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We create chemistry

Suncreen safety

Myriam Sohn, Ph.D

The „Safe“ Beauty E-Summit by The Eco Well

September 18th, 2022

Sunscreens‘ Requirements

Four Main Pillars for UV Filters / Sunscreens

Efficacy

- Absorb UV light (prevent UV damages e.g. erythema, reduce skin cancers risks, premature photoageing…)
- Photostable
- Compatible with other UV filters
- Water-resistant (keep protection during swimming, sweating…)
- Compatible with other cosmetic ingredients
- Sensory appealing to improve compliance (non sticky, non greasy, non colored,…)

Registration

- Sunscreens are either classified as cosmetics (e.g. in Europe) or as OTC (e.g. in the USA)
- In each case, UV filter molecules must be registered to be used in sunscreens
- Registration consists in a series of tests to ensure the safety of the UV filters for humans
- Registration is region-wise

Safety

- Sunscreens must be safe for humans
- Each UV filter molecule must be first approved to be used
- Safety may be reviewed when new data are available / new requirements appear (e.g. endocrine disrupting properties)

Freedom-to-operate

- Relevant for UV filter and sunscreen manufacturers
- The UV filter molecule or sunscreen product must not infringe intellectual property of a third party

Safety of Sunscreens

Human safety

- UV filter molecules must be registered to be used in sunscreens
- Registration consists in a series of toxicological tests to ensure the UV filters are safe for humans
- Registration is performed separately in each region, which explains why the number and type of approved filters may differ between the regions
- In EU: EU commission with Scientific committee consumer safety (SCCS) evaluates the safety before approval / review after approval
- In USA: FDA evaluates the safety before approval

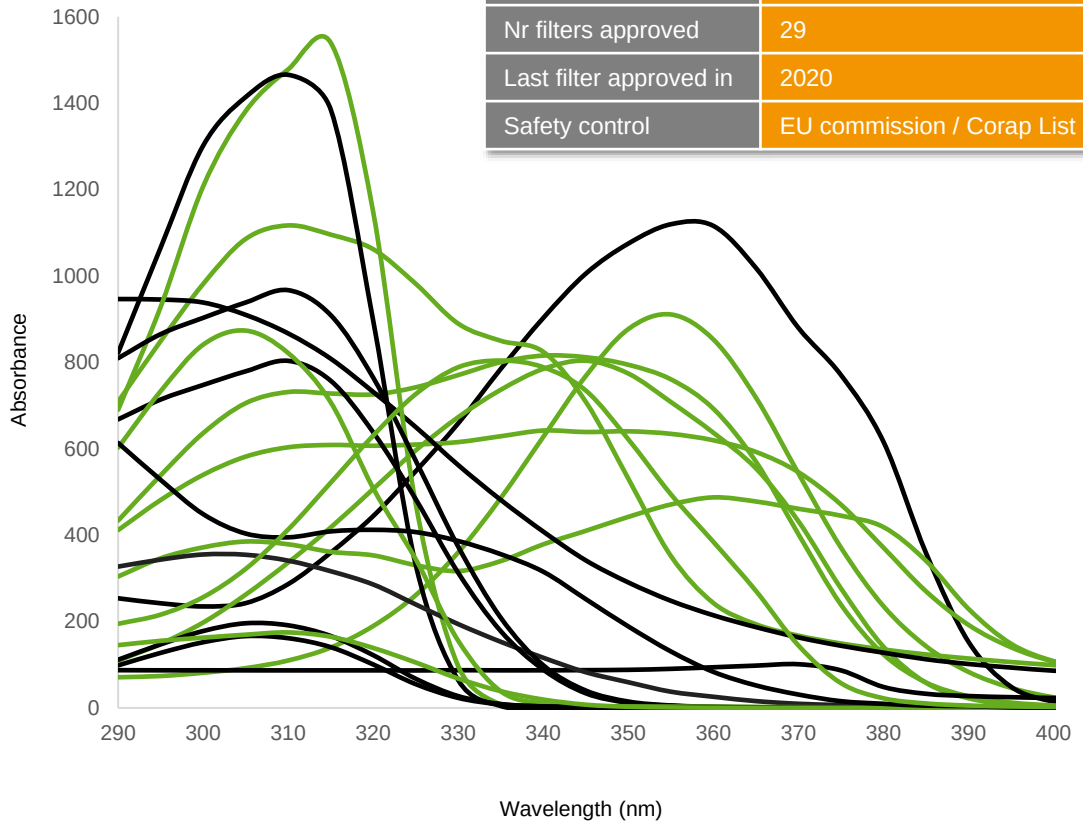
Environmental Safety

- Growing requirement (authorities, industry, end consumer)
- Environmental damage is often mainly connected to coral reef damages
- Most of coral damages are due to climate changes
- No global harmonized criterium to evaluate safety of ingredients for corals
- In EU, environmental safety is monitored by ECHA (CoRAP list for substances which need further investigations)

Absorbance of Main Approved UV Filters

Europe

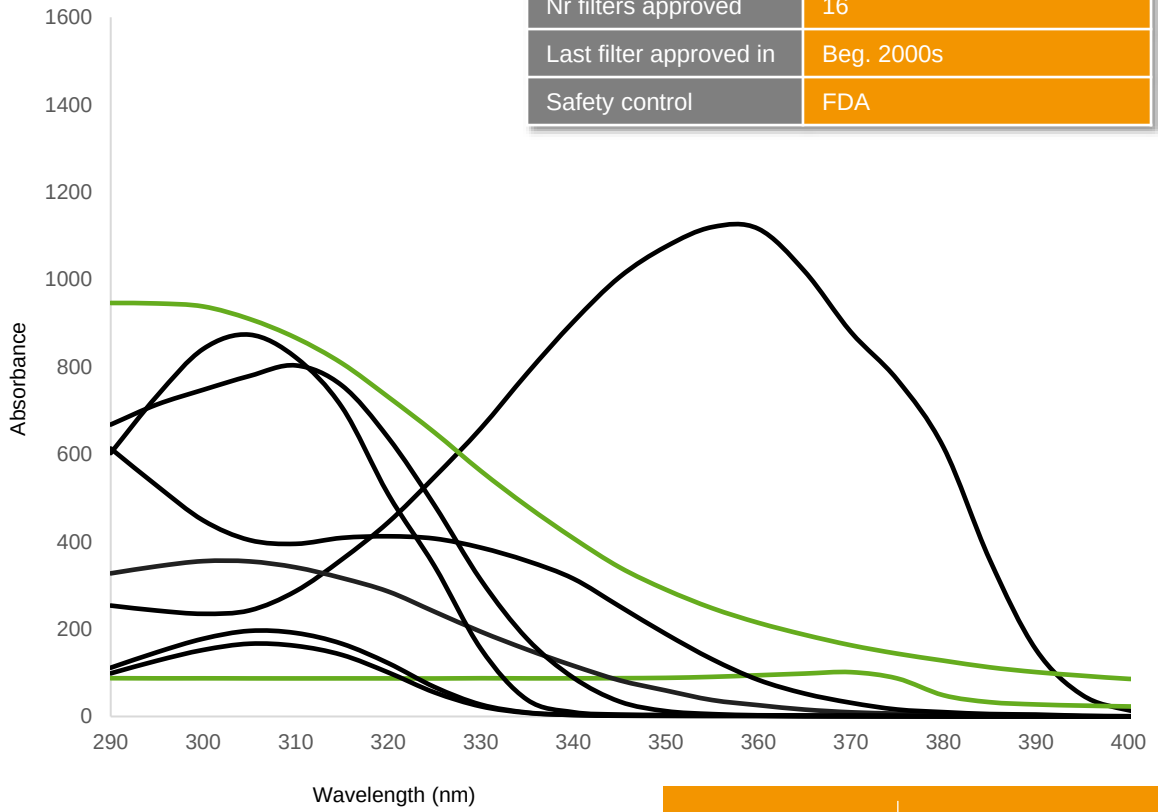
Classification	Cosmetics
Regulatory body	EU commission
Nr filters approved	29
Last filter approved in	2020
Safety control	EU commission / Corap List



Variety of UV filter molecules approved

USA

Classification	OTC
Regulatory body	FDA
Nr filters approved	16
Last filter approved in	Beg. 2000s
Safety control	FDA



Limited number of filters approved

Dr. Myriam Sohn | Global Technical Center SunCare

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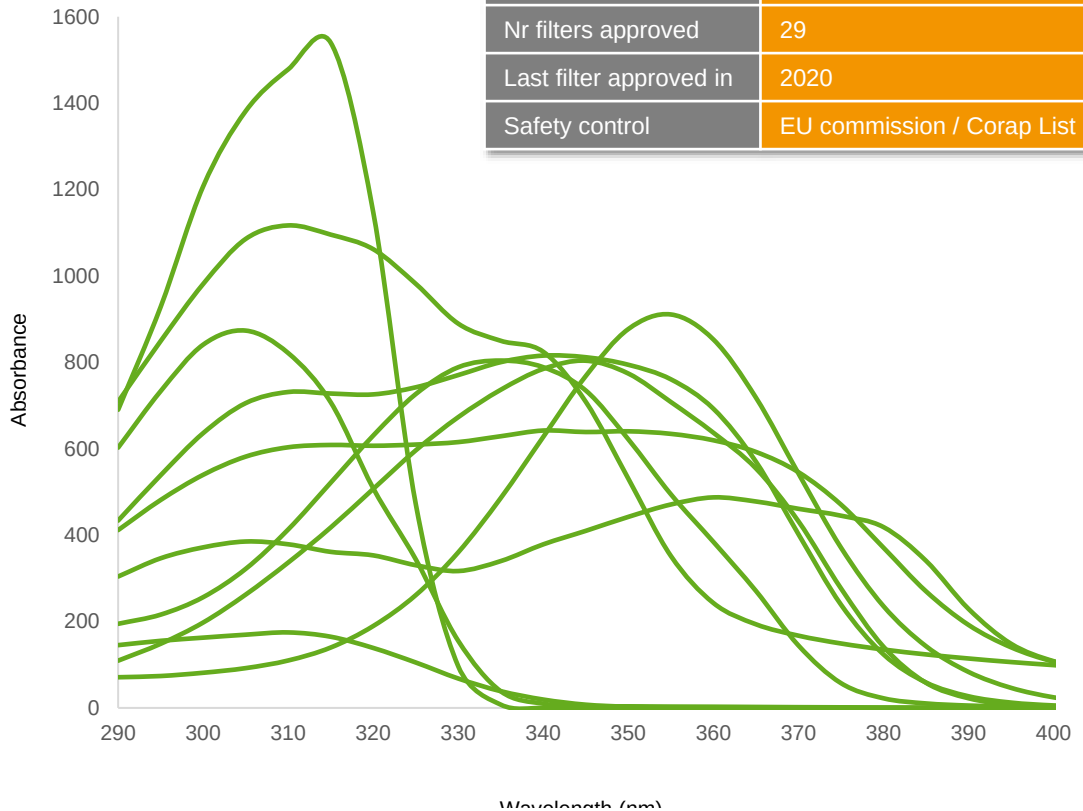
Remaining UV Filters not under Concern

Europe

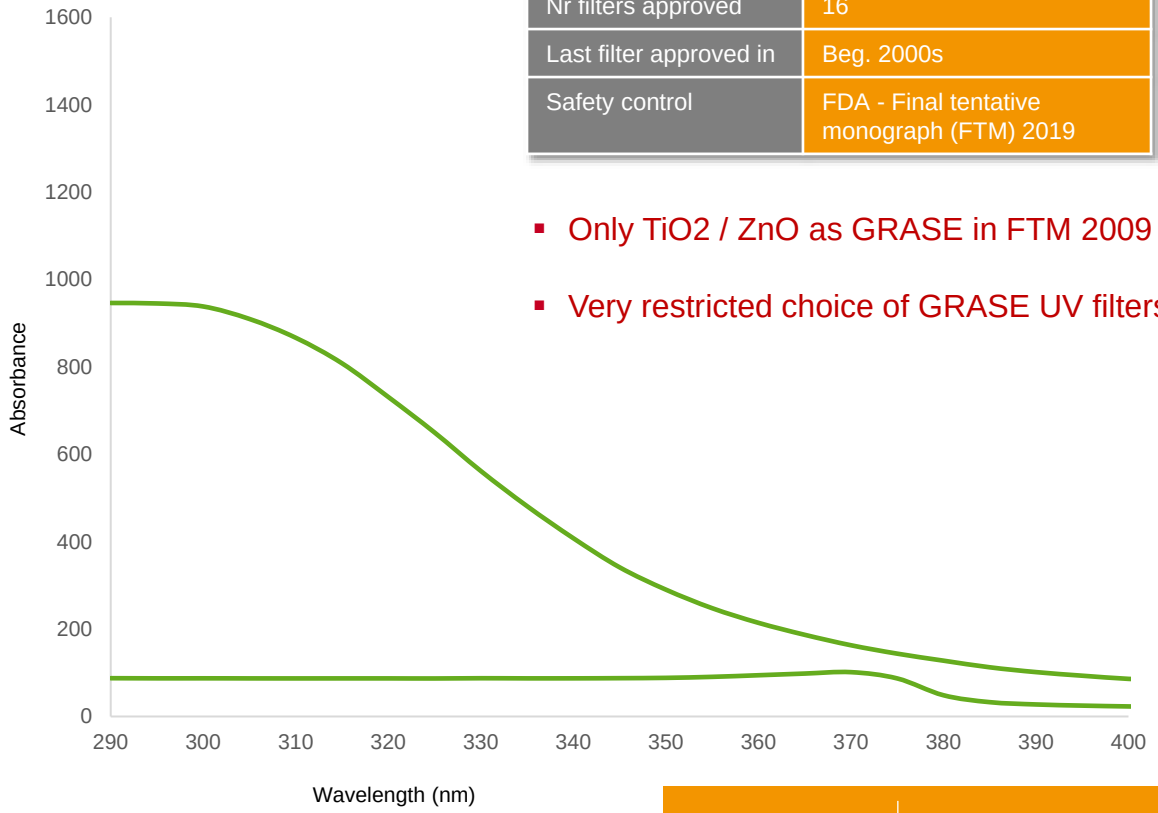
Classification	Cosmetics
Regulatory body	EU commission
Nr filters approved	29
Last filter approved in	2020
Safety control	EU commission / Corap List



USA

Classification	OTC
Regulatory body	FDA
Nr filters approved	16
Last filter approved in	Beg. 2000s
Safety control	FDA - Final tentative monograph (FTM) 2019

- Only TiO2 / ZnO as GRASE in FTM 2009
- Very restricted choice of GRASE UV filters



Still a significant number of filters available to achieve high SPF and UVA protection

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FDA Tentative Final Monograph / Feb 2019

FDA Advances Proposed Rule on Sunscreens

Proposed rule will update regulatory requirements for most sunscreen products in the US.

- Proposes that, of the 16 currently marketed active ingredients, two ingredients – zinc oxide and titanium dioxide – are GRASE for use in sunscreens; two ingredients – PABA and trolamine salicylate – are not GRASE for use in sunscreens due to safety issues. There are 12 ingredients for which there are insufficient safety data to make a positive GRASE determination at this time. To address these 12 ingredients, the FDA is asking industry and other interested parties for additional data. The FDA is working closely with industry and has published **several guidances** to make sure companies understand what data the agency believes is necessary for the FDA to evaluate safety and effectiveness for sunscreen active ingredients, including the 12 ingredients for which the FDA is seeking more data.

Based on human tox

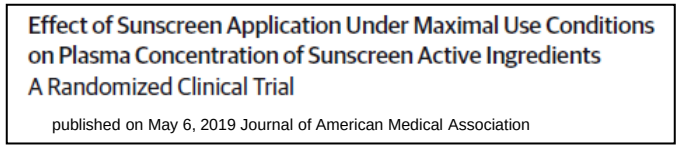
- **Only TiO2 and ZnO are GRASE**
  - Difficult to achieve the high SPF and UVA protection required in the different regions
  - Sensorial drawback of using only particulate filters
  - Protection and aesthetics for sunscreens with inorganics are highly dependent on formulation know how and using the right inorganic UV filters (specific dispersion might offer better sensory)
  - Challenge for emulsion stability

- **Additional (human tox) data requested for all other organic filters incl. MUsT studies**
  - MUsT studies = Maximal Use Trial correspond to dermal penetration studies

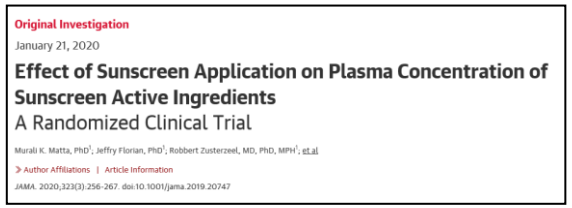
MUsT – Dermal Penetration Studies as New Requirement of FDA

- Is a standard requirement for topically applied pharmaceuticals
- Required even for grandfathered filters (not GRASE in FTM 2019)
- Triggered by life-long and frequent use of sunscreens
- Looks for blood plasma concentration after repeated dose
- Includes all different skin types of human body
- Includes different formulation compositions
- Conducted under maximum use conditions: max. concentration, max. application frequency, max. surface area
- FDA will require additional carcinogenic studies, when a threshold of 0.5 ng filter/ml blood plasma is exceeded
- Was performed as a small-scale pilot study by FDA after industry had not committed to do so

Results of FDA Small-scale Pilot Studies


Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

published on May 6, 2019 Journal of American Medical Association


Original Investigation

January 21, 2020

Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients
A Randomized Clinical Trial

Murali K. Matta, PhD[1]; Jeffry Florian, PhD[1]; Robbert Zusterzeel, MD, PhD, MPH[1]; et al

Author Affiliations | Article Information

JAMA. 2020;323(3):256-267. doi:10.1001/jama.2019.20747

- Already after one application, the systemic absorption exceeds 0.5 ng/ml blood plasma for all UV filters and were still above up to 21 days after study start
- Concentrations in blood and on the skin relatively independent of formulation type (spray, lotion,…)
- Highest amount by Oxybenzone followed by Homosalate
- Good reproducibility between the 2 studies
- Study results will be used by FDA to request more systemic toxicity data (carcinogenicity, reproduction, …), because a safety assessment based on available studies not possible

BUT FDA also explicitly commented, that the presence of UV filters in blood does not mean the filters are toxic!

Skin Penetration – Dependencies

Factors which affect skin penetration

- Lipophilicity of test substance
- Molecular weight of test substance
- Ionic charge of test substance
- Concentration of the test substance
- Vehicle
- Skin area and time of exposure
- Thickness and integrity of the stratum corneum
- Temperature, blood flow

Best Possible Practice for Low Skin Penetration

Parameter	Objective for low penetration	Effect
Molecular mass (size)	> 500 Dalton	Large molecules don‘t penetrate
Hydrophobicity	Log Pow < 1 or > 4	Very polar or very unpolar molecules don‘t penetrate
Polarity	Low to no functional groups	No interaction with skin
Melting point	Substances with MP > 50 °C	Low to no penetration

Wiechers, J.W., et al., Predicting Skin Penetration of Actives from Complex Cosmetic Formulations: an Evaluation of Inter Formulation and Inter Active Effects during Formulation Optimization for Transdermal Delivery. International Journal of Cosmetic Science, 2012. 34(6): p. 525-35.
Bos, J.D. and Meinardi. M., The 500 Dalton Rule for the Skin Penetration of Chemical Compounds and Drugs. Experimental Dermatology, 2000. 9(3): p. 165-9.

Physico-chemical Parameters and Dermal Absorption
Examples of Different UV Filters

	Filter	Molecular mass (Da)	Log Pow	Melting point °C	Water solubility	Dermal Penetration
Part of the FDA MUsT studies	Oxybenzone	228	3.45	62.5	3 mg/L	3-4 %
	Avobenzone	310	6.1	84	< 1 mg/L	< 0.5 %
	Ecamsule	562	1.35	255	> 600 g/L	0.16 %
	Octocrylene	361	6.1	< 30	<< 1 mg/L	0.12 %
	Octinoxate	290	> 6	< 30	<< 1 mg/L	4 %
	Octisalate	250	> 6	< 30	< 1 mg/L	1.1 %
Filters of newest generation approved in EP, BR, …	Bisoctrizole (Tinosorb® M)	659	> 12	195	<< 1 mg/L	< 0.1 %
	Bemotrizinol (Tinosorb® S)	627	>>6	80	<< 1 mg/L	< 0.1 %
	TBPT (Tinosorb® A2B)	537	10.4	281	<< 1 mg/L	< 0.1%
	Octyl Triazone (Uvinul® T150)	823	>>6	130	<< 1 mg/L	0.1 %

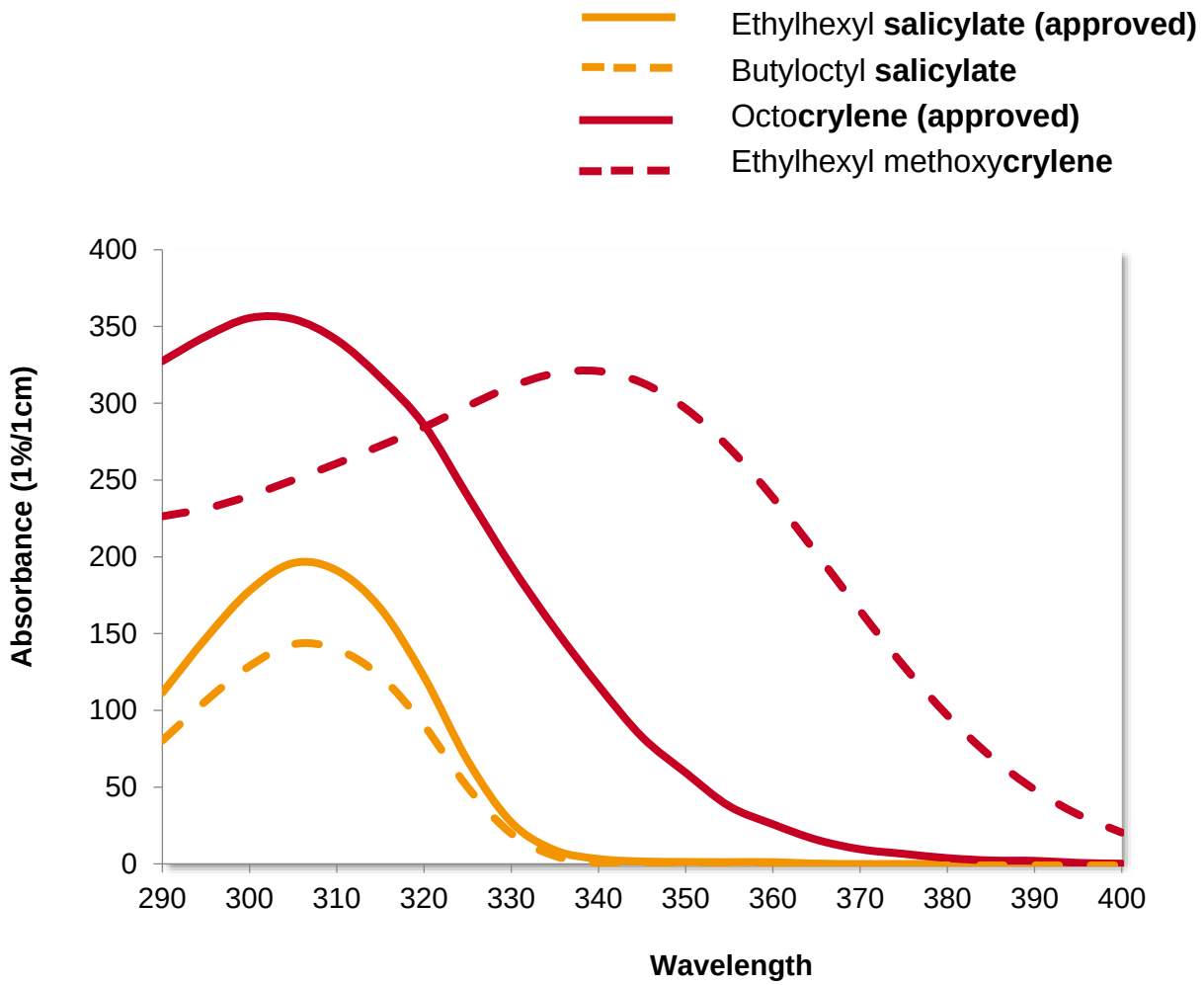
TBPT, Tris-Biphenyl Triazine

Current Situation in the US

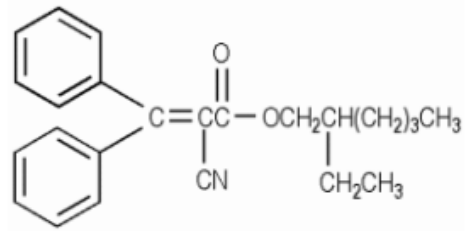
- FDA FTM of 2019 defines Titanium Dioxide and Zinc Oxide as only GRASE filters
- Additional toxicological tests required for all other grandfather (& organic) filters – costly & time consuming (no rapid final outcome expected)
- Difficult to achieve high performance, acceptable sensory, and emulsion stability with Titanium Dioxide and / or Zinc Oxide only
- Sunscreen manufacturers use boosters to reach UV performance
- Boosters can be scattering particles or film formers
- **However, boosters can also be molecules with UV absorbing function and are in that case illegal UV filters**

Illegal UV filters are similar to UV filters but have not went through the approval process for safety evaluation

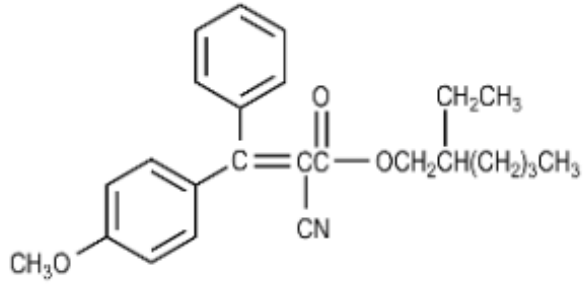
Comparison of Absorbance of Registered UV Filters vs Boosters



- Octo**crylene** (OCR), registered UV filter under focus by US FDA due to lacking MuST data



- Ethylhexyl Methoxy**crylene**, <u>similar structure to OCR</u>, non-registered UV filter no focus by FDA as <u>not approved as UV filter</u>



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US Market Product Examples

Mineral only sunscreen SPF50

active ingredients:
zinc oxide (24.08%)

inactive ingredients:
water, C12-15 alkyl benzoate, isopropyl palmitate, butyloctyl salicylate, ethylhexyl isononanoate, cetyl PEG/PPG-10/1 dimethicone, propylene glycol, cyclopentasiloxane, bis-octyldodecyl dimer dilinoleate/propanediol copolymer, dimethicone, ethylhexyl methoxycrylene, polyester-27, TEA, Camellia sinensis (leaf) extract*, giant kelp (Macrocystis pyrifera) extract*, sacred lotus (Nelumbo nucifera) extract*, triethoxycaprylylsilane, beeswax, PEG-12 dimethicone crosspolymer, tocopherol, 1,2-hexanediol, caprylyl glycol, sodium chloride
*botanical extracts

100% mineral sunscreen SPF50

active ingredients:
titanium dioxide (4.5%), zinc oxide (6.5%)

inactive ingredients:
water, caprylic/capric triglyceride, isohexadecane, butyloctyl salicylate, octyldodecyl citrate crosspolymer, cetyl PEG/PPG-10/1 dimethicone, lauryl PEG-8 dimethicone, C30-38 olefin/isopropyl maleate/MA copolymer, sodium chloride, ethylhexyl methoxycrylene, dimethicone, phenoxyethanol, caprylyl glycol, PEG-8, alumina, glycerin, sodium citrate, tocopheryl acetate

Mineral sunscreen SPF50

active ingredient:
zinc oxide (12%)

inactive ingredients:
allantoin, bisabolol, butyloctyl salicylate, C12-15 alkyl benzoate, caprylyl glycol, caprylyl methicone, dimethicone, dimethiconol/propylsilsesquioxane /silicate crosspolymer, ethylhexylglycerin, hexylene glycol, isododecane, lauryl PEG-10 tris(trimethylsiloxy) silylethyl dimethicone, lauryl PEG-8 dimethicone, niacinamide, octyldodecyl neopentanoate, PEG-10, phenoxyethanol, polymethylsilsesquioxane, propanediol , sodium chloride, sodium hydroxide, tetrasodium glutamate diacetate, tocopherol (vitamin E), trilaureth-4 phosphate, water

By asking for additional data to prove safety of already registered organic UV filters, FDA opens the door to use UV molecules not tested at all

Situation in Europe

EU Cosmetic Directive

- Market products can not use UV filters other than those listed in annex VI
- Boosters with inherent absorbance exceeding the one of registered UV filters not listed in annex VI of EC regulation are forbidden
- Boosters have no SCCS opinion and were not tested regarding their safety

- This issue of using non official registered UV filters was addressed by several organizations

- Market products had to be removed from the market due to the use of non-registered molecules showing UV absorbance

CHAPTER IV

RESTRICTIONS FOR CERTAIN SUBSTANCES

Article 14

Restrictions for substances listed in the Annexes

1. Without prejudice to Article 3, cosmetic products shall not contain any of the following:

…

(e) UV-filters

(i) UV-filters other than those listed in Annex VI and UV-filters which are listed there but not used in accordance with the conditions laid down in that Annex;

(ii) without prejudice to points (b), (c)(i) and (d)(i), substances listed in Annex VI but which are not intended to be used as UV-filters and which are not used in accordance with the conditions laid down in that Annex.

Safety Alert of EU Commission (July 13, 2022)

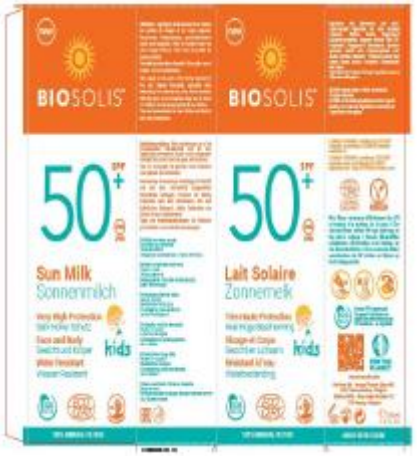
European Commission | Safety Gate Alerts

Alert number	**A11/00088/22**
Product	**Sun milk**
Risk type	**Burns**

The actual sun protection factor of the sun milk differs from the one declared. Consequently, the user may be underprotected against UV radiation increasing the risk of sunburns or skin cancer.

The product does not comply with the Cosmetic Products Regulation nor with the Commission Recommendation on the efficacy of sunscreen products and the claims made relating thereto.

Measures ordered by public authorities	**Stop of sales** **Other**
Measures taken by economic operators	**Temporary ban on the supply, offer to supply and display of the product** **Manufacturer**



INCI:
dicaprylyl carbonate, Aloe barbadensis gel*, titanium dioxide, zinc oxide, coconut alkanes, polyglyceryl-2 dipolyhydroxystearate, propanediol, Pongamia glabra (karanja) seed oil*, polyglyceryl-3 diisostearate, polyhydroxystearic acid, stearic acid, aluminum hydroxide, sodium chloride, Brassica campestris (rapeseed) oil*, Daucus carota sativa (carrot) root extract*, Helianthus annuus (sunflower) seed oil*, coco-caprylate/caprate, alumina, potassium sorbate, sodium benzoate, parfum, lactic acid, tocopherol
* ingredients from organic farming

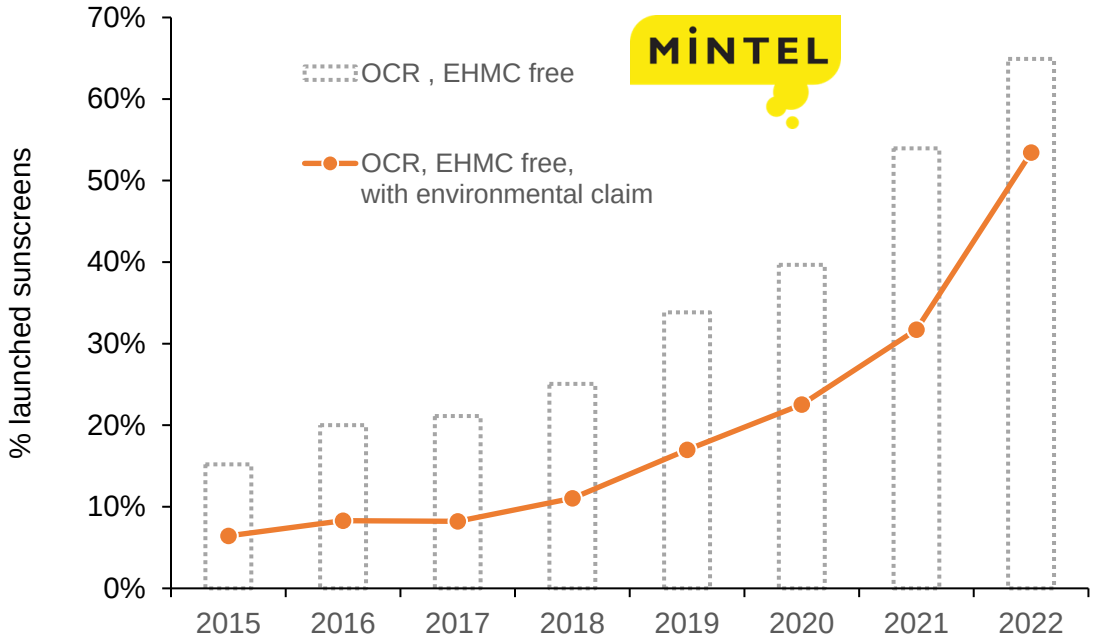
Safety of Sunscreens Situation in Europe

SCCS for Human safety

- Approves / reviews registered UV filters
- The maximum concentration of some registered UV filters has been adjusted recently
- List of UV filters to be reviewed in respect of their endocrine disrupting potential risk

ECHA for environmental aspects

- Reach registration and compliance of chemicals
- CoRAP list of substances that may pose a risk to human health or the environment
- No official / harmonized test for the impact on corals



Search for products
where Region matches Europe
and Sub-Category matches Sun - Sun/Sunbed Exposure
and Claims matches one or more of [Biodegradable; Carbon Neutral; Ethical - Environmentally Friendly Package; Ethical - Recycling; Ethical - Environmentally Friendly Product] as the claim
and Date Published is between Jan xxxx and Dec xxxx

Environmental Aspects

Current Status

- Discussion on potential damages UV filters may have on the ecosystem since they are likely to be directly released into the environment

- A major recent public concern is related to global coral bleaching
  - Current coral damaging factors are mainly due to the climate change with the increase of the water temperature, and ocean acidification, to marine debris and pollution, to physical stress by hurricanes, or fishing practices

- Independently, some authors investigated the impact of UV filters on reef corals initiating the discussion on the impact of sunscreens on corals
  - Those study protocols however do not follow approved principals of standardized test guidelines and thus important and relevant parameters (i.e. water quality) may have not been measured

Current Status

- Some governments already took drastic regulatory actions by prohibiting the sale of sunscreens containing some of the worldwide registered UV filters on base of those studies

- Such decisions are problematic since the use of sunscreens was demonstrated highly valuable for human health e.g. prevention skin cancers

Region	Banned / under discussion UV filters
Haiwaii	Benzophenone 3, Octyl Methoxycinnamate From Oct 2022 ban of all organic UV filters approved in the US
Palau	Benzophenone 3, Octyl Methoxycinnamate, Octocrylene, 4-Methyl-Benzylidene Camphor
Key West Florida US	Benzophenone 3, Octyl Methoxycinnamate
US Virgin Islands	Benzophenone 3, Octyl Methoxycinnamate
Brazil	Under discussion: Benzophenone 3, Octyl Methoxycinnamate, Octocrylene, 4-Methyl-Benzylidene Camphor
Europe	Currently 11 UV filters on CoRap list with open requests for further evaluation

Environmental Effect of UV Filters
EcoSun Pass of BASF

Environmental parameters

- Biodegradation
- Acute aquatic toxicity
- Chronic aquatic toxicity
- Bioaccumulation
- Terrestrial toxicity
- Sediment toxicity
- Endocrine properties

Ecosun pass
(WO2019207129)

The BASF EcoSun Pass

Scientific based tool to assess the environmental impact of UV-filters

EcoSun Pass for more eco-compliant sunscreens

EcoSun Pass approved.

EcoSun Pass is either a registered trademark or a trademark of BASF SE in the European Union and/or other countries.

By considering all relevant parameters, more eco-compliant sunscreen formulation can be developed

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Summary

- Only after human safety assessment UV filters can be registered and used in sunscreens
- The regulatory status of approved UV filters can always be reviewed
- The choice of UV filters is reduced globally due to open questions of authorities regarding environmental and/or human safety
- The lack of performance is sometimes filled using boosters, based on same chromophores as approved filters but have not been assessed in respect of their safety
- Penetration of organic UV filters depends on their individual properties
- Reduced choice of possible UV filters (FDA TFM 2019) will finally negatively impact the protection of end consumers which results in another health concern
- Modern organic UV filters are designed for highest UV absorption and best safety profile and outperform inorganic UV filters
- Ecosun Pass offers a possibility to design more eco-compliant sunscreens

Thank you!

The Global Technical Center SunCare
Product Stewardship Personal Care - UV Filters