HBM4EU science and policy for a healthy future

HORIZON2020 Programme
Contract No. 733032 HBM4EU

SCOPING DOCUMENT

(2nd round of prioritization)

Prioritized substance group:
UV filters - Benzophenones

Chemical Group Leader: Tamar Berman

Date: 11/03/2019 **Document version: 1.0**

Table of Contents

1. Introduction

Human Biomonitoring for Europe (HBM4EU) has established a strategy for deriving prioritized substance groups that HBM4EU will work on in 2019 and 2020. This stepwise strategy included input from national and EU policy makers and from stakeholders. The substances were nominated and prioritised according to a transparent procedure that is described in Deliverable 4.3 on the Prioritisation strategy and criteria, produced by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). The detailed description of how this prioritisation strategy was implemented in practice, the inputs received and the methodology applied for selecting substances to include in the second list of prioritised substances is the subject of the Deliverable D4.4 (lead European Environment Agency, EEA).

First, a survey was launched to understand the demands of the National Hubs, EU policy makers and members of the HBM4EU Stakeholder Forum. Subsequently an online survey requested the nomination of substances for research under HBM4EU. A long list of new nominated single substances and substance groups was produced. Substances on the long list were ranked according to the number of nominations received, enabling to reduce the list down to a short list of approximately 25 substances Background documents on the substances on the short list were produced. An expert group of HBM4EU scientists scored and ranked the substances according to their hazardous properties, exposure characteristics; and public concern. The ranked list was discussed at a joint meeting of the HBM4EU Management Board and the EU Policy Board in March 2018, where agreement was reached on the draft 2nd list of HBM4EU priority substances. The Governing Board approved the final list. The Governing Board members were asked to identify a list of candidate institutions and experts for the positions of Chemical Substance Group Leaders for the new substances/groups of substances. The substance group leaders were approved and were asked to produce the scoping documents for the new list of prioritised substances. The process is documented in D4.5 Second list of HBM4EU priority substances and Chemical Substance Group Leaders for 2019-2021.

2. Background information

2.1 Hazardous properties

- **Benzophenone 3 (BP-3)** displays a low acute toxicity profile. It is not considered as being irritating to the skin and the eyes[1]. Results from animal studies—primarily dietary studies that affected body weight gain—showed alterations in liver, kidney, and reproductive organs in rats and mice with BP-3 administered dermally and orally[2]. BP-3 is on the Community Rolling Action Plan (CoRAP) list because of potential endocrine disruption[3]. BP-3 elicited anti-androgenic activity in a human breast carcinoma cell line[4] and interferes with functions of human sperm cells in vitro[5]. Critical effects are maternal and developmental toxicity[6]. In female mice, low dose exposure causes long-lasting alterations to mammary gland morphology and function[7]. Studies in rat primary cortical neuronal cultures and neuroblastoma cell lines showed decreased cell viability after BP-3 treatment at moderate concentrations[8].
  In a study on young men from Spain, there was a significant positive association between urinary BP-3 concentrations and serum FSH levels[9]. In male adolescents in the US, urinary BP-3 was associated with lower total testosterone[10]. In a study of young Danish men, associations between male reproductive health parameters and urinary levels of benzophenones such as BP-3, BP-1 and 4-HBP were observed in filaggrin gene mutation carriers but not in controls[11]. In a study in healthy, premenopausal women, UV filter factors (BP-1, BP-3) were associated with decreased estradiol, FSH, and LH[12].

- **Benzophenone** is possibly carcinogenic to humans (Group 2B, IARC classification, based on sufficient evidence in experimental animals).[4] Benzophenone exerts tumourigenic effects in rats and mice in the liver, the kidney and in the haematopoetic system, including rare histiocytic sarcomas. Available evidence supports that benzophenone is not genotoxic. Benzophenone meets the criteria for classification as carcinogenic in category 2[13]. Benzophenone may alter endocrine signalling through multiple effects on receptors.[4] Critical effects are liver and kidney effects.[6]

- **Benzophenone-1** (BP-1) is used as a UV filter, but is also the major metabolite of BP-3. BP-1 is not irritating nor sensitizing at concentrations that may be found in cosmetic products. The toxicity studies available indicate low acute and subchronic toxicity of BP-1. BP-1 is not mutagenic. The lowest effect levels were determined for reproductive toxicity with lowest observable adverse effect levels (LOAELs) between 100-625 mg/kg and NOAELs between 100-250 mg/kg. BP-1 is on the European Commission priority list of potential endocrine disruptors.[6]
  In a study of young Danish men, associations between male reproductive health parameters and urinary levels of benzophenones such as BP-3, BP-1 and 4-HBP were observed in filaggrin gene mutation carriers but not in controls.[11] In a study in healthy, premenopausal women, UV filter factors (BP-1, BP-3) were associated with decreased estradiol, FSH, and LH.[12]

- **Benzophenone-2** (BP-2) is a UV filter used in personal care products. BP-2 may disturb thyroid hormone homeostasis by inhibiting or inactivating thyroid peroxidase, effects that are even more pronounced in the absence of iodide[14]. Both BP-2 and BP-3 were shown to exert uterotrophic effects and BP2 was shown to bind to estrogen receptors[15]. In fish and mammals, BP-2 induces a variety of reproductive disorders, including feminization of male fish, inhibition of gamete development in fish, reduction of testosterone secretions from testicular tissue, induction of uterotrophic effects in rats, changes in bone density and osteo-regulation, changes in LH, cholesterol levels, fat deposition, and an increased risk of endometriosis[16].
  In a study on exposure to UV filters and fertility, male partners' concentrations BP-2 was associated with reduced fecundity[17].

- **4-Methylbenzylidene camphor** (4-MBC) is found in cosmetics and in drinking water.[6]
  The available data suggest no genotoxicity, mutagenic potential or phototoxicity of 4-MBC. However, this chemical is suspected to have a mild endocrine disrupting effect on the thyroid gland. Experiments on rats found 4-MBC to have development toxicity.[6,18]

- **3-benzylidene camphor** (3-BC) - 3-BC is a potential endocrine disrupter. Experiments in vivo and in vitro revealed oestrogenic activity. In addition, 3-BC was found to interrupt sexual development and maturation in animal models.[14] According to the Scientific Committee on Consumer Safety, hormonal activities of 3-BC have been reported in vitro: estrogenic and anti-estrogenic effects as well anti- androgenic activities. In vivo, the expression of target genes (ERα, ERβ, SRC-1 and PR (progesterone receptor)) has been shown to be altered in both males and females rats.[15]

- **4-hydroxy benzophenone** (4-HBP) is used as an industrial UV-filter. 4-HBP has potential to disrupt endocrine activity, and fetal growth. 4-HBP exposure in women carrying a male fetus was associated with increased maternal thyroid hormone concentrations, in addition to decreased birth outcomes (lower weight and shorter head and abdominal circumferences at birth compared to the low exposure group)[19].

- **4-methylbenzophenone** (4-MBP) is used in paints and varnishes, in food packaging but not in cosmetics.[5] According to an assessment by EFSA, the currently available data on 4-methylbenzophenone are insufficient to enable the assessment of this substance with respect to its human toxicological effects. 4-MBP is expected to be a non-genotoxic carcinogen[20].

Hazardous Properties of Benzophenones

	Critical effect	Potential Endocrine Disruption	Other
BP-3	Maternal and reproductive toxicity	Suspected	Developmental neurotoxicity
BP	Liver and kidney	Suspected	Possible carcinogenic in human (IARC)
BP-1		Suspected	
BP-2		Suspected	
4-MBC	Repeated dose: thyroid effects	Suspected	
3-BC		Suspected	
4-HBP		Suspected	
4-MBP			Expected carcinogen (EFSA)

2.2 Exposure characteristics

- Benzophenone is manufactured and/or imported in the European Economic Area in 1000-10000 tonnes per year; it is used by consumers, by professional workers (widespread uses), in formulations or re-packaging and at industrial sites.
- Benzophenones are used in cosmetics and in personal care products, food contact materials, coating products, fillers, modelling clay and finger paints. UV-absorbers and UV filters including benzophenone-1 and benzophenone-3 are added to food packaging to protect the packaging itself and the contained food from harmful UV light.[6]
- Release to the environment is likely to occur from: industrial use, indoor use (e.g. machine wash detergents, personal care products, paints and coating, fragrances and air fresheners).
- Biological half-life (in serum) of 19 hours [4].
- Human biomonitoring (HBM) data: pregnant women in US (California)[21], France[22], China[23], Israel[24], general public in Belgium[25], Denmark[26], and the US[27]. Data on exposure in children in available for the US[28], Denmark[29,30,31,32], China[33], Australia[34], Taiwan[35] and Germany[36] (GerES V, publication in preparation, for HBM4EU available data on 3 to 14 year old children and adolescents; young adults: 20-29 years, Environmental Specimen Bank).
- Several biomonitoring studies (including NHANES) have focused on BP-3.[27] BP-3 has been widely detected in several biomonitoring studies with urinary levels correlated with the use of personal care products. Higher BP3 exposure has been observed in the female population, possible due to its presence in personal care products[27].

2.3 Policy relevance

- Since September 2017 the use of BP-3 in the EU is restricted to 6% in cosmetic sunscreen products and up to 0.5 % in other cosmetic products[37]. According to the Cosmetics Regulation (EU Regulation 1223/2009). BP-4 and BP-5 are permitted as UV filters in cosmetic products. 4-MBC is allowed as a UV filter in cosmetic products with a maximum concentration of 4% in ready-for-use preparations[38].
- According to the Scientific Committee on Consumer Safety, the use of 3-BC as a UV-filter in cosmetic products in a concentration up 2.0% is not safe[39].
- Benzophenone is approved as an additive in plastic food contact materials, with a specific migration limit of 0.6 mg/kg[40].
- Inks are not covered by a specific European legislation on food contact materials. The use of printing inks has to comply with the general rules of Regulation (EC) No 1935/2004 and with good manufacturing practice as laid down in Commission Regulation (EC) No 2023/2006.

2.4 Technical aspects

- BP-3 can be directly measured and quantified in urine in HBM studies. Benzophenones including BP-1 and BP-3 can be measured using an on-line LC/LC-MS/MS method for the simultaneous determination of nine parabens and seven environmental phenols in urine[41]. In addition, three oxidative metabolites (2,4-dihydroxylbenzophenone, 2,2′-dihydroxy-4-

methoxybenzophenone, and 2,3,4-trihydroxybenzophenone) can also be measured in HBM studies using quantitative analytical methods[42].

- 4 – MBC urinary metabolites (3- (4-carboxybenzylidene) camphor and 3-(4-carboxybenzylidene)-6-hydroxycamphor) can be measured using gas chromatography high resolution mass spectrometry (GC-HRMS)[43].
- LC-MS/MS based methods have been developed in Germany[36] for simultaneous biomonitoring of nine parabens and seven environmental phenols including BP-3 and BP-1 and in Denmark[32] for simultaneous biomonitoring of nine UV filters in urine (BP, BP-1, BP-2, BP-3, 3-BC, 4-MBC, 4-HBP, 4-HBP, and 5-chloro-2- hydroxybenzophenone). However, urine might not be the preferred matrix for measurements of the most lipophilic UV filters such as 3-BC and 4-MBC.

2.5 Societal concern

UV filters, including benzophenones, are widely used in cosmetics, personal care products, food contact materials, inks, textiles and other consumer products. Therefore, there is a high potential for the general public (including vulnerable populations) to be exposed to benzophenones.

While UV filters in sunscreens and cosmetics have been effective in protecting against a variety of UV-related pathologies, such as sunburns and melanomas, growing popularity of sunscreens and increasing potential exposure has led to increased societal concern about their potential impact on the environment and human health.

There are several EU regulations regarding benzophenones, such as the restriction of BP-3 to 6% in cosmetic sunscreen products and to 0.5% in other cosmetic products. However, there are regulatory gaps regarding benzophenones. There are also knowledge gaps regarding the exposure pathways kinitics, metabolism, and health effects in humans of many of the benzophenones. BP-3 was included in the Community Rolling Action Plan list because of potential endocrine disruption and fulfilling exposure criteria[44].

BP, BP-2 and BP-3 are on the SIN (“Substitute It Now”) list.

In addition, CHEMTrust nominated the group of benzophenones as a priority substance for HBM4EU. In 2018, the Environment Working Group (EWG) reviewed studies and documents regarding UV filters and recommended a thorough investigation of the safety of all ingredients currently in sunscreens to ensure that none of them damage skin or cause other toxic effects in consumers. Because of concerns regarding potential health effects, the EWG has recommended that consumers avoid sunscreens with oxybenzone (synonyme for BP-3). It is noteworthy that consumer avoidance of sunscreens because could increase public health risk from UV rays (sunburn and skin cancers); ***therefore risk- benefit analysis and risk communication is especially important with regards to benzophenones.***

It is also noteworthy that HBM studies showed that a majority of the populations were exposed to BP-3, and many of these studies cover year-round sample collection or winter time time sample collection.[29,32] Therefore, the major sources for BP-3 exposure might not be sunscreens.

Of note, due to reports on adverse effects of UV filters on coral reef, there is societal concern about ecological effects of suncreens.

3. Categorization of Substances

Table 3.1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, D, E substances (see general introduction)

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
B	BP-3	Benzophenone-3	131-57-7	Cosmetics 2017/238
C	BP	Benzophenone	119-61-9	Plastic materials in contact with food 2002/72
C	BP-1	Benzophenone-1	131-56–6	
C	BP-2	Benzophenone-2	131-55-5	
C	4-MBC	3-(4-methylbenzylidene)-camphor	36861-47-9	
C	3-BC	3-benzylidene camphor	15087-24-8	
C	4-HBP	4-hydroxy-benzophenone	1137-42-4	
C	4-MBP	4-methyl-benzophenone	134-84-9	

Justification of Grouping

We propose to categorize BP-3 in **Category B**, as European HBM data are available from some countries. Understanding of sources of human exposure is limited. For BP-3, there is a need for improved understanding of exposure levels and potential health impacts to inform policy makers.

For the remaining substances, we propose to categorize them as **Category C** as HBM data is scarce. While analytical methods have been developed, there is a need for validation and widespread collection of data using validated methods.

4. Policy-related questions

1. Are sensitive, reliable and cost effective methods and biomarkers available to measure UV filters?
2. What are current exposure levels to benzophenones in the EU population (cumulative exposure from different exposures sources)?
3. What are the major sources of exposure to benzophenones in the EU population and in vulnerable groups such as children and pregnant women? (Sunscreens, cosmetics and personal care products, plastic and other food contact materials, textiles, furnitures and building materials and others)
4. Do exposure levels differ significantly between different EU countries (possibly related to climate)?
5. Do exposure levels differ between different sub-groups: elderly, adults, and children? between males and females? Between adults of different age groups? Between individuals in different ethnic subgroups (perhaps due to differences in use of sunscreen products)?
6. Are current exposure levels safe in relation to the endocrine and carcinogenic properties of benzophenones? (for the general population and for vulnerable groups such as children and pregnant women)
7. Was the restriction of BP-3 in cosmetics in the EU (September 2017) effective in reducing public exposure? Did exposure to other benzophenone or other UV filter compounds increase as a result?

5. Research Activities to be undertaken

Table 5.1: Listing of research activities to be carried out to answer the policy questions

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
1. Are sensitive, reliable and cost effective methods and biomarkers available to measure UV filters?	Benzophenones	Methods have been reported for BP-3 and three oxidative metabolites (2,4-dihydroxylbenzophenone, 2,2′-dihydroxy-4-methoxybenzophenone, and 2,3,4-trihydroxybenzophenone); and simultaneous measurement of 9 UV filters in urine	**WP9** - Are HBM methods to measure BP-3 / its metabolites and other benzophenones quality assured? Are levels of detection and quantification adequate? - Is there a need to develop new analytical methods?
2. What are current level of exposure of the EU population to benzophenone UV-filters?	Benzophenones, emphasis on BP-3	Benzophenones are likely to be increasingly detected in the general population in the EU, due to their extensive use in personal care products (sunscreens), food contact materials, and other products.	**WP7 & WP8; WP16** Systematic collection of available HBM data on benzophenones; Generation of data in targeted studies and from bio-banked samples if available. **WP10** Is existing exposure data sufficient to derive valid estimates for the exposure of the EU population? What data is needed to derive reference values?
3. Do the exposure levels differ significantly between the countries?	Benzophenones, emphasis on BP-3	Human biomonitoring data is scarce (only available for some countries with different population groups measured, e.g. France, Denmark)	**WP7 & WP8; WP10; WP16** Systematic collection of available HBM data on benzophenones; Generation of data in targeted studies and from bio-banked samples if available.
4. What are the main sources of exposure to benzophenones?	Benzophenones	The main sources of exposure to benzophenones are cosmetics and personal care products; food packaging materials; and other uses in consumer products	**WP10** What are major sources of exposure to benzophenones in the general population and in sub-groups? (per single substance and substance group) **WP12** Estimation of the contribution of different routes of exposure to the total exposure.
5. Who are the highest exposed groups? Are there statistical differences in concentration between different ages? males and females? Ethnic subgroups? occupational vs. general population exposure.	Benzophenones, emphasis on BP-3	There is insufficient research to date to answer these questions; indications that exposure is higher in females due to increased use of personal care products and/ or cosmetics	**WP10** - Based on existing data, determine different exposure levels between: males/females, different age groups (depending on the data available) - In case occupational population data exists, determine different exposure levels in occupational populations in comparison with the general population **WP8** Targeted HBM studies on benzophenone exposure
6. How effective was the restriction of BP-3 in reducing exposures in the EU population?	BP-3 and other benzophenones	Since September 2017 the use of BP-3 has in EU been restricted to 6% in cosmetic sunscreen products and up to 0.5 % in other cosmetic products	**WP10** - Compare between exposure to regulated UV-filters (BP-3) and nonregulated UV-filters
7. Are potential health effects related to age and gender?	BP-3	The current research is not sufficient to answer this question	**WP10 & WP11** Epidemiological studies investigating endocrine effects **WP13** Investigate associations between exposure and health outcomes

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
8. How can cumulative risks of benzophenones and other UV filters be assessed for their health relevance? Are their additive (or other) effects relevant for regulation?	Benzophenones and other UV filters	The current research is not sufficient to answer these questions	**WP15** Cumulative risk assessment **WP5 & WP15** Assessing the feasibility of deriving an HBM health-based guidance value for combined UV-filter exposure
9. How can HBM4EU results feed into regulatory decisions and risk assessments (ECHA and EFSA)?	UV filters, specifically BP-3		**WP5** - Derivation of Health-based guidance values using HBM data for benzophenones **WP5** How can HBM data on benzophenones inform chemical risk assessment and management (exposure assessment, TDI evaluation)? What HBM data is needed to inform risk assessment and management? **WP12,13,14,15** Instruments to link health and exposure and to better estimate risks will be explored and their suitability in risk assessment and management will be evaluated (e.g. cumulative risk assessment)

Table 5.2: Summary of biomonitoring studies on UV filters

Study / Institution	Country	Year of publication	Study Population	Matrix	Analytes	Citation + link
NHANES	USA	2003-2004	General, includes children	Urine	BP-3	Calafat et al.
NHANES	USA	2003-2010 (sample collection)	General, includes children	Urine	BP-3	CDC Report
Bispebjerg Hospital	Denmark	2004	General	Urine, plasma	BP-3, 4-MBC	Janjua et al.
Princess Alexandra Hospital	Australia	2005	Human skin culture	Skin	BP-3, Octocrylene	Hayden et al.
Sahlgrenska University Hospital	Sweden	2006	General	Urine	BP-3	Gonzalez et al.
Southe Korean institutes	South Korea	2010-2011	General	Urine	BP-1, BP-2, BP-3, BP-4, BP-8	Kang et al
Maternal and Infant Environmental Exposure Project (MIEEP)	USA	2010-2011 (sample collection)	Pregnant women and infants	Urine	BP-3	Biomonitoring California
Biomonitoring Exposures Study (BEST) – Pilot Study and Expanded Study	USA	2011-2012 (sample collection)	Adults	Urine	BP-3	Biomonitoring California
State University of New York at Albany	USA	2012	Woman	Urine	BP-1, BP-3, , BP-2, BP-8	Kunisue et al
Institut Albert Bonniot	France	2012	Mothers giving birth	Urine	BP-3	Philippat et al
Nankai University	China	2013	children, adults, and pregnant women	Urine, blood	BP-1, BP-2, BP-3, BP-8, 4OH-BP	Zhang et al
Institut Albert Bonniot	France	2013	Pregnant women	Urine	BP-3	Philippat et al
University of Copenhagen	Denmark	2013	Children	Urine	BP, BP-1, BP-2, BP-3, BP-7, 4-MBP, 4-HBP, 4-MBC, 3-BC	Krause et al
Copenhagen University Hospital	Denmark	2013	Mother-child pairs	urine	BP-3	Frederiksen et al
Institute of Ruhr University Bochum	Germany	2014	Children and adults	urine	BP-1, BP-3, BP-8	Moos et al
University of Liege	Belgium	2014	Adults	Urine	BP-3	Dewalque et al.
University of Copenhagen	Denmark	2014	Children, adolescents, young men, and pregnant women (review)	Urine	BP-3	Frederiksen et al
Queensland	Australia	2015	Children and adults	Urine	BP-3	Heffernan et al.
Several universities	China	2015	Young children	Urine	BP, BP-1, BP-2, BP-3, BP-8, 4-HBP	Gao et al
Several universities	Denmark	2017	General	Urine	BP-1, BP-3	Morrison et al
I-Shou University	Taiwan	2017	Children and adolescents	Urine	BP-3	Chang et al
Copenhagen University Hospital	Denmark	2017	Children and adolescents	Urine	BP, BP-1, BP-2, BP-3, BP-7, 4-HBP, 4-MBP, 4-MBC, 3-BC	Frederiksen et al.
University of Bath	UK	2018	General (samples collected from a festival event)	Urine	BP-1, BP-2 ,BP-3, 3-BC, Homosalate, Octocrylene	Lopardo et al
Pregnant women in Israel	Israel	2018	Pregnant women	Urine	BP-3	Machtinger et al
University of Copenhagen	Denmark	2018	Mothers and fetus	Serum and urine	BP-1, BP-3, 4-MBP, 4-HBP	Krause et al

6. References

1. European Commission, Scientific Committee on Consumer Products. 2008. Opinion on Benzophenon-3. https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_159.pdf
2. National Toxicology Program. NTP Technical Report on Toxicity Studies of 2-Hydroxy-4-methoxybenzophenone (CAS Number: 131-57-7) Administered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice. Research Triangle Park, NC: National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services; 1992.
3. Substance Evaluation – coRap https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1806e6bdd
4. IARC, 2013, Monograph on benzophenone, vol 101, IARC
5. Rehfeld A, Dissing S, Skakkebæk NE. Chemical UV Filters Mimic the Effect of Progesterone on Ca(2+) Signaling in Human Sperm Cells. Endocrinology. 2016 Nov;157(11):4297-4308.
6. Danish Environmental Protection Agency. 2015. “Survey and Health Assessment of UV Filters: Survey of Chemical Substances in Consumer Products No. 142, 2015.” 2015. http://mst.dk/service/publikationer/publikationsarkiv/2015/okt/survey-and-health-assessment-of-uv-filters/
7. Charlotte D LaPlante, Ruby Bansal, Karen A Dunphy, D Joseph Jerry, Laura N Vandenberg. Oxybenzone Alters Mammary Gland Morphology in Mice Exposed During Pregnancy and Lactation. J Endocr Soc. 2018 Aug 1; 2(8): 903–921.
8. Ruszkiewicz, J.A., Pinkas, A., Ferrer, B., Peres, T.V., Tsatsakis, A., Aschner, M., 2017. Neurotoxic effect of active ingredients in sunscreen products, a contemporary review. Toxicology reports 4, 245-259.
9. Adoamnei E et al. Urinary concentrations of benzophenone-type ultra violet light filters and reproductive parameters in young men. Int J Hyg Environ Health. 2018 Apr;221(3):531-540. doi: 10.1016/j.ijheh.2018.02.002
10. Scinicariello F, Buser MC. Serum Testosterone Concentrations and Urinary Bisphenol A, Benzophenone-3, Triclosan, and Paraben Levels in Male and Female Children and Adolescents: NHANES 2011-2012. Environ Health Perspect. 2016 Dec;124(12):1898-1904
11. Joenen UN, Jørgensen N, Thyssen JP, Szecsi PB, Stender S, Petersen JH, Andersson AM, Frederiksen H. Urinary excretion of phenols, parabens and benzophenones in young men: Associations to reproductive hormones and semen quality are modified by mutations in the Filaggrin gene. Environ Int. 2018 Dec;121(Pt 1):365-374. doi: 10.1016/j.envint.2018.09.020.
12. Pollack AZ, Mumford SL, Krall JR, Carmichael AE, Sjaarda LA, Perkins NJ, Kannan K, Schisterman EF. Exposure to bisphenol A, chlorophenols, benzophenones, and parabens in relation to reproductive hormones in healthy women: A chemical mixture approach. Environ Int. 2018 Nov;120:137-144. doi: 10.1016/j.envint.2018.07.028. Epub 2018 Aug 10
13. ECHA. Substance Evaluation Conclusion as required by REACH Article 48 and Evaluation report 2018.
14. Schmutzler C, Bacinski A, Gotthardt I, Huhne K, Ambrugger P, Klammer H, Schlecht C, Hoang-Vu C, Grüters A, Wuttke W, Jarry H, Köhrle J. The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase Endocrinology. 2007 Jun;148(6):2835-44.
15. Schlecht C, Klammer H, Jarry H, Wuttke W. Effects of estradiol, benzophenone-2 and benzophenone-3 on the expression pattern of the estrogen receptors (ER) alpha and beta, the estrogen receptor-related receptor 1 (ERR1) and the aryl hydrocarbon receptor (AhR) in adult ovariectomized rats.Toxicology. 2004 Dec 1;205(1-2):123-30.
16. Downs CA, Kramarsky-Winter E, Fauth JE, Segal R, Bronstein O, Jeger R, Lichtenfeld Y, Woodley CM, Pennington P, Kushmaro A, Loya Y. Toxicological effects of the sunscreen UV filter, benzophenone-2, on planulae and in vitro cells of the coral, Stylophora pistillata Ecotoxicology. 2014 Mar;23(2):175-91.
17. Buck Louis GM, Kannan K, Sapra KJ, Maisog J, Sundaram R Urinary concentrations of benzophenone-type ultraviolet radiation filters and couples' fecundity. Am J Epidemiol. 2014 Dec 15;180(12):1168-75.
18. Kraue, M., A. Klit, M. Blomberg Jensen, T. Søeborg, H. Frederiksen, M. Schlumpf, W. Lichtensteiger, N. E. Skakkebaek, and K. T. Drzewiecki. 2012. “Sunscreens: Are They Beneficial for Health? An Overview of Endocrine Disrupting Properties of UV-Filters.” International Journal of Andrology 35 (3):424–36. https://doi.org/10.1111/j.1365-2605.2012.01280.x

19. Krause M et al. Maternal exposure to UV filters: associations with maternal thyroid hormones, IGF-I/IGFBP3 and birth outcomes. Endocr Connect. 2018 Feb;7(2):334-346. doi: 10.1530/EC-17-0375. Epub 2018 Jan 23.
20. EFSA. 2009a. “EFSA Statement on the Presence of 4-Methylbenzophenone Found in Breakfast Cereals.” EFSA Journal 7 (3):n/a-n/a. https://doi.org/10.2903/j.efsa.2009.243r
21. Biomonitoring California. Maternal and Infant Environmental Exposure Project (MIEEP) https://biomonitoring.ca.gov/projects/maternal-and-infant-environmental-exposure-project-mieep
22. Philippat, Claire, Mary S. Wolff, Antonia M. Calafat, Xiaoyun Ye, Rebecca Bausell, Molly Meadows, Joanne Stone, Rémy Slama, and Stephanie M. Engel. 2013. “Prenatal Exposure to Environmental Phenols: Concentrations in Amniotic Fluid and Variability in Urinary Concentrations during Pregnancy.” Environmental Health Perspectives 121 (10):1225–31. https://doi.org/10.1289/ehp.1206335
23. Zhang, T., Sun, H., Qin, X., Wu, Q., Zhang, Y., Ma, J., Kannan, K., 2013. Benzophenone-type UV filters in urine and blood from children, adults, and pregnant women in China: partitioning between blood and urine as well as maternal and fetal cord blood. The Science of the total environment 461-462, 49-55.
24. Machtnger R, Berman T, Adir M, Mansur A, Baccarelli AA, Racowsky C, Calafat AM, Hauser R, Nahum R. 2018. " Urinary concentrations of phthalate metabolites, bisphenols and personal care product chemical biomarkers in pregnant women in Israel." Environ Int. 116:319-325.
25. Dewalque L, Pirard C, Charlier C. Measurement of Urinary Biomarkers of Parabens, Benzophenone-3, and Phthalates in a Belgian Population. Biomed Res Int. 2014; 2014: 649314.
26. Morrison, Glenn C., Gabriel Bekö, Charles J. Weschler, Tobias Schripp, Tunga Salthammer, Jonathan Hill, Anna-Maria Andersson, Jørn Toftum, Geo Clausen, and Hanne Frederiksen. 2017. “Dermal Uptake of Benzophenone-3 from Clothing.” Environmental Science & Technology 51 (19):11371–79. https://doi.org/10.1021/acs.est.7b02623
27. Calafat AM, Wong LY, Ye X, Reidy JA, Needham LL. Concentrations of the sunscreen agent benzophenone-3 in residents of the United States: National Health and Nutrition Examination Survey 2003--2004. Environ Health Perspect 2008;116(7):893-897.
28. US Centers for Disease Control. National Report on Human Exposure to Environmental Chemicals https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf
29. Krause, Marianna, Anna-Maria Andersson, Niels E. Skakkebaek, and Hanne Frederiksen. 2017. “Exposure to UV Filters during Summer and Winter in Danish Kindergarten Children.” Environment International 99 (Supplement C):177–84. https://doi.org/10.1016/j.envint.2016.11.011
30. Frederiksen H., Jensen T.K., Jørgensen N., Boye Kyhl H., Husby S., Skakkebæk N.E., Main K.M., Juul A., Anderson A.-M. (2014) Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected 2006-2012. *Reproduction* 147, 555-565
31. Frederiksen H., Nielsen J.K.S., Mørck, T.A., Hansen, P.W. Nielsen, O., Anderson A.-M., Knudsen L.E. (2013) Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban populations of Danish school children and their mothers. *Int J Hygiene and Env Health*. 216, 772-783.
32. Frederiksen, Hanne, Ole Nielsen, Niels E. Skakkebaek, Anders Juul, and Anna-Maria Andersson. 2017. “UV Filters Analyzed by Isotope Diluted TurboFlow-LC-MS/MS in Urine from Danish children and adolescents. Int J Hyg Environ Health. 2017 Mar;220(2 Pt A):244-253.
33. Gao CJ, Liu LY, Ma WL2, Zhu NZ2, Jiang L, Li YF, Kannan K. Benzonphenone-type UV filters in urine of Chinese young adults: Concentration, source and exposure. Environ Pollut. 2015 Aug;203:1-6.
34. A.L.Heffernan, C. Baduel L.M.L. Toms,A.M. Calafat, X. Ye, P. Hobson, S. Broomhall, and J.F. Mueller. Use of pooled samples to assess human exposure to parabens, benzophenone-3 and triclosan in Queensland, Australia. Environ Int. 2015 Dec; 85: 77–83.
35. Chang FK, Shiea J, Tsai HJ. Urinary Concentrations of Triclosan, Benzophenone-3, and Bisphenol A in Taiwanese Children and Adolescents. Int J Environ Res Public Health. 2017 Dec 10;14(12).
36. Moos RK, Angerer J, Wittsiepe J, Wilhelm M, Brüning T, Koch HM. Rapid determination of nine parabens and seven other environmental phenols in urine. Int J Hyg Environ Health. 2014 Nov;217(8):845-53. doi: 10.1016/j.ijheh.2014.06.003.
37. COMMISSION REGULATION (EU). 2017/238.
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0238&rid=7
38. Annex VI, Last update: 14/09/2018. LIST OF UV FILTERS ALLOWED IN COSMETIC PRODUCTS. http://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex%20VI_v2.pdf
39. Scientific Committee on Consumer Safety. Opinion On 3-Benzylidene camphor. https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_134.pdf

40. Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food.
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02011R0010-20140324
41. Moos RK, Angerer J, Wittsiepe J, Wilhelm M, Brüning T, Koch HM. Rapid determination of nine parabens and seven other environmental phenols in urine samples of German children and adults. Int J Hyg Environ Health. 2014 Nov;217(8):845-53.
42. Ye X, Kuklenyik Z, Needham LL, Calafat AM. Quantification of urinary conjugates of bisphenol A, 2,5-dichlorophenol, and 2-hydroxy-4-methoxybenzophenone in humans by online solid phase extraction-high performance liquid chromatography-tandem mass spectrometry. Anal Bioanal Chem 2005;383(4):638 644.
43. Leng G, Gries W. New specific and sensitive biomonitoring methods for chemicals of emerging health relevance. Int J Hyg Environ Health. 2017 Mar;220(2 Pt A):113-122.
44. Justification for the Selection of a Substance for CoRAP Inclusion: Oxybenzone. 2014. https://echa.europa.eu/documents/10162/2463d88e-7333-46a1-8d26-7e9c01c663f3