocrylene/benzophenone products can pose a threat to individual and public health. Several jurisdictions, including the Republics of Palau and the Marshall Islands, as well as the U.S. Virgin Islands, have banned octocrylene in sunscreen and cosmetic products, effective in January 2020. It is agreeable that there needs to be a more refined and rigorously produced, unbiased data regarding exposure and toxicity of both these chemicals, and the products that contain them. Consideration must be given to the responsible regulatory response to prohibit the manufacture and sale of these octocrylene/benzophenone formulated products until industry can *prove* beyond a reasonable doubt that chronic exposure does not cause harm over any aspect of the life history of the receptor model or in public health clinical trials. An alternative to this current system of regulatory *laissez faire* would be a cogent and detailed prescriptive argument for a Precautionary Principle framework whose goal is the protection of public health<sup>69</sup>.

## ▪ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at

**Figure S1.** Tested sunscreen products purchased in December of 2018 in retail stores in France.

**Figure S2.** Tested sunscreen products purchased in January of 2019 in retail stores in the United States of America.

Methodological Description and Sample Chromatograms ([PDF](#))

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## ■ REFERENCES

- (1) U.S. Food & Drug Administration, National Drug Code Directory. March 8, 2019 database. <https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory>. Accessed Sept. 23, 2020.
- (2) Rodan & Fields. 2016. Frequently asked questions: benzophenone & octocrylene California Prop 65 ingredients. <https://lithub.com/pesticides-incendiaries-how-us-chemical-companies-endeared-themselves-to-the-public/>. Accessed Sept. 28, 2020.
- (3) Superior Court of California, Case No. 1503341. Action Filed Sept 10, 2015. Shefa LMV LLC vs. Concept 2 Cosmetics et al. Marin County Superior Court.
- (4) Robinson, D. (1958) Studies in detoxication. 74. The metabolism of benzhydrol, benzophenone and p-hydroxybenzophenone. *Biochem. J.* 68, 584-586.
- (5) Takemoto, K., Yamazaki, H., Nakajima, M., Yoko, T. (2002) Genotoxic activation of benzophenone and its two metabolites by human cytochrome P450s in SOS/umu assay. *Mutation Res.* 519, 199-204.
- (6) Wang, W-Q., Duan, H-X., Pei, Z-T., Xu R-R., Qin, Z-T., Zhu, G-C., Sun Li-Wei. (2018) Evaluation by the Ames Assay of the mutagenicity of UV filters using benzophenone and benzophenone-1. *Intl. J. Environmtl. Res. Public Health* 15, 1907.
- (7) Zhao H, Wei D, Li M, Du Y. 2013. Substituent contribution to the genotoxicity of benzophenone-type UV filters. *Ecotoxicol. Environmtl. Safety* 95, 241-246.
- (8) Charlier, M., Helene, C., Carrier, WL. (1972) Photochemical reactions of aromatic ketones with nucleic acids and their components – III. Chain breakage and thymine dimerization in benzophenone photosensitized DNA. *Photochem. Photobiol.* 15,527-536.
- (9) IARC Monograph (2013) Benzophenone. Vol 101. <https://monographs.iarc.fr/wp-content/uploads/2018/06/mono101-007.pdf>
- (10) National Toxicology Program Tech Rep. Ser. (2006) Toxicology and carcinogenesis studies of benzophenone (CAS No. 119-61-9) in F344/N rats and B6C3F1 mice (feed studies). 533,1-264.
- (11) Rhodes, M.C., Bucher, J.R., Peckham, J.C., Kissling, G.E., Hejtmancik, M.R., Chhabra, RS. (2007) Carcinogenesis studies of benzophenone in rats and mice. *Food Chem. Toxicol.* 45,843-851.
- (12) Dutta, K., Das, M., Rahman, T. (1993) Toxicological impacts of benzophenone on the liver of guinea pig (*Cavia Porcellus*). *Bull. Environ. Contam. Toxicol.* 50, 282-285.

- (13) Kawamura, Y., Mutsuga, M., Kato, T., Iida, M., Tanamoto, K. (2005) Estrogenic and anti-androgenic activities of benzophenones in human estrogen and androgen receptor mediated mammalian reporter gene assays. *J. Health Science* 51, 48-54.
- (14) Nakagawa, Y, Tayama K. (2001) Estrogenic potency of benzophenone and its metabolites in juvenile female rats. *Arch. Toxicol.* 75, 74–79.
- (15) Suzuki, T., Kitamura, S., Khota, R., Sugihara, K., Fujimoto, N., Ohta, S. (2005) Estrogenic and antiandrogenic activities of 17 benzophenone derivatives used as UV stabilizers and sunscreens. *Toxicol. Appl. Pharmacol.* 203,9-17.
- (16) Lee, J., Kim, S., Park, Y.J., Moon, H-B., Choi, K. (2018) Thyroid hormone disrupting potentials of major benzophenone in two cell lines (GH3 and FRTL-5) and embryo-larval zebrafish. *Environ. Sci. Technol.* 52, 8858-8865.
- (17) Nakagawa, Y., Suzuki, T., Tayama, S. (2000) Metabolism and toxicity of benzophenone in isolated rat hepatocytes and estrogenic activity of its metabolites in MCF-7 cells. *Toxicol.* 156, 27-36.
- (18) Nakagawa, Y., Tayama, K. (2002) Benzophenone-induced estrogenic potency in ovariectomized rats. *Arch. Toxicol.* 76,727-731.
- (19) Mikamo, E., Harada, S., Nishikawa, J., Nishihara, T. (2003) Endocrine disruptors induce cytochrome P450 by affecting transcriptional regulation via pregnane X receptor. *Toxicol. Appl. Pharmacol.* 193,66-72.
- (20) Office of Environmental Health Hazard Assessment, Proposition 65 No Significant Risk Levels for Carcinogens and Maximum Allowable Dose Levels for chemicals causing reproductive toxicity. <https://oehha.ca.gov/media/downloads/proposition-65/safeharborlist032519.pdf> Accessed 12 October, 2020.
- (21) Bronaugh, R., Wester, R.C., Buck, S D., Maibach, H.I., Sarason, R. (1990) In vivo percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. *Food Chem. Toxicol.* 28, 368-373.
- (22) Matta, M.K., Zusterzeel, R., Pilli, N.R., Patel, V., Volpe, D.A., Floria, J. et al. (2019) Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA* 321, 2082-2091.
- (23) Matta, M.K., Florian, J., Zusterzeel, R., Pilli, N.R., Patel, V., Volpe, D.A., et al. (2020) Effect of sunscreen application on plasma concentration of sunscreen active ingredients. *JAMA* 323, 256-267.

- (24) Gago-Ferrero, P., Alonso, M.B., Bertozzi, C.P., Marido, J., Barbosa, L., Cremer, M., Secchi, E., Domit, C., Azevedo, A., Laison-Brito, J., Torres, J.P.M., Malm, O., Eljarrat, E., Diaz-Cruz, M.S., Barcelo, D. (2013) First determination of UV filters in marine mammals. Octocrylene levels in Franciscana dolphins. *Environ. Sci. Technol.* 47, 5619-5625.
- (25) Picot-Groz, M., Fenet, H., Bueno, M.J.M., Rosain, D., Gomez, E. (2018) Diurnal variations in personal care products in seawater and mussels at three Mediterranean coastal sites. *Environ. Sci. Pollut. Res.* 25, 9051-9059.
- (26) Gadelha, J.R., Rocha, A.C., Camacho, C., Eljarrat, E., Peris, A., Aminot, Y., et al. (2019) Persistent and emerging pollutants assessment on aquaculture oysters (*Crassostrea gigas*) from NW Portuguese coast (Ria De Aveiro). *Sci. Total Environ.* 666, 731-742
- (27) Stien, D., Clergeaud, F., Rodrigues, A.M.S., Lebaron, K., Pillot, R., Romans, P., Fagervold, S., Lebaron, P. (2019) Metabolomics reveal that octocrylene accumulates in *Pocillopora damicornis* tissues as fatty acid conjugates and triggers coral cell mitochondrial dysfunction. *Anal. Chem.* 91,990-995.
- (28) Bury, D., Modick-Biermann, H., Leibold, E., Brüning, T., Koch, H.M. (2019) Urinary metabolites of the UV filter octocrylene in humans as biomarkers of exposure. *Toxicokinetics and Metabolism* 93, 1227-1238.
- (29) Rodrigues-Gómez, R., Zafra-Gómez, A., Dorival-Garci, B., Ballesteros, O., Navalón, A. (2015) Determination of benzophenone-UV filters in human milk samples using ultrasound-assisted extraction and clean-up with dispersive sorbents followed by UHPLC-MS/MS analysis. *Talanta* 134, 657-664.
- (30) U.S. Food & Drug Administration (2008) Guidance for industry. Drug stability guidelines. <https://www.fda.gov/media/69957/download>. Accessed February 29, 2020.
- (31) Quiñones, R., Bayline, J.L., Polvani, D.A., Neff, D., Westfall, T.D., Hijazi, A. (2016) Integrating elemental analysis and chromatography techniques by analyzing metal oxide and organic UV absorbers in commercial sunscreens. *J. Chem. Educ.* 93, 1434-1440.
- (32) Jing, H., Jing, S., Reinhard, K., Ralf, P. (2008) Process for the manufacture of substituted 2-cyano cinnamic esters. Patent Application No. WO2008EP00372 20080118. <https://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=2008089920&KC=&FT=E&locale=en> EP Accessed October 7, 2020.
- (33) Aerts, O., Kong, Y.Y., Leysen, J., De Borggraeve, W., Lambert, J., Goossens, A. (2016) Is unsubstituted benzophenone a potential screening agent to detect photocontact allergy to octocrylene? *Contact Dermatitis* 75, 60-106.
- (34) Ramsay, D.L., Cohen, H.J, Baer, R.L. (1972) Allergic reaction to benzophenone. Simultaneous occurrence of urticarial and contact sensitivities. *Arch. Dermatol.* 105, 906-908.

- (35) Knobler, E., Almeida, L., Ruzkowski, A.M., Held, J., Harber, L., DeLeo V. (1989) Photoallergy to benzophenone. *Arch. Dermatol.* 125,801-804.
- (36) Cook, N., Freeman, S. (2001) Report of 19 cases of photoallergic contact dermatitis to sunscreens seen at the Skin and Cancer Foundation. *Australas. J. Dermatol.* 42,257-259.
- (37) Nedorost, S.T. (2013). Facial erythema as a result of benzophenone allergy. *J. Am. Acad. Dermatol.* 49, S259-S261.
- (38) Heurung, A.R., Raju, S., Warshaw, E.M. (2014) Benzophenones. *Dermatitis* 25,3-10.
- (39) Melé-Ninot, G., Inglesias-Sanco, M., Bergendorff, O., Lazaro-Simo, A.I., Quintana-Codina, M., Salleras-Redonnet, M. (2019) Photoallergic contact dermatitis due to benzophenone contained in swimming goggles. *Contact Dermatitis* 82,59-60.
- (40) Tanahashi, T., Sasaki, K., Numata, M., Matsunaga, K. (2019) Three cases of photoallergic contact dermatitis induced by benzophenone in amusement park wristbands. *Contact Dermatitis* 80,191-193.
- (42) Altuntas, U., Hitay, V., Özcelik, B. (2016) Development and validation of a rapid method for identification and quantitation of benzophenone and related 17 derivatives in paper and cardboard packaging materials by gas chromatography-mass spectrometry. *Packaging Technology and Science* 29,513-524.
- (42) Blanco-Zubiaguirre, L., Zabaleta, I., Usobiaga, A., Prieto, A., Olivares, M., Zuloaga, O., Elizalde, M.P. (2020) Target and suspect screening of substances liable to migrate from food contact paper and cardboard materials using liquid chromatography-high resolution tandem mass spectrometry. *Talanta* 208,120394.
- (43) Silano, V., Bolognesi, C., Castle, L., Chipman, K., Cravei, J.P., Engel, K.H., et al. (2017) Safety of benzophenone to be used as flavouring. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. *EFSA J.* 15, e05013.
- (44) Scientific Opinion of EFSA prepared by the Panel on food contact materials, enzymes, flavourings and processing aids (CEF). Toxicological evaluation of benzophenone. (2009) *The EFSA J.* 1104,1-30.
- (45) Dutta, K., Das, M., Rahman, T. (1993) Toxicological impacts of benzophenone on the liver of guinea pig (*Cavia Porcellus*). *Bull. Environ. Contam. Toxicol.* 50,282-285.
- (46) IARC Monograph. 2013. Benzophenone. Vol 101. <https://monographs.iarc.fr/wp-content/uploads/2018/06/mono101-007.pdf>

- (47) Cook, E. (2017) Could your computer be damaging your skin? Harper's Bazaar. <https://www.harpersbazaar.com.au/beauty/computer-screen-skin-damage-7021>. Accessed October 1, 2020.
- (48) Buscemi, J. (2020) Should we wear sunscreen to protect our skin from blue light damage? Huffington Post, [https://www.huffpost.com/entry/sunscreen-blue-light\\_1\\_5ea306a1c5b6d376358eb76c](https://www.huffpost.com/entry/sunscreen-blue-light_1_5ea306a1c5b6d376358eb76c). Accessed October 1, 2020.
- (49) Gohara, M. (2020) Sunscreen for computer monitors: yes, you need it! <https://eltamd.com/live-freely/sunscreen-for-computer-monitors-yes-you-need-it/> Accessed October 2, 2020.
- (50) Saunders, N. (2020) Do you need to wear sunscreen inside? Experts weigh in. NBC News. <https://www.nbcnews.com/shopping/skin-care/sunscreen-indoors-best-sunblock-face-n1233470>. Accessed October 2, 2020.
- (51) Wong, M. (2019) Sunscreens in your blood?? That FDA study. Lab Muffin. <https://labmuffin.com/sunscreens-in-your-blood-that-fda-study/> Accessed October 2, 2020.
- (52) Goodman B. (2020) FDA sunscreen report raises concern over chemicals. <https://www.webmd.com/skin-problems-and-treatments/news/20200121/fda-skin-absorbs-dangerous-sunscreen-chemicals>. Accessed October 6, 2020.
- (53) Wong, M. (2020) More sunscreens in your blood??! The new FDA study. Lab Muffin. <https://labmuffin.com/more-sunscreens-in-your-blood-the-new-fda-study/> Accessed January 25, 2020.
- (54) Guyon, A., Smith, K.F., Charry, M.P., Champeau, O., Tremblay, L.A. (2018) Effects of chronic exposure to benzophenone and diclofenac on DNA methylation levels and reproductive success in a marine copepod. *J. Xenobiotics* 8, 7674.
- (55) Serrano, J., Tapper, M.A., Kolanczyk, R.C., Sheedy, B.R., Lahren, T., Hammermeister, D.E., et al. (2020) Metabolism of cyclic phenones in rainbow trout in vitro assays. *Xenobiotica* 50:192-208.
- (56) U.S. Patent Office, patent 2,671,016
- (57) U.S. Patent Office, patent 3,954,875
- (58) U.S. Patent Office, patent 4,120,687
- (59) Cho, Y.J., Yun, J.H., Kim, S.J., Kwon, H.Y. (2020) Nonpersistent endocrine disrupting chemicals and reproductive health of women. *Obstet. Gynecol. Sci.* 63,1-12.

- (60) Blüthgen, N., Meili, N., Chew, G., Odermatt, A., Fent, K. (2014) Accumulation and effects of the UV-filter octocrylene in adult and embryonic zebrafish (*Danio rerio*). *Sci. Total Environ.* 476-477,207-217.
- (61) Zhang, Q.Y., Ma, X.Y., Wang, X.C., Ngo, H.H. (2016) Assessment of multiple hormone activities of a UV-filter (octocrylene) in zebrafish (*Danio rerio*). *Chemosphere* 159,433-441.
- (62) Gu, J., Yuan, T., Ni, N., Ma, Y., Shen, Z., Yu, X., et al. (2019) Urinary concentration of personal care products and polycystic ovary syndrome: a case-control study. *Environ. Res.* 168,48-53.
- (63) Yan, S., Liang, M., Chen, R., Hong, X., Zha, J. (2020) Reproductive toxicity and estrogen activity in Japanese medaka (*Oryzias latipes*) exposed to environmentally relevant concentrations of octocrylene. *Environ. Pollut.* 261,114104.
- (64) Zdravković, T.P., Zdravković, B., Zdravković, M., Daris, B., Lunder, M., Ferk, P. (2019) In vitro study of the influence of octocrylene on a selected metastatic melanoma cell line. *Giornale Italiano di Dermatologia e Venereologia* 154,197-204.
- (65) Burdock, G.A., Pence, D.H., Ford, R.A. (1991) Safety evaluation of benzophenone. *Food Chem. Toxicol.* 29,741-750.
- (66) Serrano, J., Tapper, M.A., Kolanczyk, R.C., Sheedy, B.R., Lahren, T., Hammermeister, D.E., et al. (2020) Metabolism of cyclic phenones in rainbow trout in vitro assays. *Xenobiotica* 50,192-208.
- (67) Michael, D., Monforton, C. (2008) Beryllium's public relations problem: protecting workers when there is no safe exposure level. *Public Health Reports* 123, 79-88.
- (68) Eisenbud, M. (1991) An environmental odyssey: people, pollution, and politics in the life of a practical scientist. Seattle: University of Washington Press.
- (69) Sandin, P., Peterson, M., Hansson, S.O., Ruden, C., Juthe, A. (2011) Five charges against the precautionary principle. *J. Risk Res.* 5, 287-299.

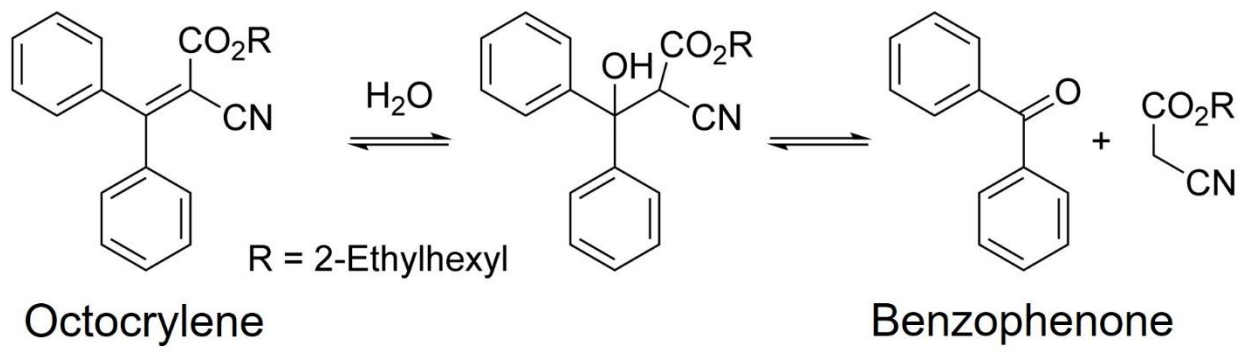
## Figure and Table Legends

**Figure 1. The retro aldol condensation reaction between octocrylene and benzophenone.**

**Table 1. List of commercial sunscreen products purchased in France and the U.S.A, presence of an active UV ingredient, concentration of an active UV ingredient (U.S.A. products only), and ingredient formulation.**

**Table 2. List of products, product lot number, product expiration date, the concentration of benzophenone (mg/kg; parts per million) at the baseline sampling, the concentration of benzophenone after the 6-week FDA accelerated stability incubation, and the percent increase of the geometric mean (GM) of benzophenone concentration for each product set between the baseline sampling and the 6-week accelerated stability sampling. The Nivea Sun SPF 50+ is the only commercial product that does not contain octocrylene in its active ingredients.**

Figure 1



**Table 1**

<b>Product</b>	<b>Active Ingredients</b>	<b>Ingredients</b>
<b>French Products</b>		
Nivea Sun SPF 50+  Control Sample – No Octocrylene	Homosalate Avobenzone Tinosorb S Octisalate Ethylhexyl Triazone Ensulizole	Aqua, Homosalate, Glycerin, Alcohol Denat., Butyl Methoxydibenzoylmethane (Avobenzone), Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine (Tinosorb S), Ethylhexyl Salicylate (Octisalate), Dibutyl Adipate, Ethylhexyl Triazone, Copernicia Cerifera Cera, Panthenol, VP/Hexadecene Copolymer, Phenylbenzimidazole Sulfonic Acid (Ensulizole), Tocopheryl Acetate, Tetrasodium Iminodisuccinate, Cellulose Gum, Acrylates/C10-30 Alkyl Acrylate Crosspolymer. Microcrystalline Cellulose, Xanthan Gum, Butylene Glycol Dicaprylate/Dicaprate, Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate, Sucrose Polystearate, Sodium Stearoyl Glutamate, Hydrogenated Polyisobutene, Trisodium EDTA, Sodium Hydroxide, Sodium Chloride, Ethylhexylglycerin, Phenoxyethanol, Linalool, Limonene, Benzyl Alcohol, Alpha-Isomethylionone, Citronellol, Geraniol, Parfum
Garnier Ambre Solaire FPS 50	Homosalate Octisalate Avobenzone <b>Octocrylene</b> Ethylhexyl Triazone Tinosorb S Ecamsule/Mexoryl SX	Aqua/Water, Glycerin, Alcohol Denat., Homosalate, Ethylhexyl Salicylate (Octisalate), Butyl Methoxydibenzoylmethane, Styrene/Acrylates Copolymer, Octocrylene, Diisopropyl Sebacate, Dicaprylyl Carbonate, Ethylhexyl Triazone, Dimethicone, Polyester-5, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Parfum/Fragrance, Drometrizole trisiloxane (Mexoryl XL), Tocopherol, PEG-8 Laurate, Ethylenediamine/Stearyl Dimer Dilinoleate Copolymer, Triethanolamine, Pentaerythrityl Tetra-Di-T-Butyl Hydroxyhydrocinnamate (Tinogard® TT), Caprylyl Glycol, Acrylates Copolymer, Terephthalylidene Dicamphor Sulfonic Acid (Ecamsule/Mexoryl SX), Disodium EDTA,
Bioderma Photoderm AR SPF 50+	<b>Octocrylene</b> Tinosorb M (nano) Avobenzone Tinosorb S Titanium Dioxide (77891),	Aqua/Water/Eau, Dicaprylyl Carbonate, Octocrylene, Dipropylene Glycol, Methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M - nano), Butyl Methoxydibenzoylmethane, Cyclopentasiloxane, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Hydroxypropyl Dimethicone Behenate, Potassium Cetyl Phosphate, Glyceryl Stearate, PEG-100 Stearate, Glycyrrhetic Acid, Gingo Biloba Leaf Extract, Tocopheryl Acetate, Ectoin, Mannitol, Xylitol, Rhamnose Fructooucosaccharides, Laminaria Ochroleuca Extract, Glycerin Soja (Soybean) Germ Extract, Propylene Glycol, Silica, Hydrogenated Vegetable Oil, Ammonium Acryloyldimethyltaurate/VP Copolymer, Xanthan Gum, Citric Acid, Trilinolein, Trilinoleinin, Triolein, Tripalmitin, Caprylic/Capric Triglyceride, Tristrin, Iron Oxides (77492), Iron Oxides (77491), Iron Oxides (77499), Titanium Dioxide (77891), Disodium EDTA, Phenoxyethanol, Chlorphenesin
Uriage Age Protect SPF 30	Octinoxate Octisalate Avobenzone <b>Octocrylene</b>	Aqua (Water, Eau), Ethylhexyl Methoxycinnamate (Octinoxate), Ethylhexyl Salicylate, Butyl Methoxydibenzoylmethane, Octocrylene, Polymethyl Methacrylate, Isononyl Isononanoate, Propanediol, Glycerin,

	CI 77891 (TiO2)	Dimethicone, Steareth-2, Steareth-21, Diisopropyl Sebacate, Propylene Glycol Dicaprylate/Dicaprate, C12-15 Alkyl Benzoate, Diisopropyl Adipate, Phenoxyethanol, Butylene Glycol, Cetyl Alcohol, Parfum (Fragrance), CI 77891 (Titanium Dioxide), Chlorphenesin, Polyacrylate-13, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Tetrasodium EDTA, Caesalpinia Spinosa Fruit Extract, Mica, Polyisobutene, Ascorbyl Tetraisopalmitate, o-Cymen-5-ol, Tocopheryl Acetate, Xanthan Gum, Retinyl Palmitate, Kappaphycus Alvarezii Extract, Adenosine, Sodium Hyaluronate, Polysorbate-20, Croton Lechleri Resin Extract, Sorbitan Isostearate, Theobroma Cacao (Cocoa) Seed Extract, Tin Oxide, BHT, Tocopherol
LaRoche-Posay SPF 50	Homosalate <b>Octocrylene</b> Octisalate Avobezone Ethylhexyl Triazone Tinosorb S Mexoryl XL Ecamsule/Mexoryl SX Titanium Dioxide TiO2 (Nano)	Aqua/Water, Homosalate, Silica, Octocrylene, Ethylhexyl Salicylate, Butyl Methoxydibenzoylmethane, Ethylhexyl Triazone, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Drometizole Trisiloxane, Aluminum Starch Octenylsuccinate, Glycerin, Pentylene Glycol, Styrene/Acrylates Copolymer, Potassium Cetyl Phosphate, Dimethicone, Perlite, Propylene Glycol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Aluminum Hydroxide, p-Anisic Acid, Caprylyl Glycol, Disodium EDTA, Inulin Lauryl Carbamate, Isopropyl Lauroyl Sarcosinate, PEG-8 Laurate, Scutellaria Baicalensis Extract, Scutellaria Baicalensis Root Extract, Silica Silylate, Stearic Acid, Stearyl Alcohol, Terephthalylidene Dicamphor Sulfonic Acid, Titanium Dioxide, Titanium Dioxide (Nano)/Titanium Dioxide, Tocopherol, Triethanolamine, Xanthan Gum, Zinc Gluconate, Parfum/Fragrance
LaRoche-Posay SPF 50 Spray	Homosalate <b>Octocrylene</b> Ethylhexyl Salicylate Avobenzone <u>Drometizole</u> <u>Trisiloxane</u> Ethylhexyl Triazone	Butane, Aqua/Water, Homosalate, Dicaprylyl Ether, Octocrylene, Ethylhexyl Salicylate, Dimethicone, Styrene/Acrylates Copolymer, Butyl Methoxydibenzoylmethane, <u>Drometizole Trisiloxane</u> , PEG-30 Dipolyhydroxystearate, Nylon-12, Dicaprylyl Carbonate, Methyl Methacrylate Crosspolymer, Cyclohexasiloxane, Polymethylsiloxane, p-Anisic Acid, Caprylyl Glycol, Disodium EDTA, Disteardimonium Hectorite, Dodecene, Ethylhexyl Triazone, <u>Isododecane</u> , Lauryl PEG-8/PPG-18/18 Methicone, PEG-8 Laurate, Phenoxyethanol, Poloxamer 407, Poly C10-30 Alkyl Acrylate, Propylene Carbonate, Sodium Chloride, Tocopherol, Parfum/Fragrance
Cosmia Sun BB Creme SPF 50	Octinoxate <b>Octocrylene</b> Avobenzone DEB Triazone Tinosorb S CI 77891 (TiO2)	Aqua, Ethylhexyl Methoxycinnamate, C12-15 Alkyl Benzoate, Octocrylene, Butyl Methoxydibenzoylmethane, Cetareth-20, Polyglyceryl-6 Stearate, Triacetyl PVP, Glycerin Soja Oil, Glycerin, Diethylhexyl Butamido Triazone (DEB Triazone), Cocos Nucifera Oil, Cetaryl Alcohol, Glyceryl Stearate, Helianthus Annuus Seed Oil, Tocopherol, Phenoxyethanol, Cyclopentasiloxane, Benzyl Alcohol, Cetareth-12, Dimethicone, Sorbitan Caprylate, Parfum, Nylon—10/10, Carbomer, Cyclohexasiloxane, Triethanolamine, Ethylparaben, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Polyglyceryl-6 Behenate, Tetrasodium EDTA,

		Trimethoxybenzylidene Pentanedione, Sodium Citrate, Xanthan Gum, CI 77891 (TiO <sub>2</sub> ), CI 77492, CI 77491, CI 77499
Cosmia Sun SPF 50	Homosalate Avobenzone DEB Triazone <b>Octocrylene</b> Tinosorb S	Aqua/Water/Eau, Alcohol Denat., C12-15 Alkyl Benzoate, Homosalate, Butyl Methoxydibenzoylmethane, Polyglyceryl-6 Stearate, Cetareth-20, Zea Mays (Corn) Starch, Dicaprylyl Carbonate, Diethylhexyl Butamido Triazone, Glycerin Soja (Soyabean), Octocrylene, Triaccontanyl PVP, Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Cetareth-12, Ceteryl Alcohol, Cocos Nucifera (Coconut) Oil, Glycerin, Glyceryl Stearate, Parfum (Fragrance), Sodium Benzoate, Polyglyceryl-6 Behenate, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Citric Acid, Potassium Sorbate, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil
L'Oreal Age Perfect FPS 20	Octisalate <b>Octocrylene</b> Avobenzone Ensulizole CI 77891 - TiO <sub>2</sub> TiO <sub>2</sub> (Nano)	Aqua/Water, Glycerin, Ethylhexyl Salicylate, Niacinamide, Dimethicone, C12-15 Alkyl Benzoate, Alcohol Denat., Octocrylene, Pentylene Glycol, Butyl Methoxydibenzoylmethane, Octyldodecanol, Isopropyl Isostearate, Triethanolamine, Behenyl Alcohol, Phenylbenzimidazole Sulfonic Acid, Ammonium Polyacryloyldimethyl Taurate, Iris Florentina Root Extract, Paeonia Suffruticosa Root Extract, Calcium Pantetheine Sulfonate, Capryloyl Salicylic Acid, Disodium EDTA, Cetyl Alcohol, Alumina, Ammonium Acryloyldimethyltaurate/Steareth-25 Methacrylate Crosspolymer, Butylene Glycol, Caprylyl Glycol, Carbomer, Ceteryl Alcohol, Ceteryl Glucoside, CI 77491/Iron Oxides, CI 77891/Titanium Dioxide, Disodium Stearoyl Glutamate, Mica, Myristic Acid, Palmitic Acid, PEG-100 Stearate, PTFE, Stearic Acid, Synthetic Fluorphlogopite, Tin Oxide, Titanium Dioxide (Nano)/Titanium Dioxide, Dimethiconol. Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Benzoate, Citronellol, Coumarin, Geraniol, Limonene, Linalool, CI 15510/Orange 4, CI 19140/Yellow 5, Silica, Phenoxyethanol, Parfum/Fragrance
<b>American Products</b>		
Coppertone Kids Sport SPF 50 Spray	3% Avobenzone 4.5% Octisalate <b>9% Octocrylene</b> 6% Oxybenzone	SD Alcohol 40-B (75.5% v/v), Neopentyl Glycol Diheptanoate, Polyester-27, Dimethicone, Tocopherol (vitamin E), Fragrance, avobenzone, octisalate, octocrylene, oxybenzone
Coppertone Defend & Care Face SPF 50 Lotion	3% Avobenzone 10% Homosalate 4.5% Octisalate <b>8% Octocrylene</b>	Water, Aluminum Starch, Octenylsuccinate, Styrene/Acrylates Copolymer, Glycerin, Polyester-27, Silica, Phenoxyethanol, Isododecane, Arachidyl Alcohol, Beeswax, Ethylhexylglycerin, Neopentyl Glycol Diheptanoate, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Behenyl Alcohol, Tocopherol, Arachidyl Glucoside, Glyceryl Stearate, PEG-100 Stearate, Potassium Hydroxide, Disodium EDTA, Sodium Ascorbyl Phosphate, avobenzone, homosalate, octisalate, octocrylene
Coppertone Water Babies SPF 50 Spray	3% Avobenzone 9% Homosalate 4.5% Octisalate <b>9% Octocrylene</b>	Water, Dimethyl Ether, Aloe Barbadosensis Leaf Juice, C12-15 Alkyl Benzoate, Neopentyl Glycol, Diheptanoate, Butylene Glycol, Styrene/Acrylates Copolymer, VP/Eicosene Copolymer, 1,2-Hexanediol, Hydroxyacetophenone, Fragrance,

		Tocopherol, Acrylates/C10-30 Alkyl Acrylate Crosspolymer, Potassium Hydroxide, Disodium EDTA , avobenzene, homosalate, octisalate, octocrylene
Coppertone Sport Clear SPF 30 (#1 & #3)	3% Avobenzene 10% Homosalate <b>6% Octocrylene</b>	SPF 30 = SD Alcohol 40-B (60.3% v/v), Dicaprylyl Ether, Ethylhexyl Isononanoate, PVP, Dimethicone/Vinyl Dimethicone Crosspolymer, Polyester-27, Silica Dimethicone Silylate, Beeswax, Acrylates/C12-22 Alkyl Methacrylate Copolymer, Fragrance, Silica, avobenzene, homosalate, octocrylene
Banana Boat Clear UltraMist SPF 30 Spray	2% Avobenzene 7% Homosalate <b>5% Octocrylene</b>	Alcohol Denat. Isobutane, Isododecane, Diisopropyl Adipate, Lauryl PEG-8 Dimethicone, Phenylisopropyl Dimethicone, Polyglyceryl-3 Stearate/Isostearate/Dimer Dilinoleate Crosspolymer, Caprylyl Glycol, Methyl Dihydroabietate, Fragrance, Ascorbyl Palmitate, Tocopheryl Acetate, Mineral Oil, Panthenol, Water, Aloe Barbadensis Leaf Juice, avobenzene, homosalate, octocrylene
Banana Boat SPF 50 Lotion	3% Avobenzene 10% Homosalate 4.5% Octisalate <b>9% Octocrylene</b> 5% Oxybenzone	Water, Cetearyl Alcohol, Stearyl Alcohol, Glycerin, Phenoxyethanol, Acrylates C12-22 Alkyl Methacrylate Copolymer, Caprylyl Glycol, Cetyl Alcohol, Carbomer, Ceteth-10 Phosphate, Dicetyl Phosphate, Coco-Glucoside, Methylparaben, Xathan Gum, Propylparaben, Sodium Hydroxide, Disodium EDTA, Lauryl PEG-8 Dimethicone, Methyl Dihydroabietate, Phenylisopropyl Dimethicone, Polyglyceryl-3 Stearate/Isostearate/Dimer Dilinoleate Crosspolymer, Sodium Ascorbyl Phosphate, Tocopheryl Acetate, Aloe Barbadensis Leaf Juice, avobenzene, homosalate, octisalate, octocrylene, oxybenzone
Neutrogena Beach Defense SPF 100 Spray	3% Avobenzene 15% Homosalate 5% Octisalate <b>10% Octocrylene</b> 6% Oxybenzone	Alcohol Denat.. Isobutane, Octyldodecyl Neopentanoate, Acrylates/Octylacrylamide Copolymer, Butyloctyl Salicylate, Dimethicone, Acrylates/Dimethicone Copolymer, Fragrance, Tocopheryl Acetate, Chrysanthemum Parthenium (feverfew) Flower/Leaf/Stem Juice, avobenzene, homosalate, octisalate, octocrylene, oxybenzone
Neutrogena Beach Defense SPF 70 Lotion	3% Avobenzene 10% Homosalate 5% Octisalate <b>4.5% Octocrylene</b> 4% Oxybenzone	Water, Styrene/Acrylates Copolymer, Dimethicone, Potassium Cetyl Phosphate, Benzyl Alcohol, Silica, Diethylhexyl 2,6-Naphthalate, Dimethicone/PEG-1-/15 Crosspolymer, Trisiloxane, Cetyl Dimethicone, Beeswax, Ethylhexylglycerin, Sodium Polyacrylate, Xanthan Gum, Ethylhexyl Stearate, Acrylates/C12-22 Alkyl Methacrylate Copolymer, Behenyl Alcohol, Trideceth-6, Disodium EDTA, Glyceryl Stearate, PEG-100 Stearate, Caprylyl Glycol, Chlorphensin, Fragrance, avobenzene, homosalate, octisalate, octocrylene, oxybenzone

Table 2

<b>Product</b>	<b>Lot # /Expiration (Exp) Date</b>	<b>Baseline mg/kg (ppm)</b>	<b>6 Week mg/kg (ppm)</b>	<b>% GM increase from baseline</b>
Nivea Sun SPF 50+ <b>(Sunscreen Control)</b>	083105007/No Exp Listed	0.0	1.5	0% No Change
	083105007/No Exp Listed	0.2	-2.9	
	083105001/No Exp Listed	-0.2	-1.1	
Garnier Ambre Solaire FPS 50	28S400 8846255 /No Exp Listed	8.7	21.2	121.6%
	28S400 8846255 /No Exp Listed	11.4	26.0	
	28S400 8846255 /No Exp Listed	10.6	20.7	
Bioderma Photoderm AR SPF 50+	13391/ Exp 05/22	21.3	31.9	46.9%
	13391/ Exp 05/22	23.0	33.1	
	13391/ Exp 05/22	22.2	32.7	
Uriage Age Protect SPF 30	91931J/Exp 07/22	6.6	9.8	55.6%
	91931J/Exp 07/22	7.3	12.8	
	91931J/Exp 07/22	5.0	6.7	
LaRoche-Posay SPF 50	54S103/Exp 01/22	5.9	16.7	43.9%
	54S400/Exp 03/22	11.7	13.9	
	54S103/Exp 01/22	14.6	15.4	
LaRoche-Posay SPF 50 Spray	14S200/Exp 02/13/22	15.1	20.3	52.7%
	14S200/Exp 02/13/22	13.1	20.1	
	14S200/Exp 02/13/22	16.7	28.3	
Cosmia Sun BB Creme SPF 50	7702C0802/Exp 03/20	64.1	79.8	38.7%
	7702B0803/Exp 02/20	64.5	87.9	
	7702A1801/Exp 01/21	28.0	49.7	
Cosmia Sun SPF 50	042419002/Exp 03/22	10.1	24.4	116.0%
	042419002/Exp 03/22	13.7	27.1	
	042319001/Exp 02/22	12.0	25.5	
L'Oreal Age Perfect FPS 20	28S900/No Exp Listed	31.1	213.9	199.4%
	28S500/No Exp Listed	80.8	163.6	
	28S500/No Exp Listed	81.9	202.6	
Coppertone Kids Sport SPF 50 Spray	CV019AX/Exp 12/2020	34.9	43.0	14.5%
	CV019AX/Exp 12/2020	33.7	40.9	
	CV019AX/Exp 12/2020	40.9	41.5	
Coppertone Defend & Care Face SPF 50 Lotion	CV01956/Exp 01/2021	27.3	40.2	59.3%
	CV01956/Exp 01/2021	22.8	38.9	
	CV01956/Exp 01/2021	24.3	39.5	
Coppertone Water Babies SPF 50 Spray	029117/Exp 02/2021	59.9	92.3	59.3%
	029117/Exp 02/2021	71.3	95.4	
	029117/Exp 02/2021	60.0	116.8	
Coppertone Sport Clear SPF 30	9B06CS/Exp 02/21	143.0	408.3	134.4%
	9B06CS/Exp 02/21	227.9	461.4	
Banana Boat Clear UltraMist SPF 30 Spray	18139FF/Exp 04/2021	17.1	19.3	59.5%
	18139FF/Exp 04/2021	8.4	17.8	
	18139FF/Exp 04/2021	7.8	16.0	
Banana Boat SPF 50 Lotion	9C12CS/Exp 03/2021	29.3	43.3	63.5%
	9C12CS/Exp 03/2021	26.2	40.1	
	9C12CS/Exp 03/2021	24.3	47.2	
Neutrogena Beach Defense SPF 100 Spray	06319F54/Exp 02/2021	65.9	86.9	45.6%
	06319F54/Exp 02/2021	71.7	112.6	
	06319F54/Exp 02/2021	71.6	105.2	
Neutrogena Beach Defense SPF 70 Lotion	1449L0640/Exp 04/2022	15.8	23.3	54.5%
	1449L0640/Exp 04/2022	11.8	21.1	
	1449L0640/Exp 04/2022	12.6	17.6	

