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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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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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 (TiO₂) 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.”

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/cdrh/cfdocs/cfotc/otcTopic3/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.

| PHYSICAL FILTERS  | Agent                        | Range         | Max %  | Function                        | Approvals and Complications of Use                                      |
|-------------------|-------------------------------|---------------|--------|---------------------------------|--------------------------------------------------------------------------|
| (Inorganic Sunscreen Filters) | Zinc Oxide (ZnO)* | UBV UVA1 UVA2 | 25% US, JP, AUS- No limit | Reflects UVA and UVB | Photostable; “white, Kabuki-like cast” AUS, EU, JP, USA- <GRASE>         |
|                    | Other Names: -Color index pigment white 4 -Color index 77947 -Zinc gelatin -Nogenol |               |        |                                 |                                                                          |
| Titanium Dioxide (TiO2)** | UBV UVA2 | 25% US, JP, AUS- No limit | Reflects UVA and UVB | Photostable; “white, Kabuki-like cast” AUS, EU, JP, USA- <GRASE>         |
| (Inorganic Sunscreen Filters) | Other Names: -Color index pigment white 6 -Color index 77891 -Titanium peroxide |               |        |                                 |                                                                          |
| CHEMICAL FILTERS  | Ecamsule™ | 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 FDA 2006. |
| (Organic Sunscreen Filters) | Other Names: -Terephthalidyldenedicamphor sulfonic acid -TDSA -Mexoryl SX® |               |        |                                 |                                                                          |
|                   | Avobenzone* | 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             |
|                   | Other Names: -Butyl methoxydibenzoylmethane -1-(4-methoxyphenyl)- 3-(4-tet-butyl) propane-1,3-dione -Parsol 1789 -Eusolex 9020 -Escalol 517™ (Ashland) -BMBM -B-MDM -Neo Helioplan357 -Milestab1789 |               |        |                                 |                                                                          |

(continued on next page)
| Sunscreen | Sun-screen | UVB | UVA | Distribution | Bioactivity | Potential Dangers |
|-----------|------------|-----|-----|--------------|-------------|-------------------|
| Octinoxate | Ethylhexyl methoxycinnamate | 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 |  | 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 |  | 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 |
| Name                  | Type       | UVB | UVA2 | Percentage US, EU, JP | Action                                      | Comments                                                                 |
|-----------------------|------------|-----|------|------------------------|---------------------------------------------|---------------------------------------------------------------------------|
| Octisalate^           | UVB, UVA2  | 5%  | 10%  | US, AUS, EU, JP         | Absorbs UV and releases thermal energy       | Photodegradation; water-resistant; oil-soluble (10-12) AUS, EU, JP, USA-NONGRASE III |
| Homosalate^           | UVB, UVA2  | 15% | 10%  | US, AUS, 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**             | UVB        | 3%  | 6%   | US, AUS                | Absorbs UV and releases thermal energy       | Slightly yellow; insoluble in water; photo-allergen (5,13,19) AUS, USA-NONGRASE III |
| Padimate O^            | UVB        | 8%  | 10%  | US, AUS, EU, JP         | Absorbs UV and releases thermal energy       | Water-insoluble PABA derivative; AUS, EU, JP, USA-NONGRASE III            |
| Ensulizole^            | UVB, UVA2  | 4%  | 8%   | US, EU, JP              | Absorbs UV and releases thermal energy       | Photostable; AUS, EU, JP, USA-NONGRASE III                                   |
| Other Names:          |            |     |      |                         |                                             |                                                                           |
| Ethylhexyl salicylate*|            |     |      |                         |                                             |                                                                           |
| -Octyl salicylate      |            |     |      |                         |                                             |                                                                           |
| -EHS                   |            |     |      |                         |                                             |                                                                           |
| -Escalol 587           |            |     |      |                         |                                             |                                                                           |
| Homomethyl salicylate* |            |     |      |                         |                                             |                                                                           |
| -HMS                   |            |     |      |                         |                                             |                                                                           |
| -Eusolex HMS           |            |     |      |                         |                                             |                                                                           |
| -Heliofan              |            |     |      |                         |                                             |                                                                           |
| Ethylhexyl dimethyl PABA* |         |     |      |                         |                                             |                                                                           |
| -OD-PABA               |            |     |      |                         |                                             |                                                                           |
| -Octydimethyl PABA     |            |     |      |                         |                                             |                                                                           |
| -EHDP                  |            |     |      |                         |                                             |                                                                           |
| -Escalol 507           |            |     |      |                         |                                             |                                                                           |
| -Sundown               |            |     |      |                         |                                             |                                                                           |
| Phenyl benzimiazole sulfonic acid* |     |     |      |                         |                                             |                                                                           |
| -Phenyl-sulfabenzimidazole |                  |     |      |                         |                                             |                                                                           |
| -Neo Heliofan Hydro    |            |     |      |                         |                                             |                                                                           |
| -PBSA                  |            |     |      |                         |                                             |                                                                           |
| -Eusolex 232           |            |     |      |                         |                                             |                                                                           |
| -Parsol HS             |            |     |      |                         |                                             |                                                                           |
| -Eusolex 6300          |            |     |      |                         |                                             |                                                                           |

(continued on next page)
| Chemical Name          | Type         | Usage      | Effect                        | Remarks                                      |
|------------------------|--------------|------------|-------------------------------|----------------------------------------------|
| Dioxybenzone^          | UVB          | 3% US, AUS.| Absorbs UV and releases thermal energy | Insoluble in water; AUS, USA- Nongrace III |
| Other Names:           |              |            |                               |                                               |
| - Benzophenone-8*      | UVA1, UVA2   | 5% US, AUS.| Absorbs UV and releases thermal energy | AUS, USA- Nongrace III                        |
| - BP-8                 |              |            |                               |                                               |
| - Spectra-sorb UV24    |              |            |                               |                                               |
| - Advastab 47          |              |            |                               |                                               |
| - Dioxibenzanum        |              |            |                               |                                               |
| Meradimate^            | UVA1, UVA2   | 5% US, AUS.| Absorbs UV and releases thermal energy |                                               |
| Other Names:           |              |            |                               |                                               |
| - Menthyl anthranilate |              |            |                               |                                               |
| - Sunarome UVA         |              |            |                               |                                               |
| Sulisobenzone^         | UVB, UVA2    | 5% EU, 10% US, JP, AUS. | Absorbs UV and releases thermal energy | Photostable; skin absorption (1-5) AUS, EU, JP, USA- Nongrace III |
| Other Names:           |              |            |                               |                                               |
| - Benzophenone-4*      |              |            |                               |                                               |
| - BP4                  |              |            |                               |                                               |
| - Uvinul MS40          |              |            |                               |                                               |
| - Escatal 577          |              |            |                               |                                               |
| - 2-hydroxy-4-methoxy benzophenone-5-sulfonic acid | | | | |
| - 3-benzoyl-4-hydroxy-6-methoxybenzene sulfonic acid | | | | |
| DEA-methoxycinnamate   |              |            |                               | Primary use as stabilizer and UV filter for hair care products. USA- Nongrace; FDA listed as 'reserved' |
| Other Names:           |              |            |                               |                                               |
| - Bernel Hydro         |              |            |                               |                                               |
| - Diethanolamine methoxycinnamate | | | | |
| Aminobenzoic acid^     | 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 |
| Other Names:           |              |            |                               |                                               |
| - PABA*                |              |            |                               |                                               |
| - Para-aminobenzoic acid |            |            |                               |                                               |
| - Pabagel              |              |            |                               |                                               |
| - Pabalate             |              |            |                               |                                               |
| Other forms:           |              |            |                               |                                               |
| - Ethyl dihydroxypropyl-PABA | | | | |
| - Amerscreen P         |              |            |                               |                                               |
| - Glyceryl-PABA        |              |            |                               |                                               |
| Ingredient                  | Spectrum | Concentration | Effect                                      | Notes |
|----------------------------|----------|---------------|---------------------------------------------|-------|
| -NIPA G.M.P.A.              |          |               |                                             |       |
| 4-aminobenzoic acid        |          |               |                                             |       |
| PEG-25 PABA                | UVB      | 10% EU        | Absorbs UV and releases thermal energy       | EU; US- PCPC |
| Other names:               |          |               |                                             |       |
| -Ethoxylated ethyl-4 -      |          |               |                                             |       |
| aminobenzoate              |          |               |                                             |       |
| Trolamine salicylate*      | UVB      | 12% US, CA, AUS. 2.5% EU. | Absorbs UV and releases thermal energy | Odorless; skin absorption; salicylamidation risk AUS, EU; US-PCPC USA-NONGRASE II |
| Other Names:               |          |               |                                             |       |
| -TEA salicylate*           |          |               |                                             |       |
| -Triethanolamine salicylate|          |               |                                             |       |
| Digalloyl triolate         |          |               | EU-banned | USA-FDA 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             | UVB      | 4% EU, AUS.   | Absorbs UV and releases thermal energy, Used in nail polish | USA-FDA NON-GRASE reserved |
| Benzophenone-1             |          |               | Linked to breast, ovarian and prostate CA; can cross placenta; endocrine disruption-potential (6,7) |       |
| Other Names:               |          |               |                                             |       |
| -BP-1                      |          |               |                                             |       |
| -Uvinul 400                |          |               |                                             |       |
| -2,4-dihydroxy             |          |               |                                             |       |

(continued on next page)
| Benzophenone-2  | UVA1   | 10% EU, AUS. | Absorbs UV and releases thermal energy |
|-----------------|--------|-------------|--------------------------------------|
| Other Names:    |        |             |                                      |
| -BP-2           |        |             |                                      |
| -2,2',4,4'-tetrahydroxy benzophenone |          |             |                                      |
| -Uvinul D-50    |        |             |                                      |

| 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  | 10% JP |             | JP                                   |
| 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    |        |             |                                      |

| 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
- Octabenzzone

**Hydroxybenzophenone**

*Family of 1900+ UVFs*

|  | UVA |
|---|-----|

**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 | 10% EU, JP, AUS |

**Bisoctrizole**

*Other Names:*
- Methylene bis-benzotriazolyl tetramethylbutylphenol
- MBBT
- Tinosorb M
- Parsol Max
- Tetramethylbutyl phenol

| UVB | UVA1 | UVA2 |
|-----|------|------|
| 10% EU, JP, AUS | 10% EU, JP, AUS |

- Absorbs UV and releases thermal energy
- Absorbs both 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
- Photostable; oil-soluble; minimal skin penetration

*Used as UV absorber in clear plastics and PVC pipe*

*Used to protect plastics*
| Name                                      | Formulation | Mode of Action                                                                 | Notes                                                                 |
|-------------------------------------------|-------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Tris-biphenyl triazine*                   | UVB UVA2    | 10% EU                                                                          |                                                                      |
| Other Names:                              |             |                                                                                  |                                                                      |
| - TBT                                     |             |                                                                                  |                                                                      |
| - TBP T                                  |             |                                                                                  |                                                                      |
| - Tinsorb A2B                             |             |                                                                                  |                                                                      |
| Drometrizole trisiloxane*                 | UVA1 UVA2   | 10% CA, 15% EU, AUS                                                             | Photostable; oil-soluble; synergistic with terephthalylidene dicamphor sulfonic acid (TDSA, Mexoryl SX) EU, AUS, CA; US- PCPC only |
| Other Names:                              |             |                                                                                  |                                                                      |
| - Mexoryl XL                              |             |                                                                                  |                                                                      |
| - DRT                                     |             |                                                                                  |                                                                      |
| Diethylhexyl butamido triazone*           | UBV UVA1 UVA2 | 10% EU, 5% JP                                                                   | EU, JP; US- PCPC only                                               |
| Other Names:                              |             |                                                                                  |                                                                      |
| - Uvasorb HEB                             |             |                                                                                  |                                                                      |
| - DBT                                     |             |                                                                                  |                                                                      |
| - Isocofrizinol                           |             |                                                                                  |                                                                      |
| Ethylhexyl triazone*                      | UBV UVA2    | 5% EU, AUS, 3% JP                                                               | Insoluble in water; water resistant AUS, EU, JP, US- PCPC only     |
| Other Names:                              |             |                                                                                  |                                                                      |
| - Octyl triazone                          |             |                                                                                  |                                                                      |
| - Uvinul T 150                            |             |                                                                                  |                                                                      |
| - EHT                                     |             |                                                                                  |                                                                      |
| - OT                                      |             |                                                                                  |                                                                      |
| Bisdisulizole disodium^                   | UVA1 UVA2   | 5% EU, AUS                                                                      | Photostable; Water soluble; cosmetic photostabilizer AUS, EU; US - PCPC only |
| Other Names:                              |             |                                                                                  |                                                                      |
| - Neo Heliolan AP                          |             |                                                                                  |                                                                      |
| - Disodium phenyl dibenzimidazole         |             |                                                                                  |                                                                      |
| tetrasulfonate*                           |             |                                                                                  |                                                                      |
| - Bisimidazylate                          |             |                                                                                  |                                                                      |
| - DPDT                                    |             |                                                                                  |                                                                      |
| Isoamyl p-methoxycinnamate*               | UBV UVA2    | 10% EU, AUS                                                                      | AUS, EU; US- PCPC only                                             |
| Other Names:                              |             |                                                                                  |                                                                      |
| - Amiloxate                               |             |                                                                                  |                                                                      |
| - IMC                                     |             |                                                                                  |                                                                      |
| - Neo Heliolan E1000                      |             |                                                                                  |                                                                      |
| - Isopentyl-4-methoxy cinnamate           |             |                                                                                  |                                                                      |
| Name                                                                 | Type    | EU, AUS, CA | Effect                                      | Notes                                      |
|----------------------------------------------------------------------|---------|-------------|---------------------------------------------|--------------------------------------------|
| Enzacamene^                                                          | UVB, UVA2| 4%          | Absorbs UV and releases thermal energy       | Endocrine disruption-potential (6,7) AUS, EU, CA |
| Other Names:                                                         |         |             |                                             |                                            |
| -4-methylbenzylidene camphor*                                        |         |             |                                             |                                            |
| -MBC                                                                 |         |             |                                             |                                            |
| -4-MBC                                                               |         |             |                                             |                                            |
| -Parsol 5000                                                         |         |             |                                             |                                            |
| -Eusolex 6300                                                        |         |             |                                             |                                            |
| 3-benzylidene camphor*                                               | UVB     | 6%          | Absorbs UV and releases thermal energy       | Endocrine disruption-potential (6,7) Banned EU; US- PCPC |
| Other Names:                                                         |         |             |                                             |                                            |
| -3BC                                                                  |         |             |                                             |                                            |
| -1,7,7-trimethyl-3-(phenylmethylene) bicyclo [2.2.1]heptan-2-one     |         |             |                                             |                                            |
| Benzylidene camphor sulfonic acid*                                   | UVB     | 6%          | Absorbs UV and releases thermal energy       | AUS, EU, JP; US- PCPC only                 |
| Other Names:                                                         |         |             |                                             |                                            |
| -BCSA                                                                 |         |             |                                             |                                            |
| -Benzenesulfonic acid                                                |         |             |                                             |                                            |
| -(3-benzylidene-7,7-dimethyl-2-oxo-1-bicyclo [2.2.1]heptanyl)methane sulfonic acid |         |             |                                             |                                            |
| Polyacrylamidomethyl benzylidene camphor*                            | UVB     | 6%          | Absorbs UV and releases thermal energy       | 6% AUS, EU; US- PCPC only                  |
| Other Names:                                                         |         |             |                                             |                                            |
| -PBC                                                                 |         |             |                                             |                                            |
| Camphor benzalkonium methosulfate*                                   | UVB     |             | Absorbs UV and releases thermal energy       | EU; US- PCPC uncommon use                  |
| Other Names:                                                         |         |             |                                             |                                            |
| -CBM                                                                  |         |             |                                             |                                            |
| -Mexoryl SO                                                          |         |             |                                             |                                            |
| Polysilicone-15*                                                     | UVB, UVA2| 10%         | Absorbs UV and releases thermal energy       | AUS, EU, JP; US- PCPC only                 |
| Other Names:                                                         |         |             |                                             |                                            |
| -Dimethicodiethylbenzal                                               |         |             |                                             |                                            |
| Material                                                                 | Filter | Concentration | Description                                      |
|-------------------------------------------------------------------------|--------|---------------|--------------------------------------------------|
| Diethylamino hydroxybenzoyl hexyl benzoate*                              | UVA1   | 10% EU, JP, AUS. | Absorbs UV and releases thermal energy            |
| **Other Names:**                                                        | UVA2   |               |                                                  |
| -Uvinul A Plus                                                          |        |               |                                                  |
| -DHHB                                                                  |        |               |                                                  |
| 4-Isopropyl dibenzoyl methane                                           | UVA    |               | Can cause contact and photocontact dermatitis-   |
| -Eusolex 8020                                                           | UVB    |               | withdrawn from market in 1990's                  |
| **Misc. Filters**                                                       |        |               |                                                  |
| -Diphenyl carbethoxy acetoxy naphthopyran                               |        |               | Surfactants, UV absorbers (16-17)                |
| -Diphenylmethyl piperazinylbenz-imidazole                               |        |               |                                                  |
| -di-t-butyl hydroxybenzylidene camphor                                    |        |               |                                                  |
| **Benzotriazole Family** (e.g. octizole)                                |        |               | industrial photostabilizers used in              |
| Hydroxyphenyltriazine Family                                            |        |               | coatings and plastics (16-17)                    |
| Oxanilide Family                                                        |        |               |                                                  |
| Silica Family                                                           |        |               |                                                  |
| -Mesoporous (Ceria) silica nanoparticles and periodic mesoporous        |        |               |                                                  |
| organosilica nanoparticles containing bridging benzene and              |        |               |                                                  |
| ethane moieties                                                         |        |               |                                                  |
| **Etocrylen**  
**Other names:**  
- Etocrline  
- 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 alky 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  
- Glycerol ethylhexanoate dimethoxy cinnamate  
- Isopropylmethoxy cinnamate  
- Potassium methoxy cinnamate |  | Used in cosmetics as fragrance additive or UV (5,13,16-19) absorber/stabilizers |
| **PABA derivatives**  
- Dimethyl PABA ethyl cetearyl dimonium tosylate  
- Ethyl dihydroxypropyl PABA  
- n-ethyl-3-nitro PABA  
- tri-PABA pантенол-рохадминате |  | 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.

PCPC only

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Table 2
Broad-spectrum or UVA I filter.

| Organism                          | Class Citation # | BP1 | BP2 | BP3 | BP4 | BP8 | EHM/OMC | OC | 4-MBC | OD-PABA | B-MDM | 3-BC | PBSA | HIMS |
|-----------------------------------|------------------|-----|-----|-----|-----|-----|---------|----|-------|----------|-------|------|------|------|
| Arthrobacter globiformis          | Bacteria 27,28    | *** | NE  | NE  |     |     |         |    |       |           |       |      |      |      |
| Isochrysis galabana               | Algae 33,26,27    |     |     |     |     |     |         |    |       |           |       |      |      |      |
| Desmodesmus subspicatus           | Algae 12          | **  | **  | **  |     |     |         |    |       |           |       |      |      |      |
| Tetrahymena thermophila           | Protozoan 6       | *** | NE  | NE  |     |     |         |    |       |           |       |      |      |      |
| Chironomus riparius               | Insect-midge 26    | NE  |     |     |     |     |         |    |       |           |       |      |      |      |
| Polypora damicornis               | Coral 29,33,35,37  | 1 or| 3  |     | 1   |     |         |    |       |           |       |      |      |      |
| Seriatopora calicardum            | Coral 33,35,37    | *   | *   | **  |     |     |         |    |       |           |       |      |      |      |
| Mytilus galloprovincialis          | Mollusk-mussel 31,32 | *   | *   |     |     |     |         |    |       |           |       |      |      |      |
| Melanoides tuberculata            | Mollusk 32        |     |     |     |     |     |         |    |       |           |       |      |      |      |
| Potamogetum antipodarum           | Mollusk-mud snail 27,28 | *** | NE  | NE  |     |     |         |    |       |           |       |      |      |      |
| Lumbricalis variegatus            | Annelid- freshwater worm 27,28 | NE  | NE  | NE  |     |     |         |    |       |           |       |      |      |      |
| Daphnia magna                     | Crustacean 12,13  | **  | *** | *** | ***  | ***  |         |    |       |           |       |      |      |      |
| Sirella armata                    | Crustacean-carnivorous worm 32 |     |     | **  | ***  |     |         |    |       |           |       |      |      |      |
| Gymnophorus fossarum              | Crustacean 11     | *   | *   | *   |     |     |         |    |       |           |       |      |      |      |
| Tigrirous japonicus               | Crustacean 30     | **  |     |     |     |     |         |    |       |           |       |      |      |      |
| Acartis tonsa                     | Crustacean 33     | *** |     |     |     |     |         |    |       |           |       |      |      |      |
| Paracentrotus dividus             | Echinoderm-sea urchin 31,32 | *   | *   | *** | **  | *   |         |    |       |           |       |      |      |      |
| Danio rerio                       | Vertebrate/fish 14–16,27,2834,36,37 | *** | *** | *** | ***  | ***  |         |    |       |           |       |      |      |      |
| Pimephales promelas               | Vertebrate/fish 13,23,25 | **  |     |     |     |     |         |    |       |           |       |      |      |      |
| Oncorhynchus mykiss               | Vertebrate/fish 4,23,24 | x    |     |     |     |     |         |    |       |           |       |      |      |      |
| Wistar rat                        | Vertebrate/mammal 9,10,16-22 | ^T3, | ^T4, | lowTSH | *** | ***  |         |    |       |           |       |      |      |      |
| Human leiomyoma,                  | Human cell line 7 | X   | X   | X   | X   |     |         |    |       |           |       |      |      |      |
| Breast cancer cells               | Human cell line 1,2 | X   | X   | X   | X   | ***  |         |    |       |           |       |      |      |      |
| FGt loss of function              | Human cell line 4 | X   | X   | X   | XXX | **   |         |    |       |           |       |      |      |      |
| Hirschsprung’s                    | 3                | X   |     |     |     |     |         |    |       |           |       |      |      |      |

Legend: 2,4-dihydroxybenzophenone (BP1), Benzophenone- 2 (BP2), Oxybenzone, Benzophenone- 3 (BP3), Sulisobenzone, Benzophenone- 4 (BP4), Dioxobenzene (BP8), 4-methylbenzylidene-camphor (4-MBC), Ethylhexyl dimethyl para-aminobenzoic acid (OD-PABA), Ethylhexylmethoxycinnamate (EHMC), also known as oxybenzyl cinnamate (OMC) or octinoxate, homosalate (HMS), Octocrylene (OC), Butyl-methoxydibenzoylmethane (B-MDM, avobenzone), 3-benzylidene camphor (3-BC), 2-phenylbenzimidazole-5-sulfonic acid (PBSA); ^星 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 flow into the ocean, mixing with the sea.
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, Qibliawi 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 endangering 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 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; Danovaro 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 1 ug/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) (Ruszkiwicz 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 (Danovaro 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, TiO2) 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
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, 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).

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 (e.g., 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. Christen et al., 2016), fathead minnows (e.g. Christen et al., 2011), and rainbow trout (e.g.
Most toxicity studies reported UVF effects in the range of 100 μg/l to 50 mg/l concentrations, with most of the published UVF concentrations in high density beach or metropoli-
tan areas being in the 10–100 ng/l range. Some locales have
reports of 10–100 μg/l concentrations of some UVFs (Balm-
er 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 sum-
marized in Table 2 (along with more extensive references), high-
lighting where specific UVFs and aquatic or marine biota overlap
on this threshold for environmentally relevant toxicity (10–100
μg/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 pron-
ceeded 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 produc-
tion, significantly fewer hatchings, as well as the induction of vitel-
genesis with uterine leiomyoma formation and increased mobility of
cancers to the distal hindgut during fetal organogenesis, specifi-
cally during weeks 5 to 12. Other studies suggest possible correla-
tions with uterine leiomyoma formation and increased mobility of
breast and lung cancer cells (Alamer and Darbre, 2018; Pollack
et al., 2015; Phiboonchaisan 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 der-
matitis as well as allergic contact and/or photo-allergens. Accord-
ing 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).

Individuals with compromised skin barrier function such as the
flaggins 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 intesti-
nal 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, specific-
ally during weeks 5 to 12. Other studies suggest possible correla-
tions with uterine leiomyoma formation and increased mobility of
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Similar to effects on aquatic and marine biota, humans can be
exposed to UVF from WWTF 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.

Thus we agree with the AAD still strongly supporting the use of both organic and inorganic UVFs 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 of bioaccumulation 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 absorption 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 blainvillii) 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 bioaccumulation 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 Milejeva-Biebesheimer, 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-TiO$_2$ can be absorbed percutaneously and cause systemic effects. Variations in particle size and whether there is a surface coating of the absorbed percutaneously and cause systemic effects. Variations in particle size and whether there is a surface coating of the

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.transparency-marketresearch.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.

Conflict of Interest

None.

Funding

None.

Study Approval

NA.
Nanoparticles are...
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