Sunscren Update

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Disclosure

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• **Investigator:**
  - Estée Lauder
  - Ferndale
  - Allergan
Learning Objectives

Be able to:

• Understand the FDA regulations on sunscreens
• Describe controversies on UV filters
• Summarize non-topical photoprotection
Photoprotection

- Shade
- Sunscreens
- Clothing
- Hat
- Sunglasses
- ? Non-topical agents

Outline

- FDA Regulations
Overview in the US
(https://www.ewg.org/sunscreen/report/. Released 5/24/16)

• Surveyed >750 sunscreen products
• SPF>70:
  • 2007: 10 products
  • 2016: 61 products (including 15 with SPF>100)
• Retinyl palmitate:
  • 2010: 40% of products
  • 2016: 16%
• Oxybenzone:
  • In 70% of non-mineral sunscreens
Time and Extend Application (TEA) (2002)
(Wang, SQ, Lim, HW. JAAD. 2011 Oct;65(4):863-9)

Pending FDA approval:
• 4 UVB filters
• 1 UVA filter
• 3 UVB + UVA filters
## UV filters Pending Approval by FDA (TEA)

<table>
<thead>
<tr>
<th>Filters</th>
<th>Abs max (nm)</th>
<th>&gt; 500 Daltons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UVA:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Ecamsule (Mexoryl SX)</td>
<td>345</td>
<td>+</td>
</tr>
<tr>
<td><strong>UVB:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Octyl triazone = ethylhexyl triazone</td>
<td>314</td>
<td>+</td>
</tr>
<tr>
<td>2 Amiloxate = isoamyl methoxycinnamate</td>
<td>308</td>
<td></td>
</tr>
<tr>
<td>3 Diethylhexyl butamido triazone</td>
<td>311</td>
<td>+</td>
</tr>
<tr>
<td>4 Enzacamene = 4 methyl benzylindene camphor*</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td><strong>UVA/UVB:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Drometrizole trisiloxane (Mexoryl XL)</td>
<td>303, 341</td>
<td>+</td>
</tr>
<tr>
<td>2 Bemotrizinol (Tinosorb S)</td>
<td>310, 343</td>
<td>+</td>
</tr>
<tr>
<td>3 Bisoctrizole (Tinosorb M)</td>
<td>305, 360</td>
<td>+</td>
</tr>
</tbody>
</table>

* No longer used in EU
Impact on New Filters in the US

• Globally, the most widely used UVB filter is octinoxate.
• It is not widely used in the US because it destabilizes avobenzone, the only longwave UVA filter approved in the US.
Impact on New Filters in the US

- Oxybenzone (benzophenone 3) is the most common photoallergen among UV filters.
- Benzophenones: 2014 ACDS Allergen of Year
- In Europe, mandatory label: “contains oxybenzone”
- It has been largely replaced with other UVA filters in EU.
- It is still commonly used in the US because lack of other UVA filters (in 70% of non-mineral sunscreens).
Impact on New Filters in the US

(Diffey, B. JAMA Dermatol. 2016;152(5):511)

- Comparison of 4 US sunscreens with 4 sunscreens sold in Europe.
- All had SPF 50 or above
- US sunscreens: transmitted 3 times more UVA compared to the European products
Outline

• FDA Regulations
• Controversies on UV filters
Safety of Oxybenzone (Benzophenone 3)
Oxybenzone

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- It has been replaced with other UVA filters.
- It is still commonly used in the US because lack of other UVA filters.
Oxybenzone

(Wang, SQ, Burnett, M, Lim, HW. Arch Dermatol, 2011; 147:865; Downs, CA. Arch Environ Contam Toxicol 2015 Oct 20. Epub)

- Endocrinologic effects in rat model
- No known safety issues in humans (has been in use in the US since early 1970s)
- Oxybenzone kills adult coral reefs, and deforms DNA in the larval stage
- Highest concentrations were found in areas popular with tourists (the Caribbean, Hawaii)
## Endocrine Effects of Sunscreens
*(Wang, SQ, Burnett, M, Lim, HW. Arch Dermatol, 2011; 147:865)*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>BSA, %</th>
<th>mg/cm²</th>
<th>Amt req’d.</th>
<th>Time, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>2</td>
<td>30 mL/d</td>
<td>34.6</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>1</td>
<td>15 mL/d</td>
<td>69.3</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>1</td>
<td>15 mL/d</td>
<td>277.0</td>
</tr>
</tbody>
</table>

Assumption: Oxybenzone 10%; absorption: 2%. Body wt: 75 kg
Safety of Oxybenzone

- Photoallergen
- No known endocrinologic effects in human
- Adverse effects on carol reefs
Retinyl Palmitate
Retinyl Palmitate (RP)
(Wang, SQ.... Lim, HW. J Am Acad Dermatol 11/10;63(5):903)

- RP is a storage form of retinol (vitamin A)
- Not a UV filter
- It is presence in many sunscreens and cosmetics as an antioxidant
- In vitro: RP + UVA can generate reactive oxygen species → may be photomutagenic
Retinyl Palmitate (RP)
(Wang, SQ…. Lim, HW. J Am Acad Dermatol 11/10;63(5):903)

• However:
  – In mice, topical RP + solar simulated radiation: did not enhance photocarcinogenesis
  – Topical retinoids have been in used for over 40 years; no evidence of photocarcinogenicity
  – Oral retinoids are used for chemoprevention of skin cancers

• No clinical data to suggest that RP is photocarcinogenic
Retinyl Palmitate

• Not a UV filter
• No strong evidence of photocarcinogenicity
• Due to the controversy:
  • 2010: 40% of products
  • 2016: 16%
Sunscreen that allows for vitamin D synthesis
Solar D®

**UVA filters:**
- Diethylamino hydroxybenzoyl hexyl benzoate (Uvinul A Plus) *
- Butyl methoxydibenzoylmethane (avobenzone)

**UVB filters:**
- Octocrylene
- Homosalate
- Octyl salicylate

* Not in FDA Monograph
Fig 1. Action spectra for erythema and for previtamin D formation in human skin and standard solar spectral irradiance at the surface of the earth.

Sun Exposure and Vit D
(Petersen, B, et al. JID 2014 Nov;134:2806)

• Sun-seekers and skiers (n=71) observed for 6 days during holiday:
  – Diaries, UVB exposure with dosimeters
  – Serum 25(OH)D, urine thymine dimers (T-T)

• Strong association between:
  – UVB exposure and post-holiday T-T dimers and 25(OH)D
  – T-T and 25(OH)D levels
Sunscreen that allows for vitamin D synthesis

- Good broad spectrum UVB/UVA protection
- Not available in the US
- *If one is concerned about vit D insufficiency, it is safer to obtain vit D through diet or supplement*
Photodamage in the Dark
In vitro:

- Murine and human melanocytes generated CPDs for > 3 hrs after UVA and UVB exposure
- Albino mouse melanocytes: peak CPD seen immediately after UVA
**In vivo:**

- Black mice (eumelanin): had dark CPD formation after UVA exposure
- Mice with red-yellow pheomelanin: dark CPDs were twice as frequent as in black mice
- *Pheomelanin is a more potent dark CPD generator*
Dark CPD Formation

(Premi, S, ... Brash, DE. Science 2015 (Feg); 347:842. Yale Univ)

• UV-induced reactive oxygen and nitrogen species $\rightarrow$ excite electron in melanin to a triplet state $\rightarrow$ energy transfer to DNA $\rightarrow$ CPD formation

• Melanin may be carcinogenic as well as protective

• ? Antioxidant might be beneficial
Photodamage in the Dark

• Dark CPD formation
• Potential role of antioxidants
Frontal Fibrosing Alopecia
Frontal Fibrosing Alopecia


• Questionnaire survey of 105 women with FFA and 100 age and sex-matched controls.

• FFA gr, vs controls:
  – Significantly more frequent use of sunscreens
  – Trend towards more frequent use of facial moisturizers and foundations (but did not reach statistical significance)
  – More common thyroid disease

• ? Causative role of sunscreens in FFA
Antioxidants in Sunscreens
Sunlight & Reactive Oxygen Species

ROS is generated following exposure to:

- UV, especially UVA
- Visible light \((\text{Liebel, F. } \text{JID 7/12; 132:1901})\)
Antioxidants & UV

(Matsui, M. JID Symp Proc 8/09; 14:56. NY Chen, AC,… Halliday, GM. Photodermatol Photoimmunol Photomed 4-6/14; 30:102. Sydney, Australia)

• Antioxidants:
  – Resveratrol
  – Vitamin E, vitamin C
  – Tea extract [(-)-epigallocatechi-3-gallate]
  – Retinyl palmitate
  – Plant extracts: tea, lutein, tamarind, flavonoids, fern (*Polypodium leukotomos*)

• Low SPF, but protect against UV-induced DNA damage, immune suppression, and depletion of Langerhans cells
Antioxidants & Sunscreens

Sunscreen + antioxidants >> sunscreen alone in:

• Suppressing UV-induced pigmentation, depletion of Langerhans cells, induction of MMP9

• Suppressing infrared A induction of MMP1
Antioxidants in Sunscreens

• Beneficial, provided they are stabilized and biologically active
Nanoparticles in Sunscreens
Organic + Inorganic UV Filters
Organic + Inorganic UV Filters

Sun

ORGANIC

Skin surface

ORG + INORG

Skin surface
Organic + Inorganic UV Filters

Sun

ORGANIC

Skin surface

ORG + INORG

Skin surface
Nanoparticles

\( \text{TiO}_2 \) and \( \text{ZnO} \) (< 100 nm)

- \textit{In vitro}: can induce free radical formation in the presence of UV → damage of viable cells.
Nanoparticles
(Schilling, K. Photochem Photobiol Sc 4/10; 9:495;
Coelho, SG,… Miller, SA. JAMA Dermatol. Feb 24, 2016. Epub)

• Current evidence:
  – Remain mostly on surface of skin
  – Lodge in hair follicles; 0.000014% of applied amount detected in dermis surrounding hair follicles

• However,
  – Nanoparticles are coated
  – Skin has antioxidant mechanism
  – No evidence of having any consequence on human health
Nanoparticles

• Not sufficient data on inflamed skin where epidermal barrier function has been compromised.
Outline

• FDA Regulations
• Controversies on UV filters
• Non-topical photoprotection
Ground Level
Spectrum of Sunlight
UVA1 vs Visible Light
(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

UVA1: 340-400 nm

Immediate

1 week
UVA1 vs Visible Light
(Mahmoud, BH, et al. J Invest Dermatol 8/10; 130:2092)

70 minutes of sun exposure

UVA1
20 J/cm²

Visible light
320 J/cm²

Immediate 1 week
Skin Type IV-VI vs Skin Type II

(Mahmoud, BH. J Invest Dermatol. 8/10; 130:2092. Detroit)
Possible Clinical Implications

• Visible light may have a role on conditions aggravated by sun exposure such as PIH and melasma, esp. in dark-skinned individuals.

• Currently available organic (chemical) UV filters are not sufficient to protect the skin from the effect of visible light.

• Antioxidants may be beneficial
Antioxidants & Sunscreens

Sunscreen + antioxidants >> sunscreen alone in:

• Suppressing UV-induced pigmentation, depletion of Langerhans cells, induction of MMP9

• Suppressing infrared A induction of MMP1
Polypodium leucotomos Extract

• Antioxidative and anti-inflammatory properties
• Suppresses:
  – Clinical changes induced by UVB, PUVA
  – Development of PMLE
• ? Role in visible light photoprotection
Acute Effects of *Polypodium leucotomos* Extract

(Kohli, I, …Elmets, C, Lim, HW, Hamzavi, I. 2015)

- PLE, 240 mg 2 hr and 1 hr before UVB irradiation resulted in:
  - Decrease of UV erythema
  - Inhibition of markers of DNA damage and apoptosis (sunburn cells, cyclobutane pyrimidine dimers), inflammation (COX-2), and proliferation (cyclin D1, Ki67, PCNA)
Oral Nicotinamide

- Nicotinic acid, niacin = Vitamin B3
- Nicotinamide (= niacinamide) is the amide of vit B3
Oral Nicotinamide


• UV inhibits ATP production → energy crisis → prevents optimal skin immune response and DNA repair

• Nicotinamide:
  – Precursor of nicotinamide adenine dinucleotide (NAD), an essential cofactor for ATP production
  – Prevents UV-induced depletion of ATP
  – Unlike niacin, does not produce flushing reaction
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

Oral Nicotinamide


• Phase 3 trial (= confirms effectiveness, monitor safety)
• Double-blind, randomized, controlled trial
• 386 participants with hx of NMSCs, randomly assigned (1:1):
  – Nicotinamide 500 mg bid
  – Placebo
• No differences in side effects
Oral Nicotinamide


Figure 3. Change from Baseline to Month 12 in Number of Actinic Keratoses.
**Oral Nicotinamide**


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo Mean No. of Lesions/person</th>
<th>Nicotinamide Mean No. of Lesions/person</th>
<th>Rate Ratio (95% CI)</th>
<th>Relative Difference, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12-mo intervention period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSCs</td>
<td>2.4</td>
<td>1.8</td>
<td>23 (4 to 38)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>BCCs</td>
<td>1.7</td>
<td>1.3</td>
<td>20 (−6 to 39)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>SCCs</td>
<td>0.7</td>
<td>0.5</td>
<td>30 (0 to 51)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td><strong>6-mo postintervention period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSCs</td>
<td>0.8</td>
<td>0.8</td>
<td>−17 (−59 to 14)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>BCCs</td>
<td>0.6</td>
<td>0.5</td>
<td>−6 (−53 to 26)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>SCCs</td>
<td>0.3</td>
<td>0.3</td>
<td>−59 (−163 to 4)</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

Nicotinamide Better vs Placebo Better
**α-MSH & Analogues**


Afamelanotide (SCENESSE®; CUV1647):

- Similar to α-MSH, linear 13 amino acid peptide.
- The 4th and 7th amino acids of α-MSH have been replaced in afamelanotide.
- Binds to MC1R
- Resistant to enzymatic breakdown, prolonging its duration of action at MC1R → stimulation of melanocyte proliferation and upregulation of tyrosinase activity
α-Melanocyte Stimulating Hormone Analogues

Haylett, AF... Rhodes, LE. BJD 2/11; 164:407. Manchester, UK)

**EPP:**
- Afamelanotide, 20 mg s.c., twice, 60 days apart

**Solar urticaria:**
- Afamelanotide, 16 mg s.c., once

**Both:**
- Increased tolerance to artificial light
- Increased melanin content
Afamelanotide
(Harms, JH. Photochem Photobiol 12/09; 85:1434. Zurich)

Skin pigmentation: before and 30 d after 1 dose

Melanin density at different body sites 30 d after one dose
Afamelanotide for EPP


- 115 adults EPP pts
- Afamelanotide 16 mg subcutaneous implants over up to 8 yrs (total: 1023 implants)
- QoL: pre: 31%; post: 74%
- Good safety profile
- 3 discontinued due to perceived lack of efficacy; none due to adverse effects (mostly: nausea)
- Approved in Italy, Switzerland, and by European Medicines Agency (EMS)
Afamelanotide for Erythropoietic Protoporphyrria

Afamelanotide for EPP: EU & US


• Randomized, double-blind, placebo-controlled study
• EU (74 pts): 5 subcutaneous implants, every 60 days
• US (94 pts): 3 implants
• Duration of pain-free time following sun exposure was longer in the treatment gr.
• Improved quality of life
• Adverse effects: headache, nausea, nasopharyngitis, and back pain
Non-topical Photoprotection

• Promising as an adjunctive photoprotective measure
• Not to replace current regimen of photoprotection
Learning Objectives

Be able to:

• Understand the FDA regulations on sunscreens
• Describe controversies on UV filters
• Summarize non-topical photoprotection