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Review

Sunscreens: UV filters to protect us: Part 2-Increasing awareness of UV filters and their potential toxicities to us and our environment

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ABSTRACT

Background: Sunscreens are topical preparations containing one or more compounds that filter, block, reflect, scatter, or absorb ultraviolet (UV) light. Part 2 of this review focuses on the environmental, ecological effects and human toxicities that have been attributed to UV filters.
Methods: Literature review using NIH databases (eg, PubMed and Medline), FDA and EPA databases, Google Scholar, the *Federal Register*, and the *Code of Federal Regulations* (*CFR*).
Limitations: This was a retrospective literature review that involved many different types of studies across a variety of species. Comparison between reports is limited by variations in methodology and criteria for toxicity.
Conclusions: *In vivo* and *in vitro* studies on the environmental and biological effects of UV filters show a wide array of unanticipated adverse effects on the environment and exposed organisms. Coral bleaching receives considerable attention from the lay press, but the scientific literature identifies potential toxicities of endocrine, neurologic, neoplastic and developmental pathways. These effects harm a vast array of aquatic and marine biota, while almost no data supports human toxicity at currently used quantities (with the exception of contact allergy). Much of these data are from experimental studies or field observations; more controlled environmental studies and long-term human use data are limited. Several jurisdictions have prohibited specific UV filters, but this does not adequately address the dichotomy of the benefits of photoprotection vs lack of eco-friendly, safe, and FDA-approved alternatives.

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Abbreviations: 4-MBC, 4-methylbenzylidene camphor; AAD, American Academy of Dermatology; BP-3, Benzophenone-3 or Oxybenzone; CDER, Center for Drug Evaluation and Research (part of FDA); EPA, Environmental Protection Agency; Europa, European Union Commission for Public Health; FDA, Food and Drug Administration; GRASE, Generally Recognized As Safe and Effective; GBRMPA, Great Barrier Reef Marine Park Authority; NHANES, National Health and Nutrition Examination Survey; OC, Octocrylene; OMC, Octyl methoxycinnamate or octinoxate; OTC, Over-the-counter; PABA, Para-aminobenzoic acid; PPCP, Pharmaceuticals and personal care products; PCPC, Personal care products and cosmetics; UV, Ultraviolet; UVF, Ultraviolet filter; WWTP, Wastewater treatment plant; NDA, New drug application; TiO_2, Titanium dioxide; NanoTiO_2, Nanoparticle titanium dioxide.

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Key Points

- Man-made UV filters are ubiquitous in the environment with human and animal absorption being well documented, long term studies and bioaccumulation have not been well characterized.
- There is little data to support direct toxicity of UV filters in humans to date beyond contact and photocontact allergy, while the mechanisms for coral bleaching and coral death are better understood and are areas of active research.
- Animal, marine and aquatic organisms have evidence for in vitro and ex vivo toxicity, but in vivo toxicity is less well characterized as much of the work to date shows water levels below toxicity thresholds. These studies lack control for high fluxes of UVF release in waste water treatment plants or at popular beaches during peak tourism.

Introduction

In Part 1, we describe the regulatory recommendations that the U.S. Food and Drug Administration (FDA) issued in February 2019 for non-prescription, over-the-counter (OTC) sunscreens to ensure their safety, efficacy, and consistency in labeling. We reviewed practical uses of UVFs and the AAD's recommendations for sun protection as well as the need for more options for safe use in children and adults. In part 2 we will review the ecologic and biologic potential toxicities of UVFs. This part of the review is a survey of data regarding UVF effects and is not meant to give guidance on choices of UVF or the appropriate use of sunscreen agents as these were reviewed in part 1 (Sabzevari N, Qiblawi S, Norton S, Fivenson D, 2020).

Definitions

When reviewing scientific data, it is essential that readers understand the terminology. For example, titanium dioxide (TiO_2) is not a *sunscreen*. It is a *UV filter (UVF)* that is included in many commercial products known as *sunscreens*.

Sunscreen: a commercial product sold to consumers for protection of human skin from UV radiation. Sunscreens contain one or more UVFs that may be physical, chemical, or both. In addition, they contain many other substances, such as emollients, preservatives or stabilizers, emulsifiers, fragrances, and coloring compounds. Broad spectrum sunscreens are defined by the FDA as products that provide UVA protection that is proportional to its UVB protection (FDA-US, 2017, 2019a).

According to the FDA, "a product that includes the term "sunscreen" in its labeling or in any other way represents or suggests that it is intended to prevent, cure, treat, or mitigate disease or to affect a structure or function of the body comes within the definition of a drug in section 201(g)(1) of the act. Sunscreen active ingredients affect the structure or function of the body by absorbing, reflecting, or scattering the harmful, burning rays of the sun, thereby altering the normal physiological response to solar radiation. These ingredients also help to prevent diseases such as sunburn and may reduce the chance of premature skin aging, skin cancer, and other harmful effects due to the sun when used in conjunction with limiting sun exposure and wearing protective clothing." https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=700.35

UV filter: a specific compound that impedes the passage of UV light. These are typically divided these into chemical (absorbing UV rays and converting to thermal energy) vs. physical agents (reflecting UV rays). Environmental chemists categorize them in several ways, for example, organic vs. inorganic, lipophilic vs. hydrophilic. The National Library of Medicine databases sometimes refer to these compounds as *sunscreening agents (confusing to all of us at times)*, and define them as chemical or physical agents that protect the skin from sunburn and erythema by absorbing or blocking ultraviolet radiation. UVFs are also used in consumer cosmetics (makeup, nail polish, shampoo, etc.) and industry (plastics, paints, sealants, etc.) to protect against photodegradation.

Environment: the surroundings or conditions in which a person, animal, or plant lives or operates.

Ecosystem: the interactions between the environment and the organisms that dwell within it. **GRASE:** defined by the FDA OTC Glossary (https://www.accessdata.fda.gov/scripts/cder/training/otc/topic3/images/Glossary.pdf)

"A drug is not considered a new drug only when it is generally recognized as safe and effective (GRASE). In order to conclude a GRASE determination, a drug must satisfy three criteria: 1. The particular drug product must have been subjected to adequate and well-controlled clinical investigations that establish the product as safe and effective. 2. Those investigations must have been published in the scientific literature available to qualified experts. 3. Experts must generally agree, based on those published studies, that the product is safe and effective for its intended uses. At a minimum, the general acceptance of a product as GRASE must be supported by the same quality and quantity of scientific and/or clinical data necessary to support the approval of a New Drug Application."

Few UVFs used in FDA-approved sunscreen products are considered GRASE but are sold under the definition of a 'Marketed Unapproved Drugs' as they have been in use for a long time, but may be lacking the rigorous testing described in this OTC Glossary definition (see Table 1) (FDA-US, 1978, Food and Drug Administration (US) (2006).

Table 1
UV filters in use worldwide.

	Agent	Range	Max %	Function	Approvals and Complications of Use
PHYSICAL FILTERS (Inorganic Sunscreen Filters)	**Zinc Oxide (ZnO)*^** Other Names: -Color index pigment white 4 -Color index. 77947 -Zinc gelatin -Nogenol	UVB UVA1 UVA2	25% US; JP, AUS- No limit	Reflects UVA and UVB	Photostable; "white, Kabuki-like cast" AUS, EU, JP, USA- GRASE I
	Titanium Dioxide (TiO_2)*^ Other Names: -Color index pigment white 6 -Color index 77891 -Titanium peroxide	UVB UVA2	25% US; JP, AUS- No limit	Reflects UVA and UVB	Photostable; "white, Kabuki-like cast" AUS, EU, JP, USA- GRASE I
CHEMICAL FILTERS (Organic Sunscreen Filters)	**Ecamsule^** Other Names: -**Terephthalylidene dicamphor sulfonic acid*** -TDSA -Mexoryl SX$^{®}$	UVA1 UVA2	3% US, 10% EU, JP, AUS.	Absorbs UV and releases thermal energy	Photostable; Water-soluble AUS, EU, USA- No GRASE rating - approved by NDA 2006.
	Avobenzone^ Other Names: -**Butyl methoxy-dibenzoyl-methane*** -1-(4-methoxyphenyl)- 3-(4-tert-butyl) propane-1,3-dione -Parsol 1789 -Eusolex 9020 -Escalol 517^{TM} (Ashland) -BMBM -B-MDM -Neo Helioplan357 -Milestab1789	UVA1	3% US, 5% EU, AUS, 10% JP	Absorbs UV and releases thermal energy	Photodegradation- micro-encapsulated avobenzone could minimize its degradation in sunlight, photo-allergen; oil soluble (7,13-16,19) AUS, EU, JP, USA- NONGRASE III

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	-BMDBM				
	Octinoxate^ Other Names: -**Ethylhexyl methoxycinnamate*** -Octyl methoxycinnamate -OMC -EHMC -Escalol 557 -Parsol MCX -Eusolex 2292 -Tinosorb OMC -Uvinul MC80	UVB UVA2	7.5% US, 10% EU, AUS. 20% JP.	Absorbs UV and releases thermal energy	Water-insoluble; photodegradation; endocrine disruption-potential; skin absorption; breast milk detection (5-8,18) AUS, EU, JP, USA-NONGRASE III
	Octocrylene*^ Other Names: -Uvinul N539T -OCR -OC -Eusolex OCR -Parsol 340 -2-ethylhexylester -2-cyano-3,3-diphenyl acrylic acid -Octyne-B -Neo Heliopan 303 -AakoSun OCR -Escalol 597UV -Chem OCR -FM-OCR	UVB UVA2	10% EU, US, AUS, JP.	Absorbs UV and releases thermal energy	Photostable; skin absorption; breast milk detection, photosensitizer -increases skin free radicals (6,13,14,18,19) AUS, EU, JP, USA-NONGRASE III
	Oxybenzone^ Other Names: -**Benzophenone-3*** -BP3 -Uvinul M40 -Eusolex 4360 -Escalol 567 -Milestab 9 -Kahscreen B2-3	UVB UVA2	6% US. 10% EU, AUS. 5% JP.	Absorbs UV and releases thermal energy	Photostable; skin absorption; possible photo-carcinogen; breast milk detection, endocrine disruption-potential (1-7,18,19) AUS, EU, JP, USA-NONGRASE III

	Octisalate^ Other Names: -**Ethylhexyl salicylate*** -Octyl salicylate -EHS -Escalol 587	UVB UVA2	5% US, AUS, EU. 10% JP.	Absorbs UV and releases thermal energy	Photodegradation; water-resistant; oil-soluble (10-12) AUS, EU, JP, USA-NONGRASE III
	Homosalate^ Other Names: -**Homomethyl salicylate*** -HMS -Eusolex HMS -Heliopan	UVB UVA2	15% US, AUS. 10% EU, JP.	Absorbs UV and releases thermal energy	Photodegradation; skin absorption; oil-soluble; endocrine disruption-potential; mother's milk (3,6,9,19) AUS, EU, JP, USA-NONGRASE III
	Cinoxate*^ Other Names: -2-Ethoxyethyl p-methoxycinnamate -2-EMC -Phiasol -Give Tan -Sundare	UVB	3% US. 6% AUS.	Absorbs UV and releases thermal energy	Slightly yellow; insoluble in water; photo-allergen (5,13,19) AUS, USA- NONGRASE III
	Padimate O^ Other Names: -**Ethylhexyl dimethyl PABA*** -OD-PABA -Octyldimethyl PABA -EHDP -Escalol 507 -Sundown	UVB	8% US, EU, AUS, JP.	Absorbs UV and releases thermal energy	Water-insoluble PABA derivative; AUS, EU, JP, USA- NONGRASE III
	Ensulizole^ Other Names: -**Phenyl benzimiazole sulfonic acid*** -Phenyl-s-sulfabenzimidazole -Neo Heliopan Hydro -PBSA -Eusolex 232 -Parsol HS -Eusolex 6300	UVB UVA2	4% US. 8% EU. 3% JP.	Absorbs UV and releases thermal energy	Photostable; AUS, EU, JP, USA- NONGRASE III

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	Dioxybenzone^ Other Names: **-Benzophenone-8*** -BP-8 -Spectra-sorb UV24 -Advastab 47 -Dioxibenzanum	UVB UVA2	3% US, AUS.	Absorbs UV and releases thermal energy	Insoluble in water; AUS, USA- NONGRASE III
	Meradimate^ Other Names: **-Menthyl anthranilate*** -Sunarome UVA	UVA1 UVA2	5% US, AUS.	Absorbs UV and releases thermal energy	AUS, USA-NONGRASE III
	Sulisobenzone^ Other Names: **-Benzophenone-4*** -BP4 -Uvinul MS40 -Escalol 577 -2-hydroxy-4- methoxy benzophenone-5-sulfonic acid -3-benzoyl-4-hydroxy-6-methoxybenzene sulfonic acid	UVB UVA2	5% EU. 10% US, JP, AUS.	Absorbs UV and releases thermal energy	Photostable; skin absorption (1-5) AUS, EU, JP, USA- NONGRASE III
	DEA-methoxycinnamate Other Names: -Bernel Hydro -Diethenolamine methoxycinnamate				Primary use as stabilizer and UV filter for hair care products. USA- NONGRASE- FDA listed as 'reserved'
	Aminobenzoic acid^ Other Names: **-PABA*** -Para-aminobenzoic acid -Pabagel -Pabalate Other forms: -Ethyl dihydroxypropyl-PABA -Amerscreen P -Glyceryl-PABA	UVB		Absorbs UV and releases thermal energy	Allergic contact dermatitis; cross-reacts with sulfonamide allergens; clothing discoloration; Increased risk of cellular UV damage, ?photo-carcinogen, banned in Europe (5,13,19) USA-Non-GRASE, II

	-NIPA G.M.P.A. -4-aminobenzoic acid				
	PEG-25 PABA Other names: -Ethoxylated ethyl-4 -aminobenzoate	UVB	10% EU	Absorbs UV and releases thermal energy	EU; US- PCPC
	Trolamine salicylate^ Other Names: - **TEA salicylate*** -Triethanolamine salicylate	UVB	12% US, CA, AUS. 2.5% EU.	Absorbs UV and releases thermal energy	Odorless; skin absorption; salicylism risk AUS, EU; US- PCPC USA--NONGRASE II
	Digalloyl triolate				EU-banned USA- NON-GRASE FDA listed as 'reserved'
	Lawsone + Dihydroacetone				USA-FDA NON-GRASE 'reserved' Oxidation product of self-tanning agent with pigment from the henna plant (*Lawsonia inermis*).
	Red Petrolatum				USA-FDA NON-GRASE 'reserved' Older form of petroleum jelly, first used for military pilots as sunscreen, now used solely in veterinary medicine.
	Benzophenone-1 Other Names: -BP-1 -Uvinul 400 -2,4-dihydroxy	UVB	4% EU, AUS.	Absorbs UV and releases thermal energy, Used in nail polish	Linked to breast, ovarian and prostate CA; can cross placenta; endocrine disruption-potential (6,7)

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	benzophenone				
	Benzophenone-2 Other Names: -BP-2 -2,2',4,4'-tetrahydroxy benzophenone -Uvinul D-50	UVA1	10% EU, AUS.	Absorbs UV and releases thermal energy	
	Benzophenone-5 Other names: -BP-5 -Sulisobenzone sodium				
	Benzophenone-6 Other Names: -BP-6 -2,2'-dihydroxy-4,4'-dimethoxybenzophenone -Uvinul D-49				
	Benzophenone-7 Other names: -BP-7 -5-chloro-2-hydroxy benzophenone				
	Benzophenone-9 Other Names: -BP-9 -CAS3121-60-6 -Sodium dihydroxy, dimethoxy, disulfo benzophenone -sodium 2,2'-dihydroxy-4,4'-dimethoxybenzophenone-5,5'-disulfonate -Uvinul 3048 -Uvinul DS49		10% JP		JP
	Benzophenone-10				

	Other Names: -BP-10 -Mexenone -2-hydroxy, 4-methoxy-4'-methyl benzophenone				
	Benzophenone-11 Other Names: -BP-11 -mixture of benzophenone-2 and benzophenone-6)				
	Benzophenone-12 Other Names: -BP-12 -Uvinul 4408 -Octabenzone				used to protect plastics
	Hydroxybenzophenone -family of 1900+ UVFs	UVA			used as UV absorber in clear plastics and PVC pipe
	Bemotrizinol^ Other Names: -**Bis-ethyl-hexyloxyphenol methoxyphenyl triazine*** -bis-ethylmethyl triazine -BEMT -Tinosorb S -Anisotriazine -Escalol S -Parsol Shield -Tinosorb S Aqua	UVB UVA1 UVA2	10% EU, JP, AUS	Absorbs both UV and releases thermal energy	photostable; oil-soluble; minimal skin penetration AUS, EU, JP; US- PCPC only
	Bisoctrizole^ Other Names: -**Methylene bis-benzotriazolyl tetramethylbutyl-phenol*** -MBBT -Tinosorb M -Parsol Max -Tetramethylbutyl phenol	UVB UVA1 UVA2	10% EU, JP, AUS	Absorbs UV and releases thermal energy, also reflects and scatters UV	little photodegradation; dissolves poorly in both oil and water; minimally absorbed by skin; microfine particles similar to nanoparticles AUS, EU, JP; US- PCPC only

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	Tris-biphenyl triazine* Other Names: -TBT -TBPT -Tinsorb A2B	UVB UVA2	10% EU		
	Drometrizole trisiloxane* Other Names: -Mexoryl XL -DRT	UVA1 UVA2	10% CA, 15% EU, AUS	Absorbs UV and releases thermal energy	Photostable; oil-soluble; synergistic with terephthalylidene dicamphor sulfonic acid (TDSA, Mexoryl SX) EU, AUS, CA; US- PCPC only
	Diethylhexyl butamido triazone* Other Names: -Uvasorb HEB -DBT -Iscotrizinol	UVB UVA1 UVA2	10% EU, 5% JP	Absorbs UV and releases thermal energy	EU, JP; US- PCPC only
	Ethylhexyl triazone* Other Names: -Octyltriazone -Uvinul T 150 -EHT -OT	UVB UVA2	5% EU, AUS, 3% JP	Absorbs UV and releases thermal energy	Insoluble in water; water resistant AUS, EU, JP, US- PCPC only
	Bisdisulizole disodium^ Other Names: -Neo Heliopan AP -**Disodium phenyl dibenzimidazole tetrasulfonate*** -Bisimidazylate -DPDT	UVA1 UVA2	5% EU, AUS	Absorbs UV and releases thermal energy	Photostable; Water soluble; cosmetic photostabilizer AUS, EU; US - PCPC only
	Isoamyl p-methoxycinnamate* Other Names: -Amiloxate -IMC -Neo Heliopan E1000 -Isopentyl-4-methoxy cinnamate	UVB UVA2	10% EU, AUS.	Absorbs UV and releases thermal energy	AUS, EU; US- PCPC only

	Enzacamene^ Other Names: **-4-methylbenzylidene camphor*** -MBC -4-MBC -Parsol 5000 -Eusolex 6300	UVB UVA2	4% EU, AUS, CA.	Absorbs UV and releases thermal energy	Endocrine disruption-potential (6,7) AUS, EU, CA
	3-benzylidene camphor* Other Names: -3BC -1,7,7-trimethyl-3-(phenylmethylene) bicyclo [2.2.1]heptan-2-one	UVB			Endocrine disruption-potential (6,7) Banned EU; US- PCPC
	Benzylidene camphor sulfonic acid* Other Names: -BCSA -Benzenesulfonic acid -(3-benzylidene-7,7-dimethyl-2-oxo-1-bicyclo [2.2.1]heptanyl)methane sulfonic acid	UVB	6% EU, AUS, JP.	Absorbs UV and releases thermal energy	AUS, EU, JP; US- PCPC only
	Polyacrylamidomethyl benzylidene camphor* Other Names: -PBC	UVB		Absorbs UV and releases thermal energy	6% AUS, EU; US- PCPC only
	Camphor benzalkonium methosulfate* Other Names: -CBM -Mexoryl SO	UVB		Absorbs UV and releases thermal energy	EU; US- PCPC uncommon use
	Polysilicone-15* Other Names: -Dimethicodiethylbenzal	UVB UVA2	10% EU, JP, AUS.	Absorbs UV and releases thermal energy	AUS, EU, JP; US- PCPC only

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	malonate -Diethylbenzylidene malonate dimethicone -Diethylmalonylbenzyliden oxypropene dimethicone -Parsol SLX -PS15				
	Diethylamino hydroxybenzoyl hexyl benzoate* Other Names: -Uvinul A Plus -DHHB	UVA1 UVA2	10% EU, JP, AUS.	Absorbs UV and releases thermal energy	
	4-Isopropyl dibenzoyl methane -Eusolex 8020	UVA UVB			Can cause contact and photocontact dermatitis-withdrawn from market in 1990's (5,13,19)
Misc. Filters	-Diphenyl carbomethoxy acetoxy naphthopyran -Diphenylmethyl piperazinylbenz-imidazole -di-t-butyl hydroxybenzylidene camphor				Surfactants, UV absorbers (16-17)
	Benzotriazole Family (e.g. octrizole) **Hydroxyphenyltriazine Family** **Oxanilide Family** **Silica Family** -Mesoporous (Ceria) silica nanoparticles and periodic mesoporous organosilica nanoparticles containing bridging benzene and ethane moieties				industrial photostabilizers used in coatings and plastics (16-17)

	Etocrylen Other names: -Etocrilene -Uvinul N-35 -MAXGARD® DPA-2 -Ethyl 2-cyano-3,3-diphenyl acrylate				Used as UV absorber in nail polish. Causes skin, eye, and respiratory irritation.
	Salicylates- -Benzyl salicylate (clove oil) -Glycol salicylate -Methyl salicylate (wintergreen oil) -Isopropylbenzyl salicylate -Tridecyl salicylate -Isodecyl salicylate -Butyloctyl salicylate -Myristyl salicylate -Ethylhexyl salicylate -Magnesium salicylate -Calcium salicylate -Potassium salicylate -Hexyldodecyl salicylate -MEA salicylate -C12-15 alkyl salicylate -Isocetyl salicylate				Used in cosmetics as fragrance additive or UV (5,13,16-19) absorber/stabilizers -common contact allergens -hair conditioners, hair dyes, anti-static agents (PABA derivatives)
	Cinnamates (cinnamon oil extracts) -Deamthoxycinnamate -Ethyl diisopropyl cinnamate -Glyceryl ethylhexanoate dimethoxycinnamate -Isopropylmethoxy cinnamate -Potassium methoxycinnamate				Used in cosmetics as fragrance additive or UV (5,13,16-19) absorber/stabilizers
	PABA derivatives -Dimethyl PABA ethyl cetearyl dimomium tosylate -Ethyl dihydroxypropyl PABA -n-ethyl-3-nitro PABA -tri-PABA pantenol-roxadminate				Used in cosmetics as UV (5,13,16-19) absorber/stabilizers

Sources: BASF Sunscreen Simulator- https://www.sunscreensimulator.basf.com/Sunscreen_Simulator/login/register, The Skin Cancer Foundation https://www.skincancer.org/skin-cancer-prevention/sun-protection/sunscreen/, in part from the FDA Fact Sheet on sunscreen issued in February of 2019 and from Federal Register FDA Proposed Rule February 2019 https://www.fda.gov/news-events/press-announcements/fda-advances-new-proposed-regulation-make-sure-sunscreens-are-safe-and-effective.

Legend:GRASE = generally recognized as safe and effective. *INCI Name = International Nomenclature for Cosmetic Ingredients. ^USAN Name = United States Adopted Name, PCPC only = Personal Care Products and Cosmetics use this UV absorber but not in sunscreen products. UVA1: 340–400 nm, UVA2: 320–340 nm, UVB: 290–320 nm

Legend:GRASE = generally recognized as safe and effective. *INCI Name = International Nomenclature for Cosmetic Ingredients. ^USAN Name = United States Adopted Name, PCPC only = Personal Care Products and Cosmetics use this UV absorber but not in sunscreen products. UVA1: 340-400nm, UVA2: 320-340nm, UVB: 290-320nm USA-FDA GRASE I, USA-FDA NONGRASE II not allowed to be used in sunscreen products, USA-FDA NONGRASE III not yet approved but currently allowed in existing sunscreen products, pending FDA review. Non-highlighted UV filters approved outside of USA, USA-FDA NONGRASE 'Reserved'

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Table 2
Broad-spectrum or UVA I filter.

		UV filter												
		BP1	BP2	BP3	BP4	BP8	EHMC/ OMC	OC	4- MBC	OD- PABA	B- MDM	3- BC	PBSA	HMS
Organism	**Class Citation #**													
Arthrobacter globiformis	Bacteria 27,28						***	NE			NE			
Isochrysis glabana	Algae 3,32 rank order			*3	*4		*1		*2					
Desmodesmus subspicatus	Algae 12			**			**		**			**		
Tetrahymena thermophila	Protozoan 6			***			NE	NE	***					
Chironomus riparius	Insect-midge 26							NE						
Pocillopora damicornis	Coral 29-33,35,37 rank order	1 or 2		2	3	1		**						
Seriatopora caliendrum	Coral 33,35,37	*				*	**	**						
Mytilus galloprovincialis	Mollusk-mussel 31,32 rank order			*2	*3		*1	**	*1	*				
Melanoides tuberculata	Mollusk 28						**							
Potamopyrgus antipodarum	Mollusk-mud snail 27,28						***	NE			NE			
Lumbriculus variegatus	Annelid- freshwater worm 27,28						NE	NE			NE			
Daphnia magna	Crustacean 12,13			**	***		**		**			***		
Siriella armata	Crustacean-carnivorous worm 32			*	*		*		*					
Gammarus fossarum	Crustacean 11											**		
Tigriopus japonicus	Crustacean 30								*					
Acartis tonsa	Crustacean 33	***												
Paracentrotus lividus	Echinoderm-sea urchin 31,32 rank order			*2	*3	***	*1	**	*1	*				
Danio rerio	Vertebrate/fish Zebrafish 14–16,27,2834,36,37		***	**	**		***	**			NE			
Pimephales promelas	Vertebrate/fishFathead minnow 13, 23, 25		**									**		
Oncorrhynchus mykiss	vertebrate/fish trout 8,23,24		x									***	*	
Wistar rat	Vertebrate/mammal 9,10,16–22		^T3, ^T4, lowTSH				***		**			***		
Human leiomyoma,	Human cell line 7	**X**	**X**	**X**	**X**	**X**								
Breast cancer cells	Human cell line 1, 2	**X**					**X**		***					**X**
FLG loss of function	Human cell line 4	**X,** **XXX**		**X,** **XXX**										
Hirschsprung's	3			**XX**										

Legend: 2,4-dihydroxybenzophenone (BP1), Benzophenone- 2 (BP2), Oxybenzone, Benzophenone- 3 (BP3), Sulisobenzone, Benzophenone- 4 (BP4), Dioxybenzone (BP8), 4-methylbenzylidene-camphor (4-MBC), Ethylhexyl dimethyl para-aminobenzoic acid (OD-PABA), Ethylhexylmethoxycinnamate (EHMC, also known as oxymethyl cinnamate [OMC] or octinoxate), homosalate (HMS), Octocrylene (OC), Butyl-methoxydibenzoylmethane (B-MDM, avobenzone), 3-benzylidene camphor (3-BC), 2-phenylbenzimidazole-5-sulfonic acid (PBSA), ^= increased, NE= no effect, *= toxicity <100ug/L, **=toxicity 100ug-1mg/L, ***=toxicity 1-100mg/L X= toxicity in vitro, not quantified, XX=clinical association, XXX=increased absorption in vivo.
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Marine: relating to bodies of saltwater such as oceans and seas.

Aquatic: relating to bodies of freshwater such as lakes, streams, rivers, ponds, etc.

Estuarine: relating to bodies of water formed where freshwater from rivers and streams flowinto the ocean, mixing with the seawater. Estuaries and the lands surrounding them are places of transition from land to sea, and from freshwater to saltwater.

Biota: living things in an ecosystem.

Legislative actions related to the environmental impacts of UV filters

In the FDA proposed rule of February 2019, under CFR 25.31 for Human Drugs and Biologics, Section XIV, (FDA in, US-FDA, 2019b,c), it is stated "this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required."

Nevertheless, many potentially harmful environmental effects of UVFs have been identified (Blitz and Norton, 2008) and led to the restriction of specific ingredients believed responsible for these changes (see Tables 1 and 2)). Hawaii, Key West and the United States Virgin Islands (USVI) have recently passed ordinances and/or legislation that prohibits the use of chemical sunscreens BP-3 and octinoxate (OMC), as correlation was found between these substances and coral reef bleaching (Bever, 2018; Fleshler, 2018; Schneider and Lim, 2019a, 2019b). There are similar bans passed or in discussion in Palau, Bonaire, Aruba, Mexico, Brazil and the EU. In June 2019, USVI joined Hawaii and Key West in banning specific sunscreen products that have been deemed harmful to coral reefs and marine life (Blum, 2019).

The Hawaii and Key West bans are set to start to take effect in January 2021 and prohibit the sale of sunscreens containing the UVFs BP-3 or OMC without a physician's prescription. The USVI began banning importation of sunscreens on December 31, 2019 with importing of sunscreens. On March 30, 2020, the sale or distribution of sunscreen products containing these UVFs was added to the ban. After January 1, 2021, transporting them into the USVI or possessing them will be completely banned, with first time violators facing potential fines of up to $1,000. The Virgin Islands National Park has stated that mineral sunscreen products with zinc oxide and titanium dioxide are the only sunscreens permitted for use by visitors and residents (Fajardo, 2019). The Hawaii ban was challenged by the AAD and the Hawaii Dermatological Society, citing that removing accessibility to broad spectrum sunscreen ingredients could create a public health concern.

These bans will lead to fewer products that can prevent skin cancers like melanoma, but may contribute to a public perception of sunscreens being unsafe products in general. Furthermore, these bans legislation does not emphasize that we are in need of newer, safer, and highly effective sunscreen ingredients as we reviewed in Part 1 of this review. (1 (Sabzevari N, Qiblawi S, Norton S, Fivenson D, 2020; AAD.ORG, 2019a, 2019b).

UV filter effects on coral reefs

BP-3, OMC, OC and sulisobenzone have been considered as threats to coral reefs around the world and an estimated 14,000 tons of sunscreen, some containing as much as 10% BP-3, are washed off swimmers into coral reef areas annually (Schneider and Lim, 2019a, 2019b; Mitchelmore et al., 2019; Du et al., 2017). The impact of sunscreen pollution is possibly being magnified by public health messaging on skin health and skin cancer prevention. However, it is important to note the magnitude of UVF effects is far below other factors endanging coral reefs, (e.g. rising ocean temperatures, acidification and loss of CO2 metabolism from plankton) which is expanded below in section 4 (Schneider and Lim, 2019a, 2019b; 2018).

Coral bleaching refers to the loss of the essential symbiotic unicellular algae called zooxanthellae (*Symbiodinium* spp), that live within the newly developing tips of living coral called coral polyps. This results in a loss of color on the outer margins and a whitening or bleaching effect. Coral reef ecosystems support many marine biota, so many other species can be affected by repeated bleaching events that lead to coral death.

Numerous studies have shown that some UVFs may contribute to and exacerbate widespread coral bleaching in marine ecosystems especially in coastal areas popular with recreational swimmers (Mitchelmore et al., 2019; Environmental Working Group, 2019a, 2019b; Corinaldesi et al., 2018; Wood, 2018; Danorvaro et al., 2008). These studies have included UVF concentration data from many beaches and urban ports as well as remote and unpopulated marine environments. Most studies suggest that UVFs are present in beach water and sand in steady state concentrations ranging from 10 ng/L to 1ug/L but changes occur in relation to degrees of human activity (Scheil et al., 2008; Downs et al., 2016; Mao et al., 2018; Mitchelmore et al., 2019). There is little data on the high flux of UVF washing off swimmers or divers at peak recreational times or sites. Recent studies along beaches of the French Riviera, Hawaii, as well as rivers and lakes near these tourist populations do support this as a toxicity risk (Kung et al., 2018; Mitchelmore et al., 2019; Tovar-Sanchez et al., 2013, 2019; Labille et al., 2020; Gou et al., 2020; Tang et al., 2018)

Several species of hard coral have been studied *in situ* using living corals in laboratories that keep cultures bathed in seawater circulated from adjacent beachfronts. Other studies use in vitro cultures of algae to test toxicity of UVF exposure directly (Sieratowicz et al., 2011; He et al., 2019a, 2019b). The studies have shown that toxicity is found in the ranges of 10-300ug/L depending on UVF and species (10-100x the reported concentrations from various locales worldwide (Labille et al., 2020; Mitchelmore et al., 2019; Downs et al., 2016; Du et al., 2017; Narla and Lim, 2020). Gross effects were noticed within 18–48 hours, followed by complete bleaching within 96 hours. Untreated controls showed no change.

There is also a suggestion that UVF promote the propagation of latent viral infections in the zooxanthellae which force them to enter a lytic cycle and then be expelled from the coral polyp (Danovaro and Corinaldesi, 2003; Downs et al., 2014; Paredes et al., 2013; Giraldo et al., 2017; Corinaldesi et al., 2018). The subsequent die-off of zooxanthellae creates stressful survival conditions for the coral. Corals can survive the stress of a transient bleaching event, but when corals are stressed they are subject to mortality. Recovery can begin once the stress is removed and algae repopulate the tender coral polyps, however, continued exposure can kill corals. Other studies have shown UVFs to have direct effects on ossification and DNA structure of larval coral (Fig. 1 NOAA Infographic- https://oceanservice.noaa.gov/news/sunscreen-corals.html,) (Ruszkiewicz et al., 2017; Downs et al., 2016, see references with Table 2). Approximately 60% of the world's coral ecosystems are currently threatened due to various causes, many of which are anthropogenic (i.e. related to human activity), including UVF contamination (Danorvaro et al., 2008). Thus coral bleaching may be a consequence of UVF pollution but the magnitude of their effects is not clear as many other factors can affect corals (see below). Caution with use of organic/chemical UVF containing sunscreens with preferences for inorganic/physical UVF products containing ZnO and/or TiO2 is still the best advice for patients, along with UV-protective clothing and avoidance of peak hours of sun exposure and follows the guidelines of the AAD.

Other causes of coral bleaching

Warming of ocean water temperatures (as well as sudden cooling) can also lead to coral bleaching, with numerous cycles of this phenomenon reported in the Pacific over the last century (Narla and Lim, 2020; Cheng et al., 2019; Slattery et al., 2019; Hughes et al., 2019; Great Barrier Reef Marine Park Authority [GBRMPA], 2016; Barkley et al., 2018). Thus global warming and changes in warmer ocean currents (el niño) can impact coral health (Eakin, 2016). Inorganic UVF (eg. ZnO, TiO_2) and organic UVF (eg. BP-3, octinoxate and OCTO) may also promote this effect in ocean water (Corinaldesi et al., 2018; Jovanovic and Guzman, 2014; Schneider and Lim, 2019a, 2019b). By absorbing or refracting UV rays, UVFs transfer thermal energy which creates localized increases in water temperatures, much the same as when applied to human skin (Lim, Thomas, Rigel Photoprotection in Photoaging, Marcel Dekker 2008). Blocking UV transmission through water can also indirectly damage coral by inhibiting photosynthesis within zooxanthellae (Danovaro et al., 2008).

While studies quantifying the magnitude of these UVF effects, it is generally accepted that they are smaller than other factors which are toxic to corals. Rising temperatures also due to higher CO2 in the atmosphere, acidification due to CO2 dissolving in oceans, toxic chemicals and microplastic pollution with resulting die-off of plankton are all major factors. According to Dryden, if our oceans were clean and had healthy plankton (which are one of most efficient metabolizers of CO2), they could absorb twice the CO2 they

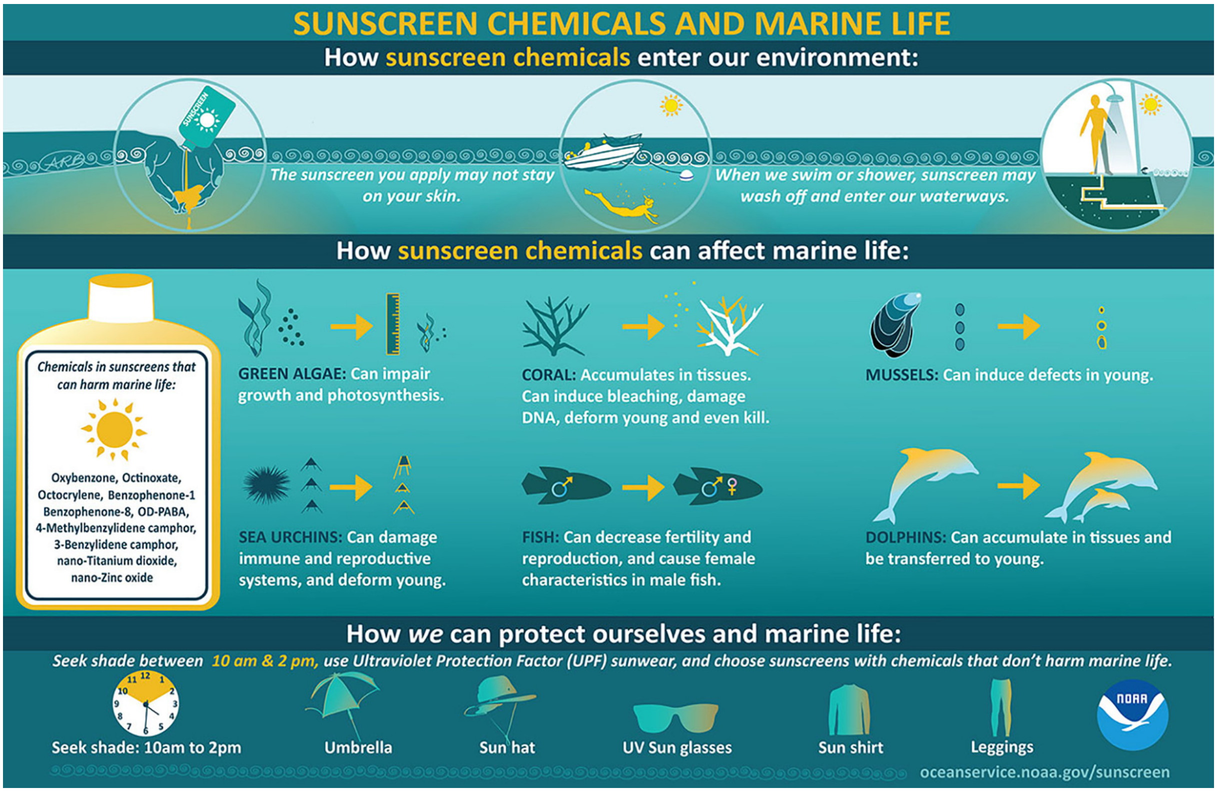

Fig. 1. NOAA's National Ocean Service Sunscreen Infographic. Published with permission of National Oceanic and Atmospheric Administration, National Ocean Service. *New NOAA infographic V2 here* Infographic: Sunscreen Chemicals and Marine Life.

do today – (12 to 24 billion (giga) tonnes/year (current human-related CO2 emissions are estimated 16–17 billion (giga) tonnes per year (Dryden, 2020). Thus UVF pollution is only one of many factors that lead to coral bleaching and premature death.

UVF pollution is ubiquitous

Human water sources are also affected by UV filters in the environment. Studies have shown that man-made organic UVFs, such as BP-3, OCTO, octinoxate, and ethylhexyl salicylate have been found in almost all water sources worldwide. Reviews by DiNardo and Downs (2016, 2017), Schneider and Lim (2018) and Narla and Lim (2020), note that wastewater treatment plants (WWTP) are not effective at removing these compounds due to their innate chemical properties (low water solubility, high lipophilicity, and high organic carbon–water coefficient). Ozonation is a common method of disinfection in WWTPs and has been shown to not reduce toxicity of BP-3, OMC and OC (Hopkins et al., 2017). WWTP influents have been shown to have BP-3 concentrations > 10 ug/L in some locales (Kim and Choi, 2014; Wu et al., 2018). The organic filters are found in higher concentrations in urban areas, and tend to fluctuate based on the season, density of near shore beach activity and with currents (Balmer et al., 2005; Ekeghere et al., 2016; Tovar-Sanchez et al., 2019).

Studies in marine and aquatic locations with higher density of human activity (see section 3) have also drawn attention to the possibility that UVFs can persist for a long time in water and sediments, and that tides and currents might carry them great distances to previously pristine areas (Balmer et al., 2005; Emnet et al., 2014; Tang et al., 2018). UVFs were identified in the sewage of two large Antarctic research stations, McMurdo Station and Scott Base, and the same compounds were also identified in the surrounding seawater up to 25 km away (Emnet et al., 2014). The presence of these UVFs is particularly concerning in the Antarctic because the environment factors (long periods of darkness, presence of sea ice, and cold temperatures) slow down microbial and photo-degradation of these compounds as well as increasing ocean temperatures that speed ice melting (Downs et al., 2016; Blitz and Norton, 2008; Emnet et al., 2014).

In addition to natural water sources, organic UVFs have also been found in chlorinated water sources like swimming pools and WWTP discharges. In vitro studies with human diploid fibroblast cultures have shown that chlorinated BP-3, OMC, BP-3 and avobenzone lead to a higher rate of cell death compared to non-chlorinated controls in vitro (Manasfi et al., 2017; Sherwood et al., 2012). It is unknown what impact these chlorinated byproducts have on human health and further studies are necessary (see Table 2) (Schneider and Lim, 2019a, 2019b).

UV filters from industrial use as protectants against photodegradation and from other PCPCuses (makeup, nailpolish, shampoo, conditioners, etc.) also make their way through WWTP and rainwater runoff into our waterways and add to the burden of UVF pollution as well (Hahladakisa et al., 2018).

UVF effects on aquatic and marine organisms

In late 2019 and early 2020 we performed a series of literature searches using NIH databases (eg, PubMed and Medline), EPA databases and Google Scholar using the terms UV filter, sunscreen, toxicity and aquatic life. These resulted in studies on 20 different species including corals (He et al., 2019a, 2019b), planktonic crustaceans (e.g. Sieratowicz et al., 2011), amphipod crustaceans (e.g. Scheil et al., 2007), mollusks (e.g. Kaiser et al., 2012), algae (e.g. Paredes et al., 2014), bacteria (e.g. Gao et al., 2013), sea urchins (e.g. Giraldo et al., 2017), zebrafish (e.g Fong et al., 2016), fathead minnows (e.g. Christen et al., 2011), and rainbow trout (e.g.

Grabicova et al., 2013). Most toxicity studies reported UVF effects in the range of 100 ug/l to5 mg/l concentrations, with most of the published UVF concentrations in high density beach or metropolitan areas being in the 10–1000 ng/l range. Some locales have reports of 10–100 ug/l concentrations of some UVFs (Balmer et al., 2005; Ekpeghere et al., 2016; Langford et al., 2015; Gou et al., 2020; Tang et al., 2018; Kung et al., 2018; Kusk et al., 2011). The organisms and relative toxicities of UV filters are summarized in Table 2 (along with more extensive references), highlighting where specific UVFs and aquatic or marine biota overlap on this threshold for environmentally relevant toxicity (10–100 ug/l). This table of specific organisms and the reported UVF effects highlights the diversity of environmental, metabolic and toxic effects reported across human cell lines, other mammals, fish, coral, mollusks, algae and bacteria.

Laboratory studies have also shown that there are some pronounced effects of UV filters in fish (Kunz et al., 2006b; Fent et al., 2008). In zebra fish, octocrylene alters the development of the brain and liver (Fong et al., 2016). In Japanese rice fish, high levels of BP-3 in a laboratory setting led to decreased egg production, significantly fewer hatchings, as well as the induction of vitellogenin protein, a precursor of the egg yolk only found in females, in male fish (Schneider and Lim, 2019a, 2019b; Wang et al., 2016). Species vary considerably as Chen et al. (2018) have shown no effects of BP-3 in the false clown anemonefish which inhabits many coral reefs, as well as in Siamese fighting fish (Chen et al., 2016).

As mentioned earlier, these are steady state findings and do not take into account the potentially higher levels locally seen near wastewater discharge or when a group of divers all jump into a prime reef sightseeing location and all that freshly applied sunscreen begins to wash off (Blitz and Norton, 2008; Mitchelmore et al., 2019; Matta et al., 2019; Bhatia and Friedman, 2019; Downs et al., 2016; Akhiyat and Harken, 2019; Tingley, 2019; Wang and Lim, 2019).

Taken together, UVF pollution appears to have relevant in vitro and in vivo effects on marine biota but the long term implications of these effects are still unknown. Concentrations of these agents range from 10-1000x fold lower in local waters compared to that of the amount associated with biologic effects (Table 2). The reader is advised to follow local regulations when going to bodies of water for recreation and preferentially use TiO_2 or ZnO sunscreen products, wear UV-protective clothing, and/or avoid peak hours of exposure whenever possible to mitigate the potential effects of organic/chemical UVFs on local biota.

Human health impact of UV filter exposure

Historically, studies on the environmental effects of man-made chemicals have attempted to assess the disruption of normal endocrine pathways in a variety of species (NIH (US), 2020; EPA (US), 2010a, 2010b). In 2001, the first articles to suggest that UVFs can disrupt endocrine pathways created an immediate concern among European environmental scientists and the European Union's Commission for Public Health (Europa) asked its Scientific Committee on Cosmetic Products and Non-Food Products for further evaluation (Europa, 2001; Schlumpf et al., 2001; Schlumpf and Lichtensteiger, 2001; Nash, 2006). In vivo studies in humans, rats, frogs, fish and worms, as well as in vitro studies suggest that many commonly used organic UVFs have endocrine-disrupting properties, however these studies vary widely in dosage and exposure to specific UVFs (Janjua et al., 2004; Schneider et al., 2005; Schlumpf et al., 2001, 2004; Morohoshi et al., 2005; Carou et al., 2008, 2009; Fent et al., 2008; Kunz et al., 2006a, 2006b; Weisbrod et al., 2017; Klammer et al., 2007; Carbone et al., 2010; Szwarcfarb et al., 2008; Holbech et al., 2002; Wang et al., 2011).

Endocrine disruption has been associated with several organic UVFs (Heneweer et al., 2005; Schlumpf et al., 2001; Coronado et al., 2008; Krause et al., 2012; Broniowska et al., 2018; Krzyzanowska et al., 2018) (see Table 2). BP-3 has also been reported to have systemic effects on sex and thyroid hormone pathways in animal models (Schreurs et al., 2002; Krause et al., 2012; Broniowska et al., 2018; Akhiyat and Harken, 2019). OMC has been associated with lower levels of thyroid hormone (T4) due to its ability to inhibit 5′-deiodinase (Ma et al., 2003; Janjua et al., 2007; Krause et al., 2012; Broniowska et al., 2018). This enzyme is responsible for converting the inactive form of thyroid hormone (T4) to the active triiodothyronine (T3). BP-3, 4-MBC, and OMC have also been associated with minor changes in testosterone, estradiol, and inhibin B in male patients, decreased sperm counts, and delayed puberty (Joensen et al., 2017; Mueller et al., 2003; Schlumpf et al., 2008). None of these human studies have yet to show any real world human biologic consequences.

BP-3 can be absorbed at a rate of 1% to 9% with topical application in some models (Klimova et al., 2015; Environmental Working Group, 2019a, 2019b). Recent single application (2 mg/m^2 to 75% of body surface area) and maximal use application studies (TEA testing in 2011 Final Rule) (75% of body surface area, four times daily) result in plasma and stratum corneum levels 10–2000 times the FDA guideline of 0.5 ng/ml for plasma levels of organic UV filters. Tissue levels were 10–1000 fold higher than plasma levels (Klimova et al., 2015; Janjua et al., 2004, 2007; Matta et al., 2019, 2020). The Matta et al., studies showed detectable plasma and skin levels of all UV filters beyond the 21d study duration. As with the endocrine studies in humans, no acute or chronic toxicity data has been reported from these absorption studies (Klimova et al., 2015; Matta et al., 2019, 2020). Earlier work by Walters et al., has suggested that some of the salicylate UVFs can increase the risk for salicylism through percutaneous absorption (Walters et al., 1978).

Individuals with compromised skin barrier function such as the filaggrin loss-of-function mutations (FLG null- see in 40+% of atopic dermatitis patients) may absorb UVFs more rapidly (Joensen et al., 2017). UVFs have been found in breast milk (Schlumpf et al., 2008, 2001), placental tissues (Kim and Choi, 2014) and is detected in nearly every American's urine (Olson, 2006; Dinardo and Downs, 2018; Environmental Working Group, 2019a, 2019b). Exposure to BP-3 during pregnancy has been reported to be associated with an increased incidence of Hirschprung's disease, a neonatal intestinal dysfunction (Huo et al., 2016; Dinardo and Downs, 2019). The pathogenesis is likely related to the failure of neural crest cells to migrate to the distal hindgut during fetal organogenesis, specifically during weeks 5 to 12. Other studies suggest possible correlations with uterine leiomyoma formation and increased mobility of breast and lung cancer cells (Alamer and Darbre, 2018; Pollack et al., 2015; Phiboonchaiyanan et al., 2017; Wang et al., 2018) (see Table 2).

The UVFs (especially BP-3, OC, amiloxate, avobenzone and PABA) have been reported to cause various forms of irritant dermatitis as well as allergic contact and/or photo-allergens. According to a study by the European Scientific Committee on Consumer Safety, out of 6378 patients, 159 tested positive on photo patch tests for BP-3 between 1981 and 2003 (Lim, Thomas, Rigel Photoprotection in Photoaging, Marcel Dekker, 2004, DiNardo and Downs, 2019). The spectrum of allergic reactions to UVF has been extensively reviewed elsewhere and will not be reviewed here (Schauder and Ippen, 1997; Heurung et al., 2014).

Similar to effects on aquatic and marine biota, humans can be exposed to UVF from WWTP and other industrial and cosmetic sources as well as from sunscreens (Schneider and Lim, 2019a, 2019b; Matta et al., 2019, 2020; daSilva et al., 2015; Balmer et al., 2005; Brausch and Rand, 2011; Mitchelmore et al., 2019). As mentioned earlier, in vivo studies in which subjects ingest or undergo subcutaneous injection with UVFs found evidence of broad endocrine disruption biochemically but without any lasting effects (Schlumpf et al., 2004, 2001; Bolt et al., 2001).

Public health agencies including the EU's Commission for Public Health (Europa - Hansen and Baun 2012), the NIH (US, 2020), EPA (US) (2010a); EPA (US) (2010b) and FDA (US - Matta et al., 2020) have all concluded that current organic UVFs do not pose short or long-term endocrinologic risks to human health. These regulatory bodies have not been able to effectively address long-term effects on humans or the environment from sustained systemic exposure to UVFs and with their prolonged existence in the environment (see below bioaccumulation and biomagnification), low level exposures may continue for much of a human's lifetime.

Narla and Lim (2020) nicely summarize these potential human biological effects, pointing out that UVF-induced disruptions in thyroid and sex hormones in experimental animals were reversible. In humans, similar dose-dependent endocrinopathies would require 30–250 years of daily use under real world use conditions (Ma et al., 2003; Heneweer et al., 2005; Schlumpf et al., 2001; Coronado et al., 2008; Janjua et al., 2007).

Thus we agree with the AAD still strongly supporting the use of both organic and inorganic UVF as part of their 'Practice Safe Sun' initiatives, as reviewed in part 1 of this review.

UV filter effects on the marine food chain and bioaccumulation

Organic/lipophilic substances cross cell membranes easily and are therefore more likely to be biologically active and capable of altering physiologic processes (Emnet et al., 2014). Many organic UVFs are also lipophilic and have been found to accumulate in the fat of many freshwater and marine species, making them theoretically capable ofbioaccumulation up the food chain. Bioaccumulation in human adipose tissue has been well documented with freshwater fish consumption in areas including the Great Lakes with mercury, DDT, polychlorinated biphenyls (PCBs) (EPA-US) 2017). Organic UVFs have been shown to follow similar metabolic pathways, thus when people eat those fish, the lipophilic compounds are further concentrated in human adipose tissue (Balmer et al., 2005; Langford et al., 2015; Saunders et al., 2019).

Trace amounts of UV filters, mostly 4-MBC, were found in fish species including: perch, white fish, and roach in lakes in Switzerland (Balmer et al., 2005; Buser et al., 2006). Surveys of Swiss rivers detected hormonally active UVFs in all fauna samples (mussels, several fish species, and cormorants). The concentrations of UVFs in the biota's tissues increased as one ascended trophic levels of the aquatic food web, suggesting biomagnification of these compounds (Fent et al., 2010a). In Norway, cod liver specimens contained organic UV filters, most notably octocrylene (found in 80% of specimens) and BP-3 (found in 50% of specimens). In Spain, similar UV filters were found in fish species including: white fish, rainbow trout, barb, perch, chub, and mussels (Blitz and Norton, 2008; Schneider and Lim, 2019a, 2019b; Narla and Lim, 2020; Saunders et al., 2020). Similar findings have also been seen in aquatic biota in the Pearl River Estuarine of the South China Sea (Peng et al., 2017).

Laboratory studies have also shown that there to be variability between species of UVF absorptioned in (Kunz et al., 2006b; Fent et al., 2008). In zebra fish, OC alters the development of the brain and liver (Fong et al., 2016). In Japanese rice fish, high levels of BP-3 in a laboratory setting led to decreased egg production, significantly fewer hatchings, as well as the induction of vitellogenin protein, a precursor of the egg yolk only found in females, in male fish (Schneider and Lim, 2019a, 2019b; Wang et al., 2016). Many of these toxicology studies are summarized in Table 2.

Bioaccumulation of UVF in marine mammals was first reported by Gago-Ferrero et al. (2013) in a Brazilian coastal study. These authors screened liver tissue samples, from dead LaPlata dolphins (*Pontoporia blainvillei*) that had been beached or accidentally caught, for UV filters. OC was found in 21 of 56 specimens at concentrations between 89 and 782 ng/g lipid and mirrored the local levels found in biota consumed by these dolphins (Gago-Ferrero et al., 2013). Marine UVF bioaccummulation has also been shown in vivo over a 10 year span in mollusks from the Chinese Bohai Sea (Liao and Kannan, 2019), in Japan's Ariake Sea of invertebrates, hammerhead sharks and coastal birds (Nakata et al., 2009).

Thus long term studies of these marine biosystems should provide more meaningful data to guide future human use recommendations as the bioaccumulation of UVF up the food chain is now well established.

Human bioaccumulation

These findings imply that humans with a mainly seafood-based diet may be at risk for bioaccumulating UVFs, but there limited long term studies compared to those for PCBs or mercury as mentioned above (Gago-Ferrero et al., 2012). During a 2003–4 NHANES survey, Calafat et al. (2008) detected BP-3 in 96.8% of urine samples from 2517 US adults. The mean level was 22.9 μg/L, varying from 0.4 μg/L to 21,700 μg/L and a subset of 30 volunteers with no documented exposure to BP-3 had it detected in 90% of urine samples. Schlumpf et al. (2008) reported the results of a 2004–2006 Swiss study on BP-3, 4-MBC, OMC, OC, and other common UVFs in the breastmilk of 34 women. 27 women reported current use of some type of UVF-containing cosmetic product. UVFs were detected in 26 breast milk samples, with a strong correlation found between exposure to a specific UVF and its presence in the individual's milk sample. These findings reflect the widespread presence of BP-3 in PPCPs (various cosmetics and sunscreens) as well as possible consequences of indirect exposure to BP-3 through the environment (as mentioned above) (EPA (US), 2005). As mentioned above, there are some correlations also reported for UVFs in relationship to uterine leiomyoma (Pollack et al., 2015) and on the motility of breast and lung cancer cell lines (Alamer et al., 2018), making the potential for bioaccumulation effects more poignant for the average woman's diet.

Thus human bioaccumulation remains unproven and an area that the FDA could encourage further research, especially long term studies. Sunscreen recommendations should not be altered at this time, but these findings should give us pause and require further study. Women in particular should carefully weigh the risks and benefits of these agents in light of these data, and consider use of physical blockers, UV protective clothing, and sun avoidance when possible, especially during pregnancy.

Nanoparticle UV filters

The use of nanotechnology has become commonplace in a wide array of chemical and biological products and processes. Nanoparticles, named for sizes in the nanometer range (one-billionth of a meter), are chemically identical to the conventional forms. However, the small size of nanoparticles confers increased photoelectric reactivity due to the relatively greater surface area per unit of mass (EPA-US, 2010). This technology employs the use of particles on the microscopic or atomic scale to improve the performance of hundreds of consumer products, ranging from energy drinks, protective clothing, sports equipment, cosmetics, storage containers, pharmaceuticals, and sunscreens.

Although TiO_2 and ZnO have long been used as physical blockers in sunscreens, nanoparticulate versions are relatively new and have become popular as they appear 'relatively' transparent on the skin compared to older formulations with their telltale thick, pasty white appearance (EPA-US, 2010, Schlossman et al., 2015). Nanoparticles (especially nano-TiO_2) are often coated with compounds to prevent or reduce photoelectric reactions. Although the ecotoxicological effects of nanoparticles on marine and aquatic organisms have not been studied extensively, scientists caution that these particles may have adverse biological and environmental effects at concentrations as low as ug/L, the equivalent of a few drops of liquid in an Olympic-sized swimming pool (Gruden and Mileyeva-Biebescheimer, 2009; Schlossman et al., 2006).

We mentioned earlier that inorganic UVFs can block UV rays from coral algae and inhibit photosynthesis and may add local increases in water temperatures. Nanoparticle ZnO and TiO_2 should be assumed to do the same but data is less robust. Nano-TiO_2 was shown to affect algae by Jovanovic and Guzman (2014), and nano-ZnO was more toxic to algae than ZnO (Narla and Lim, 2020; Miller et al., 2012). Both nano-TiO_2 and nano-ZnO can aggregate on organism's surfaces, where they can be toxic even without entering the cells (Corinaldesi et al., 2018).

Federici et al. (2007) observed severe damage to gills of trout from environmental exposure to TiO_2, and, dietary contamination with nano-TiO_2 is toxic in some species of fish (Ramsden et al., 2009, 2013; Chen et al., 2011; Fouqueray et al., 2013). While some aspects of nanoparticle ecotoxicity are beginning to be understood, the degradable nanomaterial coating these particles has been studied very little, both release of these agents in vivo and unmasking of the free radical oxygen on the surface of nanoparticles are potentially causes of damage to biota (Fouqueray et al., 2013; Handy et al., 2008).

Human use of nano-ZnO and nano-TiO_2 make the application and appearance of these sunscreen products more cosmetically appealing (see part 1 of these reviews, Narla and Lim, 2020). Some studies indicate that large doses of these nanoparticles can harm human cells and organs (mainly when inhaled), but no evidence has been published that enough nano-ZnO or nano-TiO2 can be absorbed percutaneously and cause systemic effects. Variations in particle size and whether there is a surface coating of the nanoparticles (mainly TiO_2 using silica, magnesium or aluminum (Lewicka et al., 2013; Grande and Tucci, 2016) in sunscreen products to neutralize free radical oxygen moieties) remain variables in need of further toxicology research (Schneider and Lim, 2018; Schilling et al., 2010). Inhaled nanoparticles are difficult for the lungs to clear, and can be transferred to the bloodstream and may be pulmonary carcinogens. Nanoparticles in the bloodstream can cause organ damage through oxidative stress and/or activation of proinflammatory pathways (Grande and Tucci, 2016; Nohynek and Dufour, 2012; Hansen and Baun, 2012; Europa, 2007; Ze et al., 2014). Based on these findings, the International Agency for Research on Carcinogens has classified nano-TiO2 as a possible carcinogen when inhaled in large doses.

There is also some evidence that nanoparticles have environmental effects, including coral bleaching (inhibition of photosynthesis) and adding to ocean temperatures by transmission of heat energy when blocking UV (similar to other UVFs}. Marine and or aquatic biota that ingest nanoparticles may be at increased risks for carcinogenesis and genotoxicity over time (bioaccumulation) In support of this are reports showing both nano-ZnO and nano-TiO2can have cumulative neurotoxicity to microglia (Kwon et al., 2014; Rihane et al., 2016; Schneider and Lim, 2018; Corinaldesi et al., 2018). Bioaccummulation studies with nano-TiO2 have shown that algae bathed in nano-TiO2-laden growth medium, then fed to freshwater fleas (Daphnia magna), and finally feeding the fleas to zebrafish resulted in no nanoTiO2 accumulation (Chen et al., 2011; Fouqueray et al., 2013; Zucchi et al., 2011).

Thus, nanoparticles may have far more complex biologic effects than the older forms of ZnO and TiO2, and caution is advisable when counselling patients, especially with spray sunscreen products which have higher risk for inhalation.

Expanding options for UV filters in the US market and beyond

The global sunscreen industry is estimated to be worth in excess of $24B USD by 2024 with approximately one third of that being in the North American market. (https://www.transparencymarketresearch.com/sun-care-market.html). As part of the 2019 Final Rule, the FDA is encouraging manufacturers to accelerate testing and applications for approval to GRASE status or through the NDA process (FDA-US 2019). High throughput testing has been proposed to help with some of the toxicity studies needed for this process (Erickson, 2018; Matta et al., 2020; Wang and Lim, 2011).

In such a competitive market, the testing and approval processes may seem a deterrent to new product development. Gradual decreases in successive batches of the concentrations of UVF that have the most evidence of toxic effects, might lead to competitive edge for environmentally conscious manufacturers. Partnering with EU and Australian manufacturers may also help bring more eco-friendly products to the US market. We encourage the FDA to do whatever it can to help make it financially viable for manufacturers to perform the necessary testing, as well as to bring other agents (as in Europe) into the US market are part of the NDA process (a well-traveled path for pharmaceuticals entering the US).

Conclusion – call to action (opinions of the authors)

The use of sunscreen has been shown to reduce the incidence of squamous cell carcinoma by 40% and melanoma by 50% (AAD.ORG, 2019a, 2019b; Green et al., 2011). New legislation in Hawaii, the USVI, and other locations have begun to ban the use of certain organic UVFs in PPCPs. Currently the evolution of regulatory guidelines about sunscreen products is not keeping pace with the growing bodies of research on toxicities we have reviewed. Consequently, there is concern amongst dermatologists that a growing skepticism about certain sunscreens may lead to an overall decrease in their use (Schwen, 2005). To prevent this, and provide safe eco-friendly product options, it is imperative that more research on both the long term human effects and the cumulative effects on our environment, be done before deeming certain organic and/or inorganic UVFs as safe (GRASE) or unsafe for use. The AAD and FDA still recommend using sunscreen to protect the skin from UV to prevent skin cancer and photoaging. We hope that there can be better collaboration between regulatory, industry and advocacy groups to move the process forward to best provide a portfolio of safe, effective options to help protect our patients from UV damage and skin cancer, as well as protect our environment.

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Study Approval

NA.

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