The presence of benzophenone in sunscreens and cosmetics containing the organic UV-filter octocrylene: a laboratory study.

Kenn Foubert^{1*}, Ella Dendooven^{1,2,3*}, Mart Theunis¹, Tania Naessens¹, Boryana Ivanova¹, Luc Pieters¹, Liesbeth Gilissen⁴, Sara Huygens⁴, Wim De Borggraeve⁵, Julien Lambert^{2,3}, An Goossens⁴, and Olivier Aerts^{2,3}.

**These authors contributed equally to this manuscript.*

¹Research group Natural Products & Food Research and Analysis (NatuRA), Department of Pharmaceutical Sciences, University of Antwerp (UA), Universiteitsplein 1, B-2610 Antwerp, Belgium.

²Department of Dermatology, University Hospital Antwerp (UZA), Wilrijkstraat 10, B-2650 Edegem, Belgium.

³Research group Immunology, Infla-Med Centre of Excellence, University of Antwerp, Universiteitsplein A, B-2610 Antwerp, Belgium.

⁴Department of Dermatology, University Hospitals KU Leuven, Herestraat 49, B-3000, Leuven, Belgium.

⁵Department of Chemistry, KU Leuven Chem&Tech, Celestijnenlaan 200F bus 2404, B-3001 Leuven, Belgium.

Corresponding author: Prof. Olivier Aerts, Department of Dermatology, University Hospital Antwerp (UZA), B-2650 Antwerp, Belgium. Olivier.aerts@uza.be / +32 3 821 4272

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Key words: unsubstituted benzophenone, CAS no. 119-61-9, cosmetics, environment, impurities, ketoprofen, octocrylene, toxicology, sunscreens, photo-contact allergy.

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ABSTRACT

Background: The reason why patients photosensitized to the drug ketoprofen (KP) may develop severe photo-allergic skin reactions to octocrylene (OCT), an organic UV-filter in sunscreens and cosmetics, remains largely unknown. OCT can be synthesized by using unsubstituted benzophenone (BP), a possible human carcinogen.

Objectives: To verify if, and to what extent, BP residues are present in OCT-containing consumer products.

Methods: The raw material of OCT and 39 skincare products, of which 28 containing OCT, were chemically analyzed for the presence of BP by means of Liquid Chromatography (LC).

Results: In the OCT raw material and in all 28 OCT-containing products the presence of BP could be demonstrated, mostly in concentrations above 10 ppm (0.001%), whereas a majority of OCT-free products (8/11; 73%) did not contain BP. Moreover, BP concentrations significantly increased, in a time- and temperature-dependent manner, likely due to the additional degradation of OCT.

Conclusions: Photo-allergic contact dermatitis from OCT in patients photo-sensitized to KP might rely on residual BP impurities. Toxicological and ecological studies that evaluate the safety of OCT might also need to consider the concomitant presence of BP.

MANUSCRIPT

1.Introduction

A recently published FDA rule outlined that there is a need to conduct more human safety studies on organic (chemical) UV-filters.¹⁻³ In Europe, where sunscreens fall under the Cosmetic Regulation (Annex VI, EC No. 1223/2009), the European Chemicals Agency (ECHA) has requested similar safety data.⁴⁻⁵ One of many controversial organic UV-filters is octocrylene (OCT)(**Figure 1A**), used up to a concentration of 10% in sunscreens and cosmetics in the US and the European Union (EU).⁶ Although its use appears to be safe, only few human studies are available, which highlight that OCT, although being a rare contact allergen⁷, may cause (severe) photo-allergic skin reactions, especially in subjects previously photosensitized to the (topical) non-steroidal anti-inflammatory drug ketoprofen (KP). The latter is, however, a molecule with a different, benzophenone-like, chemical structure (**Figure 1B**) and concomitant photo-sensitization to both molecules keeps many clinicians puzzled^{5-6,8}. Interestingly, OCT can be prepared industrially by using unsubstituted benzophenone (BP), a possible human carcinogen (**Figure 1C**).⁹⁻¹¹ BP residues might thus still be present in OCT-containing products, although manufacturers claim that these only concern “trace amounts” [(i.e. below 10 ppm, or 0.001%), without clinical significance, and thus not requiring any labeling].¹²

The aim of this study is to verify if, and to what extent, unsubstituted BP impurities are present in OCT-containing products, and to briefly discuss the potential implications this may have.

2. Materials and Methods

2.1. Reagents

Methanol (MeOH) (High Performance Liquid Chromatography [HPLC] grade), acetonitrile for UV (ACN) (HPLC grade; analytical reagent grade) and formic acid (FA) (98+%, pure, analytical reagent grade) were all acquired from Acros Organics (Geel, Belgium). Formic acid (FA) (99%, Ultrapformance Liquid Chromatography – Mass Spectrometry [UPLC/MS] grade) and acetonitrile for LC-MS analysis were acquired from Biosolve Chimie (Dieuze, France). Phosphoric acid (H₃PO₄) was obtained from Fisher Scientific (Leicestershire, UK). Ultrapure water with a resistivity of $18.2 \times M\Omega \times cm$ at 25 °C (Milli-Q, Waters, Milford, MA, USA) was used as extraction solvent and for mobile phase preparation. Octocrylene (OCT; 97%) and unsubstituted benzophenone (BP; CAS no. 119-61-9; 99%) were purchased from Sigma-Aldrich (Steinheim, Germany).

2.2. Method validation

For the quantitative determination of the amount of unsubstituted BP the following method was validated, according to the International Council for Harmonisation (ICH) guidelines on the validation of analytical methods, using skincare product no. 5 (**Table 1**).¹³ To (approx.) 1 g of the skincare product 8 mL MeOH (100%) was added. The sample was subsequently vortexed, sonicated during 30 min, and centrifuged for 10 min at 3500 rpm. The upper layer was then transferred to a measuring flask of 10 ml and filled with MeOH (100%). The solution was subsequently centrifuged for 30 min at 14000 rpm, and injected (20 µL) for HPLC-UV analysis. Unsubstituted BP in MeOH (2.275 µg/mL) was used as an external standard.

HPLC analysis was performed on an Agilent 1200 with a diode array detector using a Kinetix EVO C18 100 A column (250 x 4.6 mm, 5 µm); column temperature: 22 °C; detector: 250.4 nm; flow rate: 1 mL/min; solvent A: 1% MeOH + 0.1% H₃PO₄ + MilliQ water; solvent B: 1% MeOH + 0.1% H₃PO₄ + ACN for UV for HPLC; gradient: 10 min 25% B – from 25 to 51% B in 20 min – from 51 to 90% B in 1 min – 9 min at 90% B – from 90 to 25% B in 3 min – 5 min 25% B.

2.3. Liquid Chromatography – Mass Spectrometry (LC-UV-MS) analysis

Confirmation of the actual presence of BP in OCT raw material, as well as in skincare product no. 5, was performed on an ACQUITY LC system (Waters, Milford, MA, US) equipped with an Acquity UPLC BEH Shield C₁₈ column (2.1 × 100 mm; 1.7 µm, Waters, Milford, MA, US). For the mass spectrometric analysis of OCT about 0.12 g was subjected to the sample preparation method and subsequently diluted (1000 x), whereas of sample nr. 5 a 100-fold dilution was made before injection. An unsubstituted BP solution was used as reference standard. Elution was conducted with a mobile phase consisting of H₂O + 0.1% FA (A) and ACN + 0.1% FA (B), which were pumped at a rate of 0.4 mL/min. The gradient program was set as follows: 5% B initial, 100 % B at 24 min, 100% B (24-26 min), 100 to 5% B (26-27 min), 5% B (27-30 min). The column oven was set at 40 °C and the injection volume was 6 µL. UV detection was performed at 250 nm. UPLC-High Resolution [HR]-MS/MS analyses were achieved by coupling the LC system ESI Xevo G2-XS QT of spectrometer equipped with MassLynx version 4.1 software.

Full-scan data were recorded in ESI+ ionization mode from *m/z* 50 to 1500 and the analyser was set in sensitivity mode (approximate resolution: 22,000 FWHM). The spray voltage was set at +1.0 kV and cone voltage at 40 V; cone gas flow and desolvation gas flow at 50 L/h and 1000 L/h, respectively; source temperature and desolvation temperature were set at 120 °C and 550 °C, respectively. Leucine-Enkephalin was used as lock mass.

2.4. Quantification of benzophenone (BP) in OCT raw material, sunscreens and cosmetics.

Thirty-nine skincare products, that is, 29 sunscreen products (of which 21 for adults, 7 for children, and 1 for use by both) and 10 day creams (of which 6 anti-aging) were purchased at different Belgian retail stores and pharmacies (**Table 1**). Products for which such information was available had very divergent production (2014-2017) and expiration (2017-2021) dates, various SPF's (from 0 to 100+) and galenic forms (cream-gels, creams, milks, lotions, fluids, and sprays). All products contained various UV-filters, and 28 products contained OCT according to their (obligatory) labelling. OCT as raw material, as well as all 39 samples were qualitatively and quantitatively analyzed at room temperature for their presence of unsubstituted BP. All cosmetics were analyzed before their expiration date, or within 30 months shelf life, except for products no. 7, 24 and 28. One OCT-containing product (no. 22, new batch from Oct. 2018) was deliberately stored in a glass recipient instead of its plastic packaging, at room temperature

(control), 40°C and 80 °C, respectively, and re-analyzed at baseline, 1, 2, and 3 weeks. Also OCT raw material, in a headspace glass vial, was subjected to these conditions and re-analyzed. Of note, in an early onset experiment control samples (raw material of OCT, cosmetics and sunscreens) had been stored in glass containers and subjected to a day/night light cycle. No statistically significant differences of the BP content within these samples, at different time points, were observed, hence excluding photo-degradation of OCT into BP (data on file). This is in line with the literature stating that OCT is a highly photostable UV filter⁶.

3. Results

3.1. Method validation

The results of the method validation (calibration model, precision, accuracy, limits of detection and quantification) demonstrate the suitability and reliability of the developed method (**Online Supplemental file**). The limit of detection (LOD) and limit of quantification (LOQ) were determined at 0.00038% (3.8 ppm) and 0.0013% (13 ppm), respectively.

3.2. Liquid Chromatography – Mass Spectrometry (LC-UV-MS)

Mass-spectrometric (MS) analysis of both the OCT raw material and the sunscreen product no. 5 clearly confirmed the presence of a pseudo-molecular ion m/z 183.081 $[M+H]^+$ at Rt 10.66 min, which, based on the standard, could be identified as unsubstituted BP (**Figures S2-S3**).

3.3. Quantitative results

Twenty-five out of 28 OCT-containing products (89%) contained unsubstituted BP, i.e. 21 products (75%) with quantifiable amounts of BP ($> LOD$ and $> LOQ$), in contrast to 4 products (no. 9, 12, 21, and 29) in which only traces of BP ($> LOD$, but $< LOQ$) were detected. Interestingly, all 21 products with quantifiable BP amounts contained this impurity at levels above 10 ppm (0.001%) with a median and mean level of 30 ppm (0.0030%) and 106 ppm (0.0106%), respectively (range: 13-1194 ppm). Four of these (no. 11, 24, 27 and 28) had BP concentrations above 100 ppm (0.01%), while the BP content of one of these (no. 27, a day cream) even exceeded 1000 ppm (0.1%). Three OCT-labeled products (no. 2, 14 and 15) were free from BP ($< LOD$) at the moment of analysis (**Table 1**), however, verification of the

chromatograms of these 3 products showed that they contained OCT, thus excluding mislabeling. Single re-analysis of these 3 products, at a later time, beyond their shelf life, did reveal the presence of (unquantifiable) trace amounts of BP.

BP was absent in 8 out of 11 (73%) OCT-free products, however, present in 3 of them: in product no. 35 unquantifiable traces of BP ($> \text{LOD}$, but $< \text{LOQ}$) were present, and in products no. 18 and 20 the presence of BP could be demonstrated at $0,00200 (\pm 0,00008)\%$ (20 ppm) and at $0.0786 (\pm 0.0007)\%$ (786 ppm), respectively. Verification of the chromatograms of these 3 products showed that they did not contain OCT, again excluding mislabeling, and indicating that the BP content stems from an origin other than OCT.

Overall, the results suggest that the combined presence of OCT and BP within one and the same skincare product is not coincidental ($p < 0.00001$) (**Table S4**).

Exposure of product no. 22 in a glass recipient to higher temperatures ($40\text{ }^{\circ}\text{C}$ and $80\text{ }^{\circ}\text{C}$) revealed statistically significant increases (e.g. $p \leq 0.001$ after 7, 14, and 21 days at 80°C) of BP, i.e. an additional *de novo* formation of BP, particularly with a major impact of the temperature applied (**Figure 4**). A less pronounced, yet again statistically significant, increase in BP formation was also observed when the OCT raw material was subjected to $80\text{ }^{\circ}\text{C}$ ($p \leq 0.001$ after 21 days at 80°C) (**Figure S5**). The initial concentration of BP measured in the OCT raw material was $0.0209\% \pm 0.0003\%$, which increased to $0.0257\% \pm 0.0001\%$ after 21 days at $80\text{ }^{\circ}\text{C}$.

4. Discussion

In this study we have shown that OCT-containing sunscreens and cosmetics always contain unsubstituted BP residues in concentrations mostly above 10 ppm. Moreover, these concentrations further increase in time, and even more so when the products are exposed to high temperatures, likely as a result of the degradation of OCT, and apparently independent from their plastic packagings.¹⁴ The chosen temperature conditions are relevant as exposure to 40°C and 80°C may clinically translate in the use of sunscreens at the beach, or when storing products in a heated car. These results thus suggest that OCT-containing products may need to carry a warning sign (e.g. ‘protect from excessive heat’), and that they should only be used for a limited amount of time starting from the production date. Moreover, these findings may also have consequences for the manufacture, storage, distribution and transport of OCT-containing products.

Although a large majority of OCT-free products did not contain BP, it could still be detected in 3 products. Its origin might occasionally still relate to some plastic packagings, or to other ingredients.¹⁴ For example, there is an increasing trend to use plant-derived substances (extracts) in cosmetics as an alternative for synthetic agents in order to provide protection against UV radiation.¹⁵ BP may be present in plants due to environmental contamination with OCT and benzophenone derivatives; benzophenones might also have been added to plant materials.^{16,17}

Notwithstanding that previous studies have suggested that KP and OCT might give rise to very similar photo-allergenic BP-type chemicals⁶, also the demonstration of unsubstituted BP in OCT-containing products can explain why subjects photo-sensitized to KP develop (severe) photo-contact allergy to such products.^{6, 18-20} Indeed, as KP contains a benzophenone moiety in its chemical structure (**Figure 1B**), it can be regarded as a “substituted” benzophenone; upon irradiation with UV, 3-ethyl-benzophenone is also formed, explaining its potential cross-reactivity with benzophenones in general²¹. Photo cross-reactivity between KP and other substituted benzophenones, mainly BP-3 and BP-10, has already been well-documented^{21,22}. Moreover, Infante Hernando L et al. detailed a patient photosensitized to KP who developed photo-allergic skin reactions to BP-containing magazine inks (type unspecified, yet the patient was shown to be photo-allergic to BP-3). Interestingly, the authors of this particular paper also photo-patch tested OCT, which, just like KP, resulted in extreme positive (++++) reactions;

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unsubstituted BP, which might have explained the latter reaction, was, however, not tested²³. In the same line, Melé-Ninot G et al. described a patient with photo-allergic skin reactions from swimming goggles containing unsubstituted BP (as shown by chemical analyses), and who also showed a positive photo-patch test to BP-10²⁴. This lead these authors to suggest that cross-reactivity had occurred between BP-10 and unsubstituted BP; unfortunately, in this paper, unsubstituted BP nor KP were tested, and OCT remained entirely negative. In view of the literature^{18-19,25}, and the results of the current laboratory research, that particular OCT patch test preparation might have resulted in a false-negative reaction. Indeed, with regard to OCT-containing patch test materials our data might offer an explanation for the recently observed decrease in positive photo-patch test reactions to commercialized patch test preparations of OCT in patients photo-sensitized to KP^{6,18-19,25}. Although different batches of OCT-containing patch test materials were not analyzed within the frame of the current study, it has been suggested that overly pure patch test preparations of OCT, containing little to no BP, might be in use^{18-19,25}. It might therefore be interesting to photo-patch test patients, not only to BP (e.g. 1% pet.), but also to OCT-containing patch test preparations of different origin, as we have previously done¹⁹.

To date only very few studies have provided actual evidence that patients photo-sensitized to KP indeed show positive photo-patch test reactions to unsubstituted BP. Le Coz et al. photo-patch tested 12 patients (strongly or severely) photo-sensitized to KP to BP 1% pet. and found that a large majority of them (11 of 12 patients) were equally strongly photo-sensitized to BP, illustrating cross-reactivity. These authors added that, in individual cases, perhaps even higher test concentrations of unsubstituted BP might be required²⁰. Tanahashi T et al. reported 3 patients with previous photosensitization to KP who developed photo-allergic skin reactions from unsubstituted BP in wristbands²⁶. Both papers, however, did not photo-patch test OCT in their patients^{20,26}.

We are not aware of any published reports where photo-patch testing has been performed with lower test concentrations of BP, i.e. with those found in the current study (i.e. approx. 10 – 1000 ppm, or 0.001% – 0.1%). However, for a potentially strong photo-contact allergen such as BP, even relatively low amounts such as 10 ppm might already suffice to elicit clinically relevant skin photo-allergic reactions. Although this would have to be formally demonstrated in a clinical study, data from the abovementioned publications indirectly support this^{20,26}: patients photo-

sensitized to KP have usually shown extreme (i.e. +++/bullous) photo-patch test reactions to BP 1% pet., which, in fact, indicates that they will probably not tolerate the low amounts of BP found in OCT-containing products. Given the time- and temperature dependent increase of unsubstituted BP in OCT-containing products, patients may be even more at risk when using older (“aged”) cosmetics, or when applying products that have been stored at (too) high temperatures. Although not the objective of the current study, we have already photo-patch tested patients photosensitized to KP to BP 1% pet. (obtained from Chemotechnique Diagnostics as a “delivery on request [DOR]”) in our patch test clinic, and these patients have often shown strong (++) or severe (+++; bullous) photo-patch test reactions to it (data on file). In this regard, we would like to draw attention to the fact that also for (the chemically very similar) KP the (photo) patch test concentration of (initially) 5% pet. had to be lowered to 2%, and eventually even to 1%, as extreme (+++) photo-patch test reactions often occurred to it²¹. Whether also patients not photo-sensitized to KP, but who do develop photo-allergic contact dermatitis from OCT, are also photo-reactive to residual unsubstituted BP impurities, remains to be demonstrated. In our patch test clinic no such data are available at this moment; this might be a future focus of interest for (photo) patch testers. Moreover, it also remains to be demonstrated whether the low BP levels found might actively sensitize patients. We feel this can probably not be entirely excluded, especially considering that OCT-(BP)-containing products are often repeatedly applied to damaged (sunburned) skin, and that BP is likely, similar to KP, a strong photo-contact allergen.

Additionally, OCT has also been reported as a cause of (delayed) contact urticaria, and it is tempting to speculate that this might also have been due to unsubstituted BP. Substituted benzophenones, mainly BP-3, but also BP-8 and BP-10, have previously been held accountable for (photo-induced) contact urticaria, and even anaphylaxis/anaphylactoid reactions²⁷⁻²⁹.

Human systemic absorption studies recently also demonstrated that OCT is readily absorbed through the skin, and reaches significant plasma concentrations in levels above the 0.5 ng/mL threshold established by the FDA.^{2,3,30} Additionally, the metabolic fate of OCT itself inside the human body has also been studied³¹. However, the concomitant presence of BP in OCT-containing products has not yet been considered in this regard, and might equally be of interest to researchers who wish to explore any potential toxicological side-effects (e.g. endocrine

disrupting, carcinogenic, reproductive and developmental risks) associated with products containing this UV-filter.

Similarly, environmental studies dealing with OCT have also found that this UV filter can be detected in various species of fish, soils and surface waters, from which it cannot be easily removed, and OCT may potentially also contribute to coral reef decline (“bleaching”)³². Again, also ecological studies might need to consider the concomitant presence of BP.

To conclude, this study showed that residues of the potentially strong photosensitizer BP are present in non-negligible concentrations in sunscreens and cosmetics containing the organic UV filter OCT. These findings might explain why patients photo-sensitized to KP may develop (severe) photo-contact allergy from OCT-containing consumer products, and this risk might even be higher when older (“aged”) products and/or products exposed to higher temperatures are involved. Future clinical studies are warranted in this regard, for example by including BP 1% (and/or 5% pet.) in a photo-patch test series. Toxicological and ecological studies that evaluate the safety of OCT might also need to consider the concomitant presence of BP.

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Table 1. Sunscreen products and cosmetics, with (blue) or without (green) octocrylene (OCT), and their corresponding unsubstituted benzophenone (BP) content.

Number of the product	Production date	Octocrylene (OCT) ranking*	Sun protection factor (SPF)	UV filter (**)	Galenic form	Product's intended use	Benzophenone (BP) concentration (in %)	Benzophenone (BP) concentration (in ppm)	Expiration date
1	Dec 2016	2	50	1a, 2a, 2b, 2e, 2i, 2m	Fluid	Sunscreen (adults)	0.0033 ± 0.0001	± 33	May 2019
2	Jun 2017 (batch n°)	40	30	1a, 2a, 2b, 2f, 2i, 2j, 2k, 2m, 2p	Cream	Sunscreen (adults)	Not detected (<LOD)	0 (→ traces)***	Not stated
3	Jun 2017 (batch n°)	10	50+	1a, 2a, 2b, 2i, 2j, 2m, 2p	Cream	Sunscreen (adults and children)	0.0035 ± 0.0001	± 35	Not stated
4	Not clear based on batch n°	2	50	1a, 2b, 2d, 2i, 2m, 2n	Cream	Sunscreen (children)	0.00303 ± 0.00007	± 30	Aug 2019
5	Not clear based on batch n°	2	50+	1a, 2a, 2b, 2i, 2k, 2m, 2n	Milk	Sunscreen (children)	0.00244 ± 0.00009	± 24	Jul 2019
6	May 2017 (batch n°)	6	20	1a, 2b, 2i, 2m, 2p	Milk	Sunscreen (adults)	0.00142 ± 0.00004	± 14	Not stated
7	Nov 2014 (batch n°)	8	50+	2a, 2b, 2f, 2i, 2j, 2m, 2p	Milk	Sunscreen (adults)	0.00441 ± 0.00002	± 44	Not stated
8	Not clear based on batch n°	2	30	2b, 2i, 2m, 2n	Spray	Sunscreen (adults)	0.00190 ± 0.00007	± 19	Feb 2020
9	Jun 2017 (batch n°)	5	20	2b, 2i, 2k, 2m, 2o	Spray	Sunscreen (adults)	>LOD; <LOQ	Traces	Not stated
10	Nov 2017 (batch n°)	10	15	2b, 2i, 2m, 2o	Cream	Day cream (anti-age)	0.0037 ± 0.0001	± 37	Not stated
11	Mar 2017 (batch n°)	6	30	2b, 2i, 2k, 2m, 2n	Cream	Day cream (anti-age)	0.01227 ± 0.00008	± 123	Not stated
12	Nov 2017 (batch n°)	5	30	1a, 2b, 2i, 2m, 2n, 3a	Cream	Day cream (anti-age)	>LOD; <LOQ	Traces	Not stated
13	May 2016 (batch n°)	10	50+	2b, 2f, 2i, 2j, 2k, 2m	Spray	Sunscreen (children)	0.00199 ± 0.00005	± 20	Not stated
14	Nov 2017 (batch n°)	10	15	2b, 2i, 2m, 2n, 3a	Cream	Day cream	Not detected (<LOD)	0 (→ traces)***	Not stated
15	Oct 2017 (batch n°)	10	15	1a, 1b, 2b, 2i, 2m, 2n	Cream	Day cream (anti-age)	Not detected (<LOD)	0 (→ traces)***	Not stated
16	Feb 2017 (batch n°)	3	50	2a, 2b, 2i, 2k, 2m	Cream-gel	Sunscreen (adults)	0.00189 ± 0.00005	± 19	Not stated
17	Sep 2016 (batch n°)	No OCT	50+	2a, 2d, 2h, 2i, 2j, 2k	Cream	Sunscreen (adults)	Not detected (<LOD)	0	Sep 2019

18	Mar 2016 (batch n°)	No OCT	50+	2a, 2d, 2h, 2i, 2j	Lotion	Sunscreen (children)	0.00200 ± 0.00008	± 20	not stated
19	Mar 2018 (batch n°)	No OCT	50+	1a, 2a, 2b, 2e, 2f, 2i, 2p	Lotion	Sunscreen (children)	Not detected (<LOD)	0	Feb 2021
20	Not clear based on batch n°	No OCT	50+	1a, 1b, 2c, 2g	Fluid	Sunscreen (adults)	0.0786 ± 0.0007	± 786	Mar 2020
21	Nov 2017 (batch n°)	7	50+	2b, 2i, 2k, 2m, 2n	cream-gel	Sunscreen (adults)	>LOD; <LOQ	Traces	Not stated
22	Dec 2016 (batch n°)	3	50+	1a, 2a, 2b, 2m	Lotion	Sunscreen (children)	0.00211 ± 0.00004	± 21	Nov 2018
23	Sep 2016 (batch n°)	5	15	1a, 2b, 2i, 2m	Cream	Day cream	0.00142 ± 0.00004	± 14	Aug 2018
24	Apr 2015 (batch n°)	6	0	2a, 2b, 2m	Cream	Day cream (anti-age)	0.0327 ± 0.0012	± 327	Mar 2017
25	Feb 2017 (batch n°)	4	50+	1a, 2a, 2b, 2f, 2i, 2j, 2k, 2m, 2p, 3a	Cream-gel	Sunscreen (adults)	0.00132 ± 0.00002	± 13	Jan 2020
26	Feb 2017 (batch n°)	8	50+	2a, 2b, 2f, 2j, 2m, 2p	Fluid	Sunscreen (adults)	0.00185 ± 0.00006	± 19	Jan 2020
27	July 2016 (batch n°)	11	50+	1a, 2a, 2b, 2f, 2i, 2j, 2m, 2p	Cream	Day cream	0.1194 ± 0.0009	± 1194	Jul 2019
28	July 2014 (batch n°)	5	30	1a, 2h, 2i, 2m	Cream	Day cream	0.0128 ± 0.0005	± 128	Jul 2017
29	Sept 2017 (batch n°)	11	50+	1a, 2a, 2b, 2f, 2i, 2j, 2k, 2m, 2p, 3a	Emulsion	Sunscreen (adults)	>LOD (but < LOQ)	Traces	Not stated
30	Mar 2017 (batch n°)	2	30	1a, 2b, 2i, 2k, 2m	Cream	Day cream (anti-age)	0.00250 ± 0.00004	± 25	Not stated
31	Feb 2016 (batch n°)	3	50+	2a, 2b, 2l, 2m	Fluid	Sunscreen (adults)	0.0031 ± 0.0004	± 31	Feb 19
32	Not clear based on batch n°	3	100+	1a, 2a, 2b, 2m	Fluid	Sunscreen (adults)	0.0049 ± 0.0004	± 49	Mar 2018
33	Not clear based on batch n°	No OCT	50+	1a, 2a, 2d, 2j, 2n	Milk	Sunscreen (children)	Not detected (<LOD)	0	Not stated
34	Not clear based on batch n°	No OCT	50+	2a, 2b, 2e, 2l, 3a	Fluid	Sunscreen (adult)	Not detected (<LOD)	0	Mar 2020
35	Not clear based on batch n°	No OCT	50+	1a	Cream	Sunscreen (adult)	>LOD; <LOQ	Traces	Nov 2018
36	Not clear based on batch n°	No OCT	50+	2a, 2b, 2e, 2l, 3a	Cream	Sunscreen (adult)	Not detected (<LOD)	0	Oct 2020
37	Not clear based on batch n°	No OCT	50+	2a, 2b, 2e, 2l, 3a	Cream	Sunscreen (adults)	Not detected (<LOD)	0	Feb 2020
38	Not clear based on batch n°	No OCT	50+	2a, 2b, 2e, 2l, 3a	Cream	Sunscreen (adults)	Not detected (<LOD)	0	Dec 2020
39	Mar 2018	No OCT	50+	1a, 2a, 2b, 2f, 2j, 2p	Cream	Sunscreen (adults)	Not detected (<LOD)	0	Mar 2021

Date (batch no.): the production date as retrieved from the manufacturer's batch number

OCT: octocrylene

BP: unsubstituted benzophenone

SPF: sun protection factor

LOD: limit of detection

LOQ: limit of quantification

*The numerical ranking of OCT in the ingredient list of the product.

****Type of UV filter(s) in the product: 1: Physical (inorganic) filters** with 1a: Titanium dioxide, 1b: Zinc oxide; **2: Chemical (organic) filters** with 2a: Bis-ethyl-hexyloxyphenol methoxyphenyl triazine, 2b: Butyl methoxy-dibenzoyl-methane, 2c: Butyloctyl salicylate, 2d: Diethylamino hydroxybenzoyl hexyl benzoate, 2e: Diethylhexyl butamido triazone, 2f: Drometrizole trisiloxane, 2g: Ethylhexyl ferulate, 2h: Ethylhexyl methoxycinnamate, 2i: Ethylhexyl salicylate, 2j: Ethylhexyl triazone, 2k: Homosalate, 2l: Methylene bis-benzotriazolyl tetramethylbutyl-phenol, 2m: Octocrylene, 2n: Phenylbenzimidazole sulfonic acid, 2o: Sodium phenylbenzimidazole sulfonate, 2p: Terephthalylidene dicamphor sulfonic acid; **3: Sun Protection Factor (SPF) factor enhancer** with 3a: Aluminum starch octenylsuccinate

***Traces of BP were found in these 3 products upon re-analysis.

Figure legends

Figure 1. Chemical structures of (A) octocrylene (OCT), (B) ketoprofen (KP), and (C) unsubstituted benzophenone (BP). Note the strong chemical similarity between KP and BP.

Figure S2. Extracted ion chromatogram (m/z 183.081 $[M+H]^+$)(top) and UV chromatogram (250 nm, zoomed x6)(bottom) of the octocrylene (OCT) raw material sample. The LC-UV chromatogram displays all (chemically different) compounds, including OCT at 17.19 min. The extracted ion chromatogram, on the other hand, only displays the compound with the selected mass of 183.081 $[M+H]^+$, being the mass of BP. This confirms that BP is undeniably present in the OCT raw material.

Figure S3. Extracted ion chromatogram (m/z 183.081 $[M+H]^+$) and UV chromatogram (250 nm, zoomed x6) of sunscreen product no. 5. The LC-UV chromatogram displays all (chemically different) compounds, including OCT at 17.19 min. The extracted ion chromatogram, on the other hand, only displays the compound with the selected mass of 183.081 $[M+H]^+$, being the mass of BP. This confirms that BP is undeniably present in the OCT-containing sunscreen product no. 5.

Figure 4. Influence of time and temperature on the amount of unsubstituted benzophenone (BP) measured in sunscreen product no. 22 contained in a glass vial, at room temperature (control, ▲), at 40°C (■) and at 80°C (●) (; (X-axis: time (in days), Y-axis: concentration of BP found (in %)). Statistically significant increases of the BP content in product no. 22 can be observed at 7, 14 and 21 days, especially when the product is exposed to 80°C, and to a lesser extent when it is exposed to 40°C. As the analyses were done with the product in a glass vial, this BP formation occurs within the product, i.e. most likely stems from the degradation of OCT, and in any case occurs independently from any plastic packaging.

Figure S5. Influence of time and temperature on the amount of unsubstituted benzophenone (BP) measured in octocrylene (OCT) raw material contained in a glass vial, at room temperature (control, ●) and at 80°C (■). (X-axis: time (in days), Y-axis: concentration of BP found (in %)).

A statistically significant increase of the BP content in the OCT raw material can be observed when it is exposed to 80°C, after 7 days, and even more so after 21 days. This confirms that OCT can indeed degrade into BP, in a time-and especially temperature-dependent manner, and this in turn may explain why (increasing) BP concentrations can be found in OCT-containing consumer products exposed to high temperatures.

A