Safer Sunscreens

Nature's Approach to UV Protection

Team players: Amanda, Angela, Sophia, Steven, Tessa

Source: flickr.com

Palau Bans Many Kinds of Sunscreen, Citing Threat to Coral

The New York Times

Hawaii bans sunscreens that harm coral reefs

CNN

Science & Environment

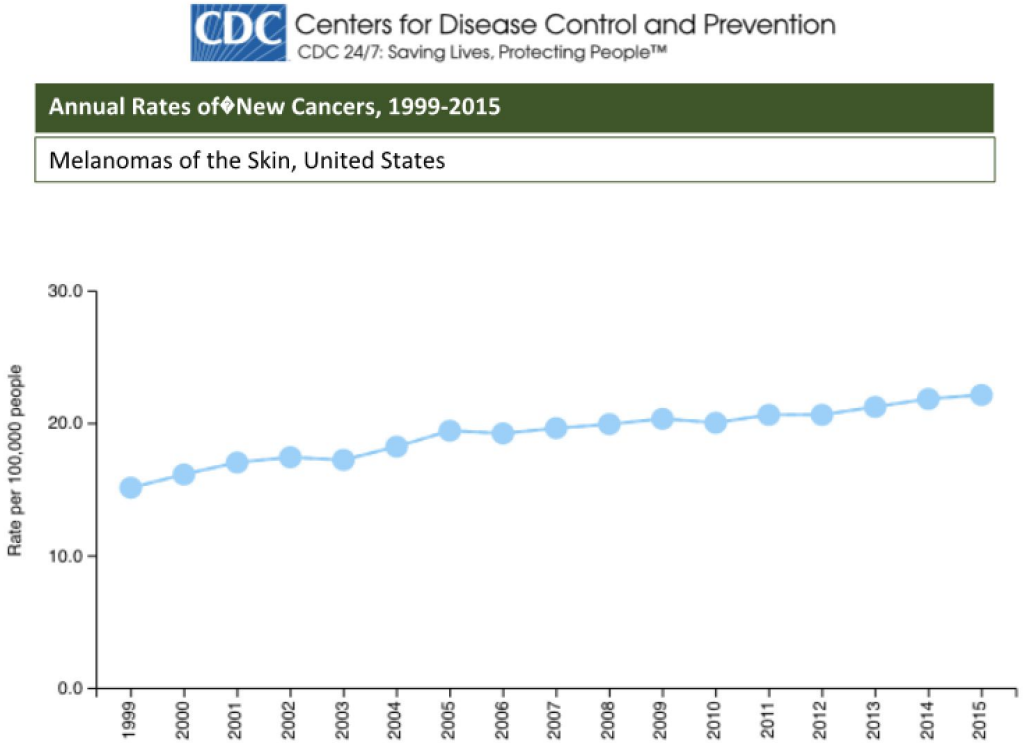
BBC NEWS

Sign in

Coral: Palau to ban sunscreen products to protect reefs

Method - “People against dirty”-wants to do better!
Can we find safer alternatives for sunscreen?

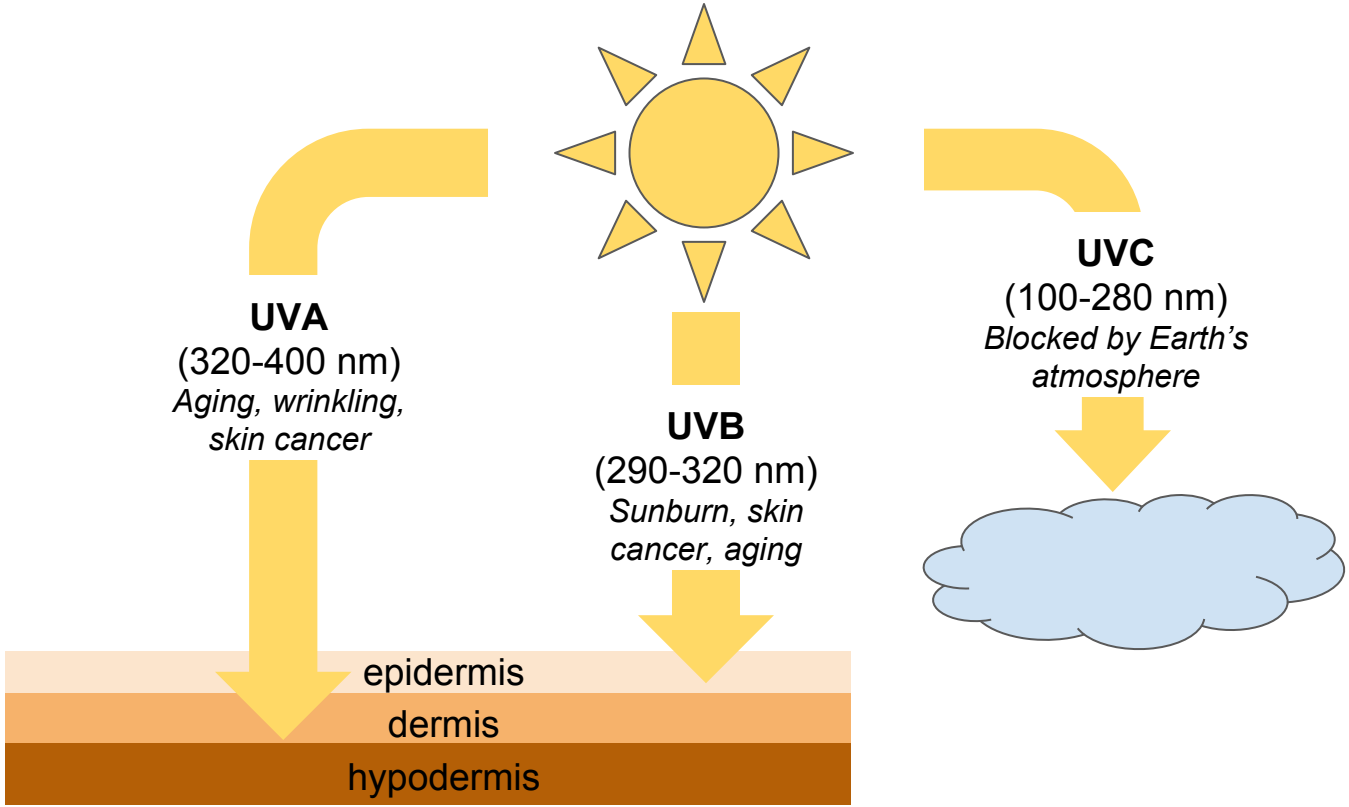
Beyond the burn: why do we need sunscreen?



- Ultraviolet (UV) radiation causes **cellular and DNA damage**
- ~90,000 cases of skin cancer annually with **10% mortality rate**
- 5 bad sunburns early in life can **increase melanoma risk by 80%**

Wu, S. et al. AACR (2014).

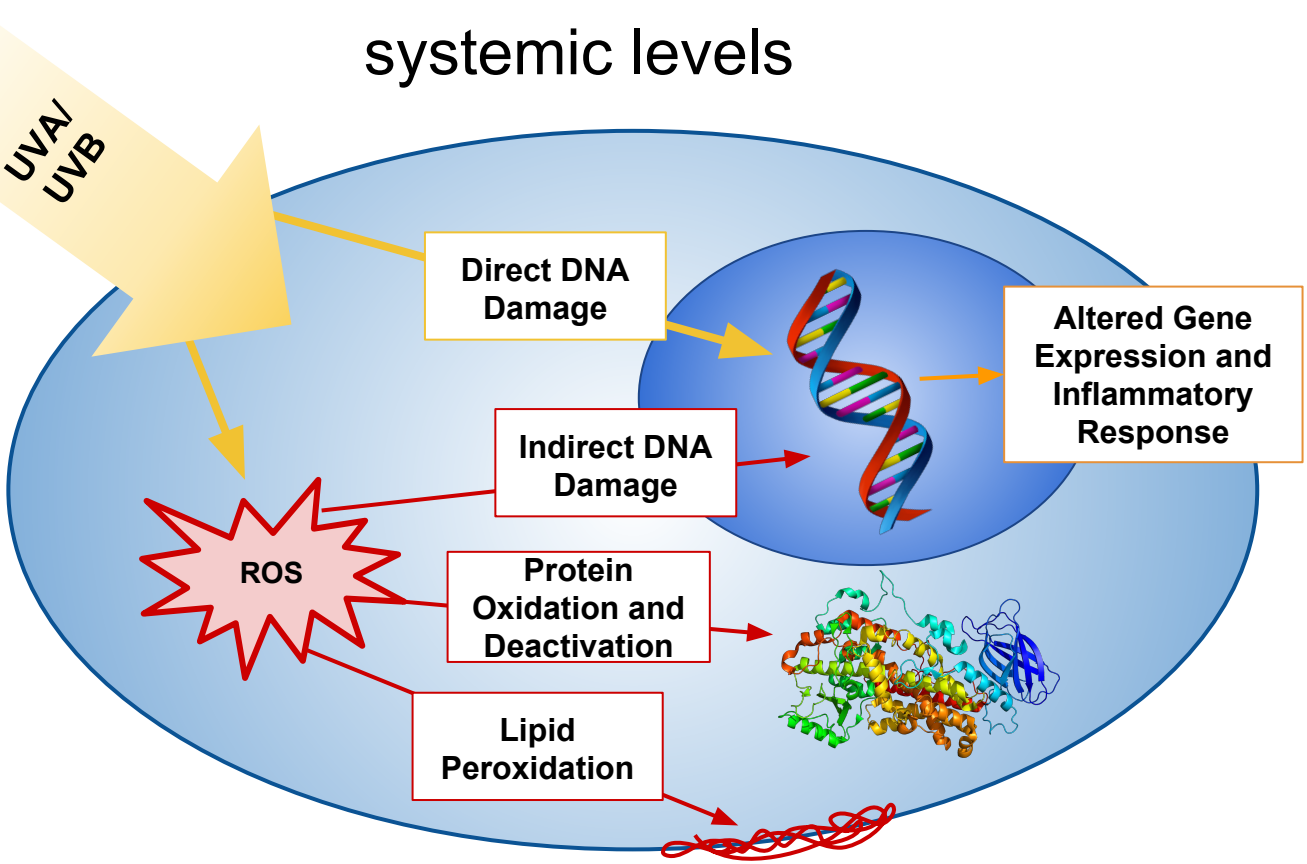
How does UV radiation penetrate skin?



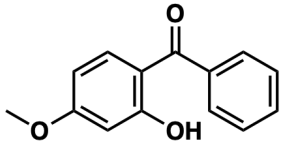
UV radiation causes detrimental effects at the cellular and systemic levels

ROS

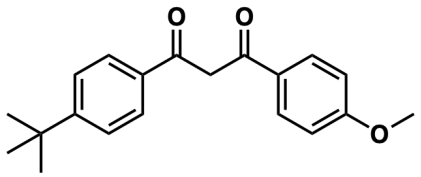
Reactive Oxygen Species



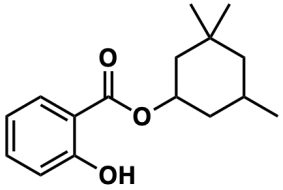
Common active ingredients in your sunscreen



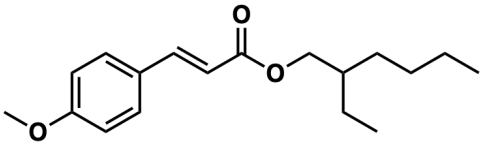
oxybenzone



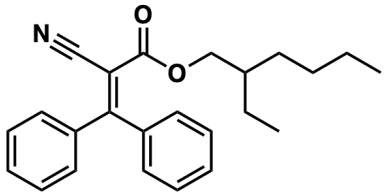
avobenzone



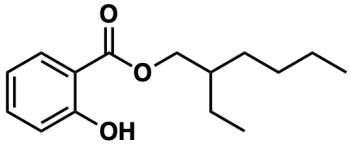
homosalate



octinoxate

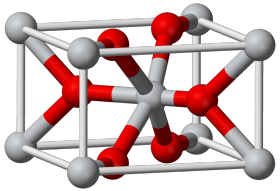


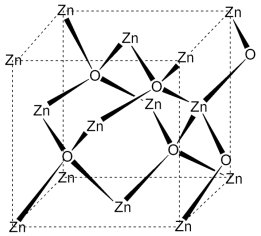
octocrylene



octisalate

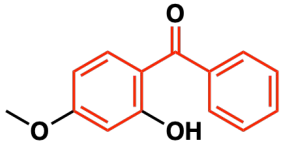
What structural attributes make these ingredients ‘sunscreens’?


titanium dioxide

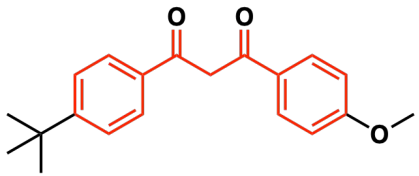


zinc oxide

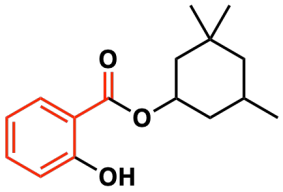
Common active ingredients in your sunscreen



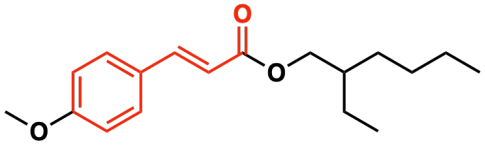
oxybenzone



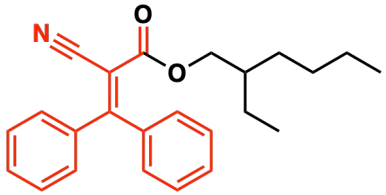
avobenzone



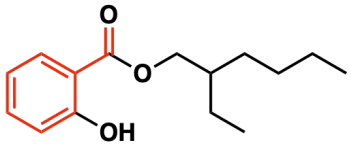
homosalate



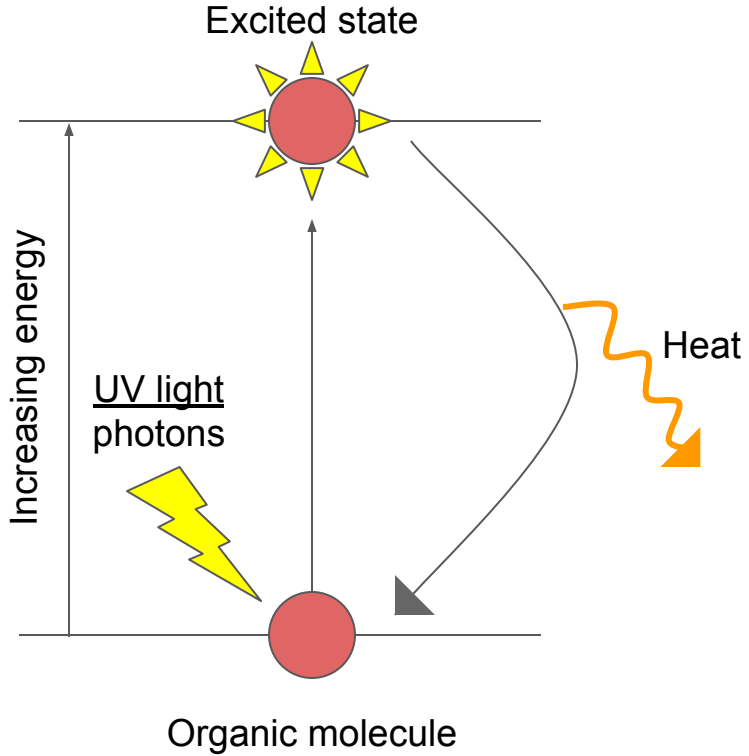
octinoxate



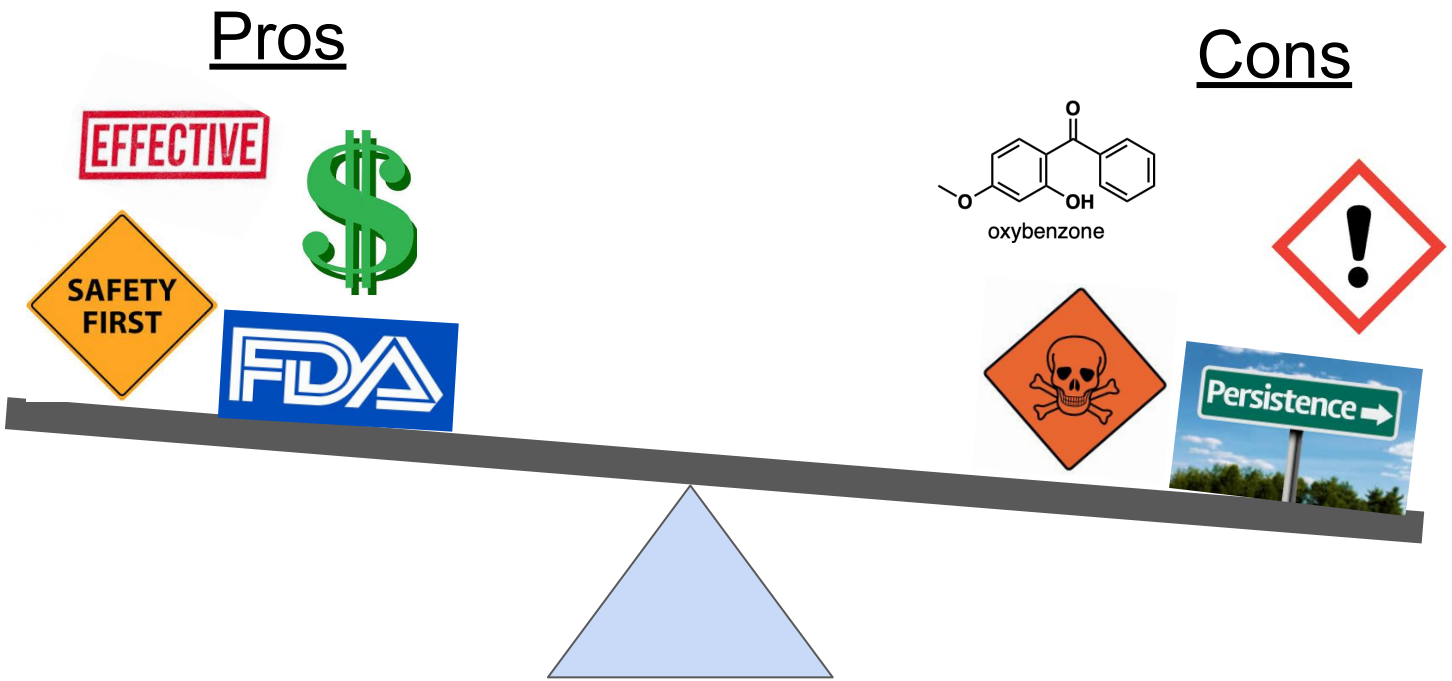
octocrylene



octisalate



Chemical absorbers: more harm than good

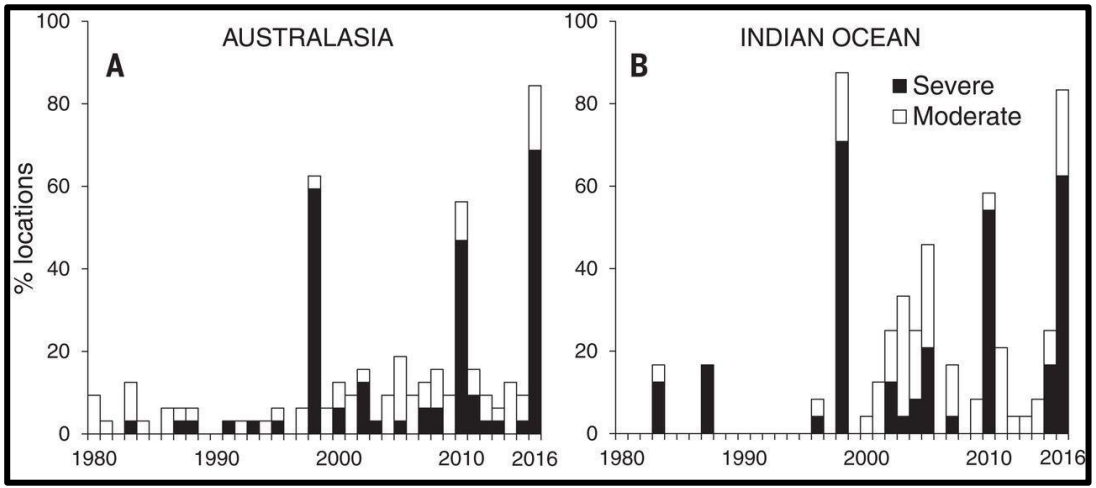


Current products are bleaching coral

Image: Healthy fire coral compared with bleached coral - Images taken in Bermuda by Jayne Jenkins of the Catlin Seaview Survey.

Current products are bleaching coral

Image: Healthy fire coral compared with bleached coral - Images taken in Bermuda by Jayne Jenkins of the Catlin Seaview Survey.



Chemical UV blockers damage marine ecosystems in many ways

1. Endocrine disruption

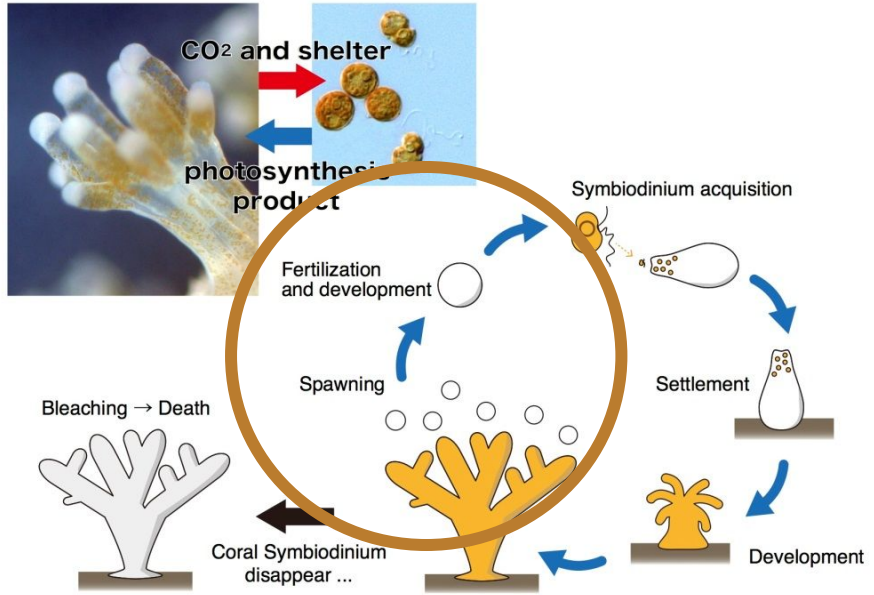


Figure 2. A symbiotic relationship between corals and Symbiodinium

Okinawa Institute of Science and Technology Graduate University (www.oist.jp)

Chemical UV blockers damage marine ecosystems in many ways

1. Endocrine disruption
2. Decreased coral larvae activity

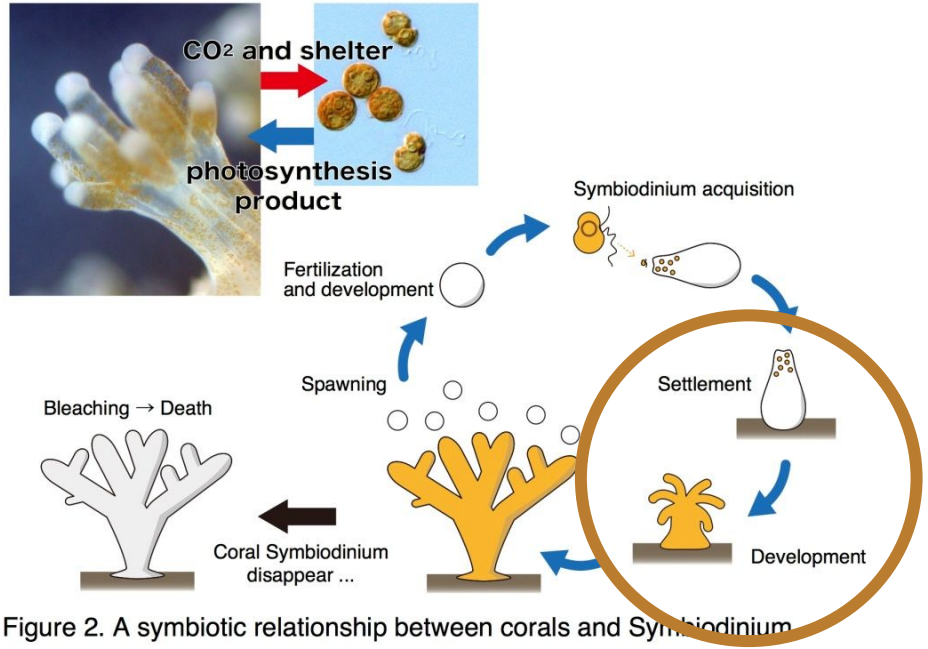
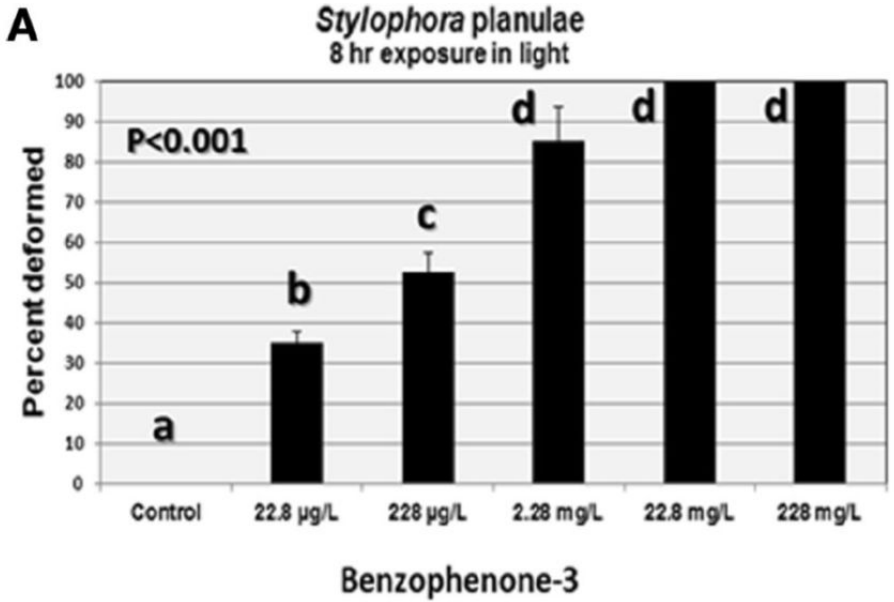


Figure 2. A symbiotic relationship between corals and Symbiodinium

Okinawa Institute of Science and Technology Graduate University (www.oist.jp)

Chemical UV blockers damage marine ecosystems in many ways

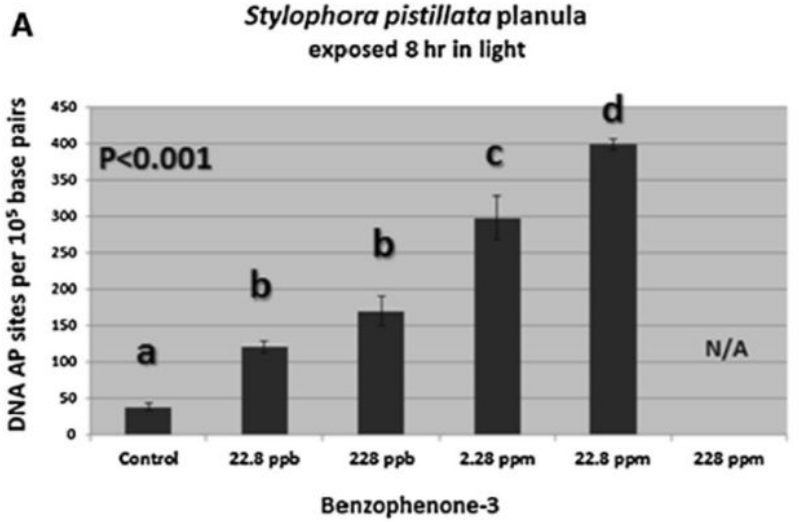
1. Endocrine disruption
2. Decreased coral larvae activity
3. Morphological deformities



(Downs et al., *Ecotoxicology*, 2016)

Chemical UV blockers damage marine ecosystems in many ways

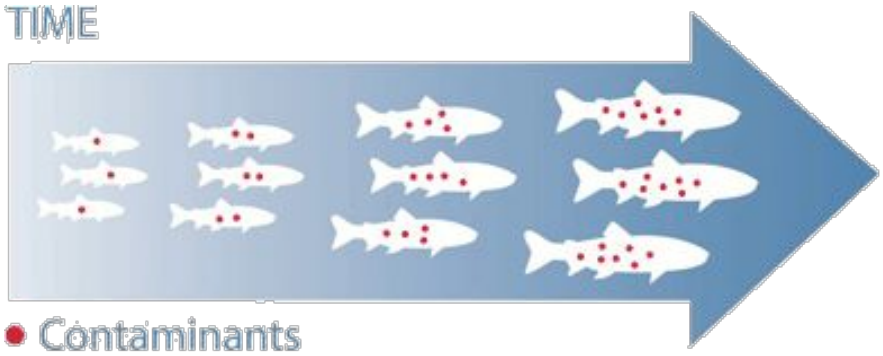
1. Endocrine disruption
2. Decreased coral larvae activity
3. Morphological deformities
4. DNA damage



(Downs et al., *Ecotoxicology*, 2016)

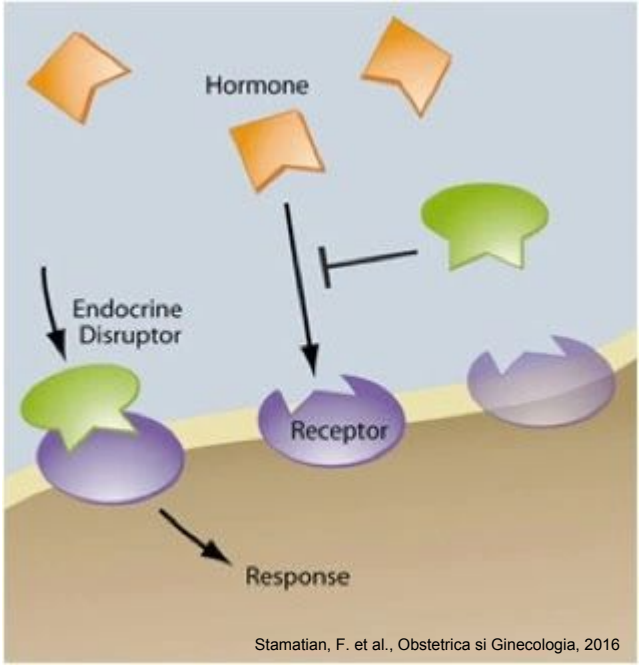
Chemical UV blockers damage marine ecosystems in many ways

1. Endocrine disruption
2. Decreased coral larvae activity
3. Morphological deformities
4. DNA damage
5. Bioaccumulates in fish

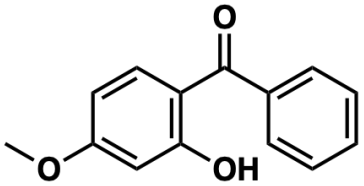


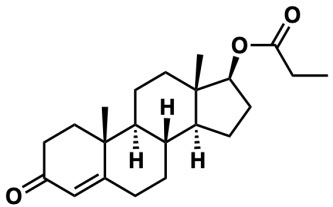
https://socratic.org/questions/what-is-bioaccumulation-2

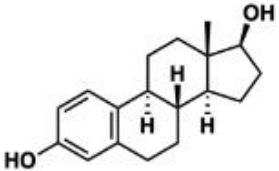
Current chemical UV blockers are known human endocrine disruptors

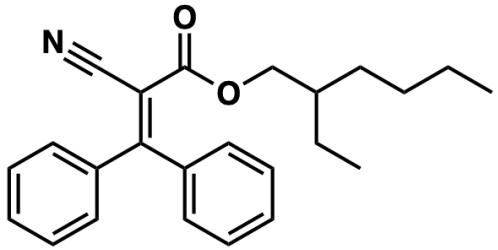


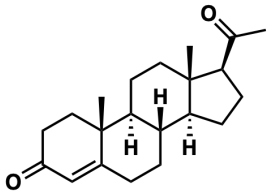
Stamatian, F. et al., Obstetrica si Ginecologia, 2016


oxybenzone

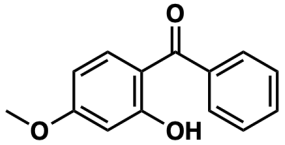

androgen


estradiol

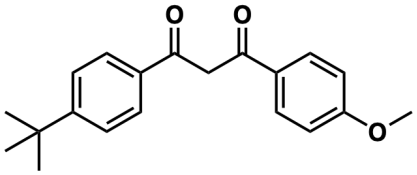

octocrylene


progesterone

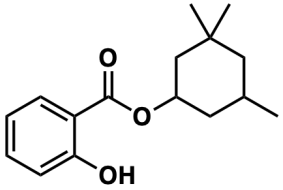
Common active ingredients in your sunscreen



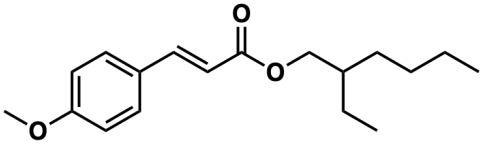
oxybenzone



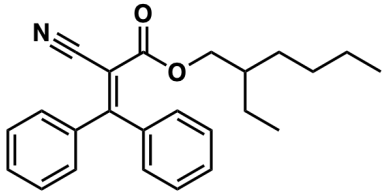
avobenzone



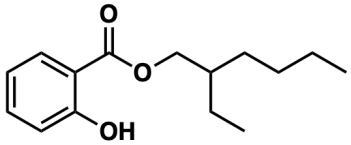
homosalate



octinoxate

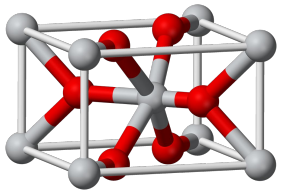


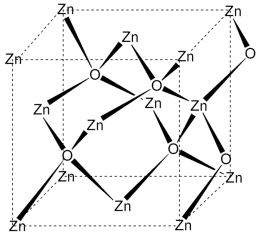
octocrylene



octisalate

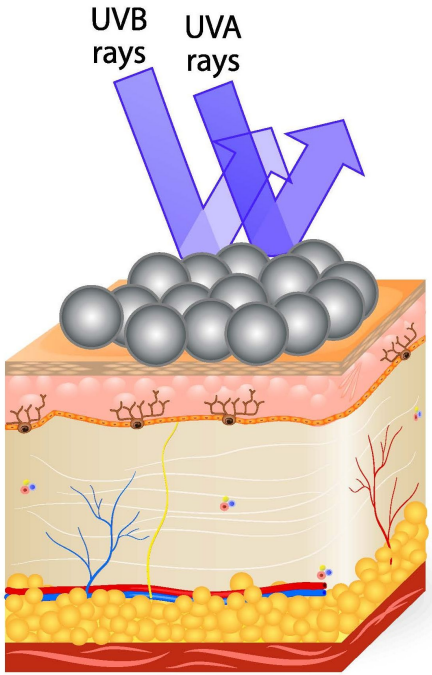
How to mineral blockers work?


titanium dioxide

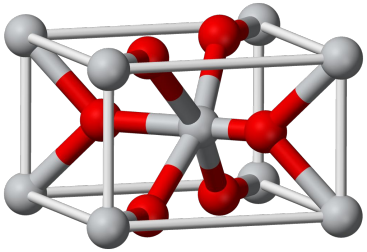


zinc oxide

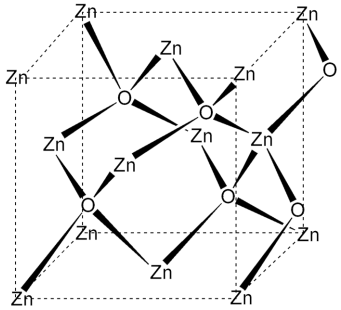
Mineral blockers **reflect** UV light



https://inchemistry.acs.org/content/inchemistry/en/atomic-news/suncreen-science.html



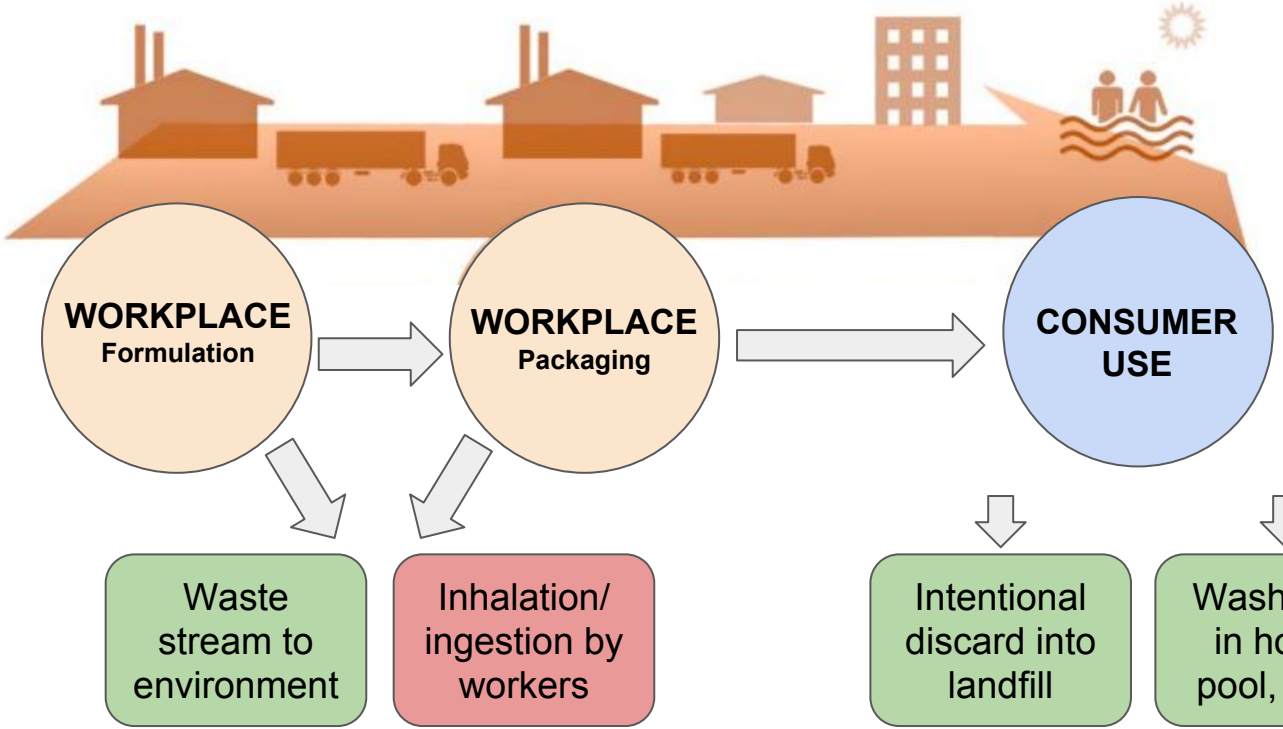
titanium dioxide



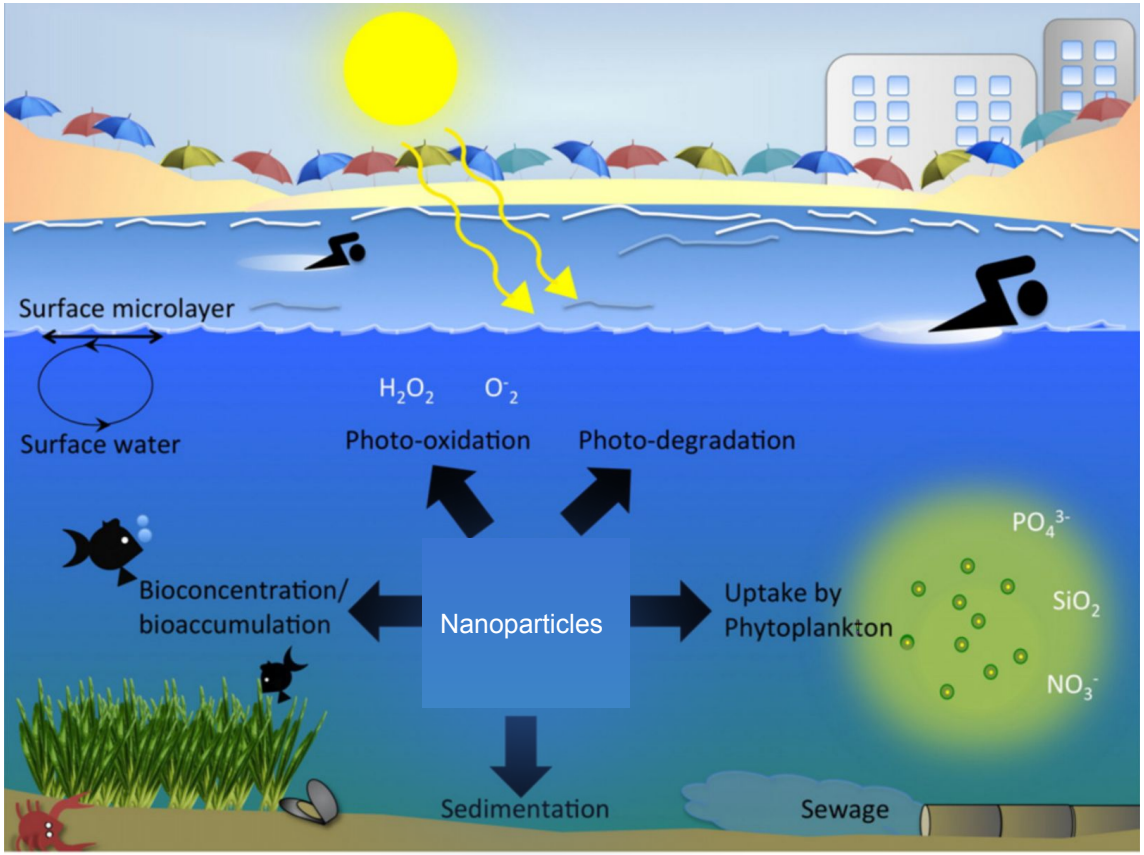
zinc oxide

Incorporated into formulations as **nanoparticles** to avoid streaky white appearance of sunscreen

Nanoparticles have multiple points of exposure and environmental release



Nanoparticles: the pitfall of mineral sunscreens



Johnson, E.C. NSU Works. (2018)

- Protective **coating breaks down**
- Biggest threat is **ROS generation**
- **Chemosensitizers** - increase toxicity of other chemicals

Mineral sunscreen hazard assessment: Group I & II endpoints

Chemical Name	Group I Human					Group II and II* Human								
	Carcinogenicity	Mutagenicity	Reproductive	Developmental	Endocrine Activity	Acute Mammalian	Systemic	Systemic (>1 exposure)	Neurotox	Neurotox (>1 exposure)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation
Zinc Oxide	L	M*	L*	L*	DG	L*	L*	H*	DG	DG	L*	H	L*	L*
Titanium Dioxide	H	-	-	M-L	H-M	-	-	-	-	-	-	-	-	M

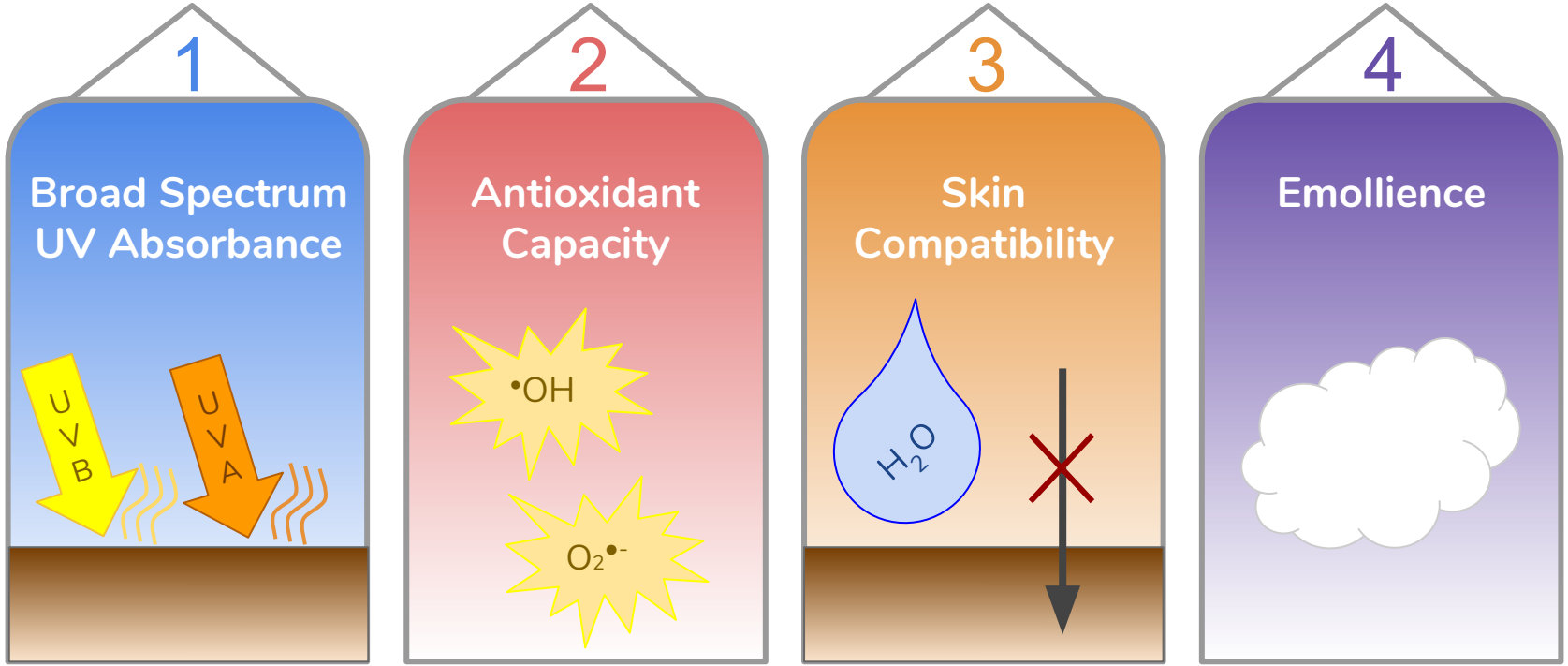
	Key		
L	Low hazard	H	High hazard
M-L	Moderate to low hazard	DG	Data gap
M	Moderate hazard	*	High confidence
H-M	High to moderate hazard		

Mineral sunscreen hazard assessment: Environmental endpoints

Chemical Name	Ecotox			Fate		Physical		Mult
	Acute Aquatic	Chronic Aquatic	Terrestrial Ecotox	Persistence	Bioaccumulation	Reactivity	Flammability	Mult
Zinc Oxide	vH*	vH*	-	vH*	DG	L*	L*	-
Titanium Dioxide	-	M	-	Vh-H	-	-	-	H

Key			
L	Low hazard	vH	Very high hazard
M	Moderate hazard	DG	Data gap
H	High hazard	*	High confidence
Vh-H	Very high to high hazard		

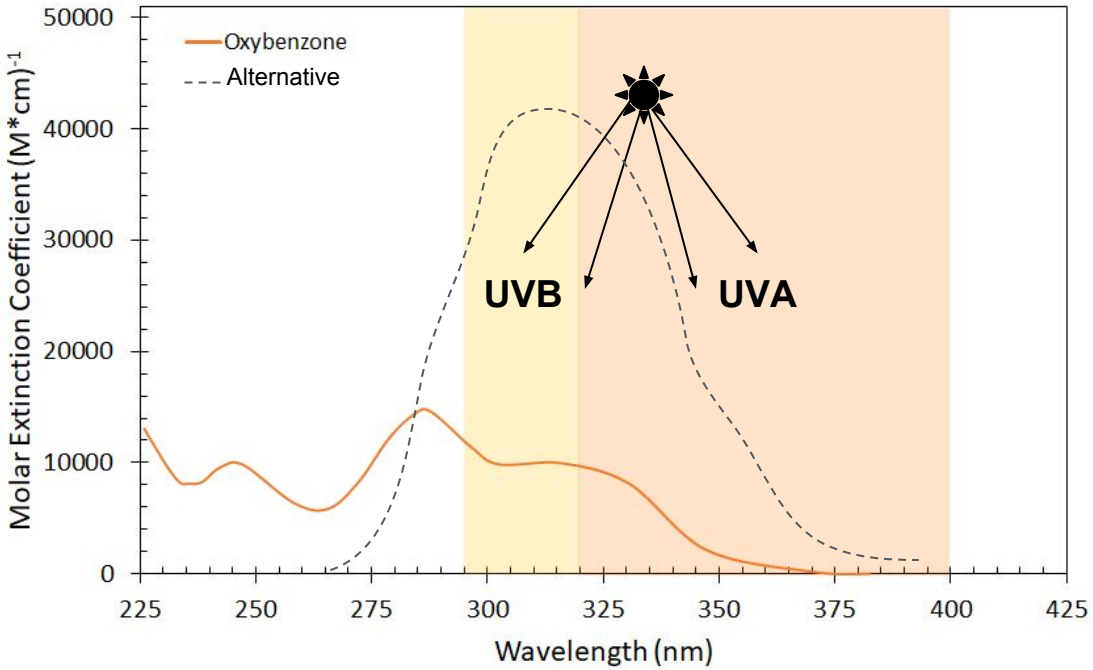
Technical Performance Criteria:
How can we identify effective alternatives?



Broad spectrum UVA/UVB absorbance to prevent cellular damage

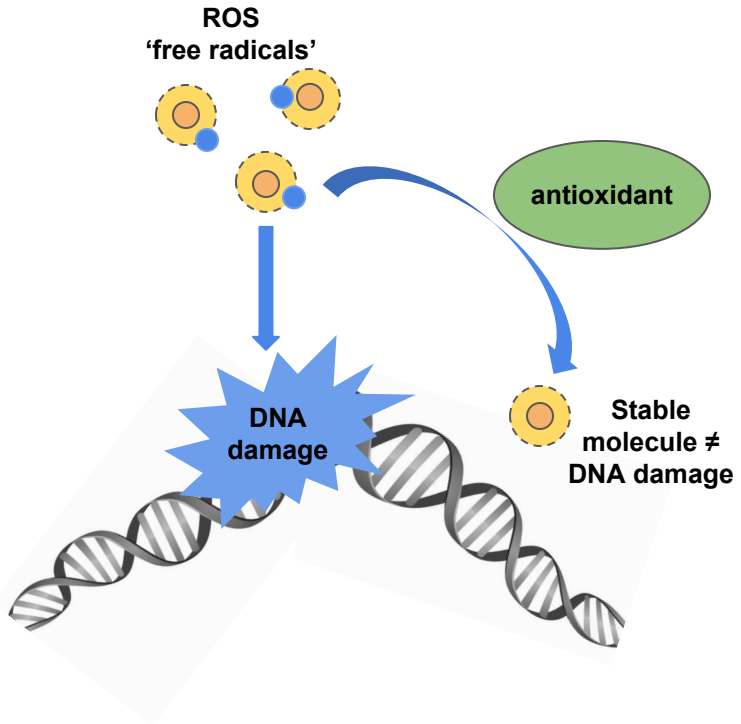
Molar extinction coefficient

How strongly a substance absorbs light



Antioxidant additives to eliminate ROS species

- Antioxidants eliminate reactive oxygen species such as O_2^1, •OH, and NO•
- Skin naturally uses antioxidants obtained from dietary sources to protect against sun damage
- Topically applied antioxidants can be effective protection against sun damage



Skin compatibility:
Will a compound be dermally absorbed?

High hydrophobicity

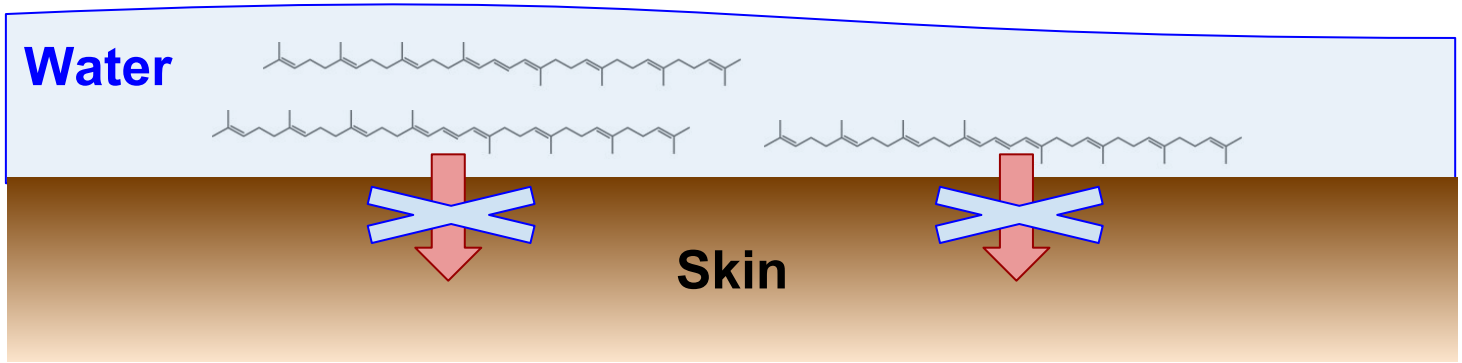
↓

Remains on skin,
May penetrate skin

High Molecular Weight

↓

Little skin penetration



Emollience provides a smooth on-skin feel

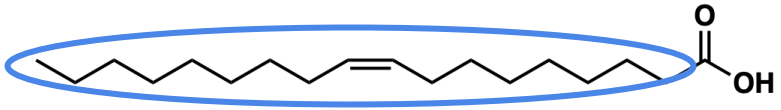
Emollients are derived from petrochemical or natural sources, such as vegetable oils and fats.

Key Structural Components

saturated hydrocarbon

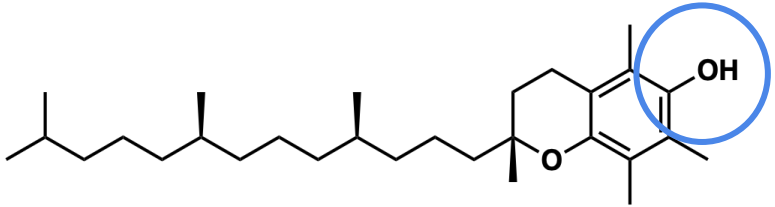
lauric acid

unsaturated hydrocarbon



oleic acid

alcohols



vitamin e

Human & Environmental Health Criteria: Can we find bio-compatible ingredients?

1

Non-Toxic to Humans

2

Non-Toxic to Aquatic Life

3

Biodegradable

Hazard assessment process

Chemical Name	Group I Human					Group II and II* Human								
	Carcinogenicity	Mutagenicity	Reproductive	Developmental	Endocrine Activity	Acute Mammalian	Systemic	Systemic (>1 exposure)	Neurotox	Neurotox (>1 exposure)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation
Carotenoids														
Lycopene	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta-carotene	-	-	-	-	H-M	pC	-	-	-	-	-	-	-	-
Canthaxanthin	-	-	pC	-	-	-	-	-	-	-	-	-	-	-
Xanthophyll	-	-	-	-	-	pC	-	-	-	-	-	-	-	-
Squalane	-	-	-	-	-	pC	pC	-	-	-	-	-	pC	pC
Squalene	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MMA's														
Mycosporine Glycine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shinorine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Antioxidants														
Vitamin C	-	-	-	-	-	-	-	-	-	-	-	-	M	H
Vitamin E	-	-	-	-	H-M	-	-	-	-	-	-	-	-	-
Anthocyanins	-	-	-	-	-	-	-	-	-	-	-	-	-	H
Epigallocatechin Gallate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Resveratrol	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Hazard Assessment

1. Literature review
2. Comparison of structural analogs
3. Health & environmental criteria
   a. Endocrine disruption
   b. Safety of related structures
   c. Environmental fate
   d. Positive health impacts

Inferences on data gaps cannot replace safety testing

Chemical Name	Group I Human					Group II and II* Human								
	Carcinogenicity	Mutagenicity	Reproductive	Developmental	Endocrine Activity	Acute Mammalian	Systemic	Systemic (>1 exposure)	Neurotox	Neurotox (>1 exposure)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation
Carotenoids														
Lycopene	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Beta-carotene	-	-	-	-	H-M	pC	-	-	-	-	-	-	-	-
Canthaxanthin	-	-	pC	-	-	-	-	-	-	-	-	-	-	-
Xanthophyll	-	-	-	-	-	pC	-	-	-	-	-	-	-	-
Squalane	-	-	-	-	-	pC	pC	-	-	-	-	-	pC	pC
Squalene	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MMA's														
Mycosporine Glycine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Shinorine	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Antioxidants														
Vitamin C	-	-	-	-	-	-	-	-	-	-	-	-	M	H
Vitamin E	-	-	-	-	H-M	-	-	-	-	-	-	-	-	-
Anthocyanins	-	-	-	-	-	-	-	-	-	-	-	-	-	H
Epigallocatechin Gallate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Resveratrol	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Hazard Assessment

1. Literature review
2. Comparison of structural analogs
3. Health & environmental criteria
   a. Endocrine disruption
   b. Safety of related structures
   c. Environmental fate
   d. Positive health impacts

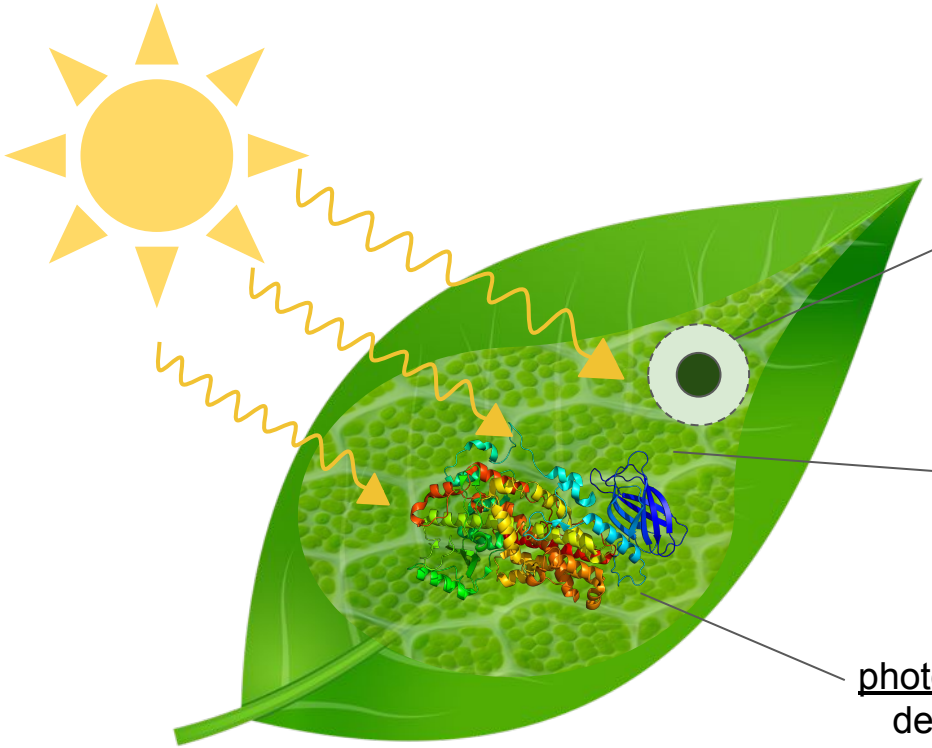
Looking to nature for alternatives: Bio-inspired design, bio-compatible formulation

How do plants protect themselves from UV damage?

Are there UV blocking compounds that exist naturally in aquatic ecosystems?

Can we use plant-derived ingredients with established health benefits?

How do plants avoid sunburn?

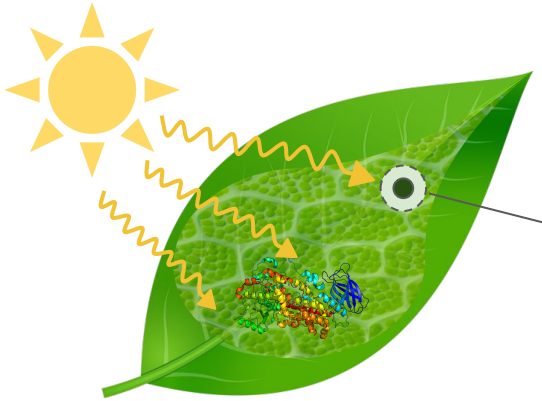


chlorophyll
absorbs light energy
to convert CO_2, H_2O
to sugars, O_2

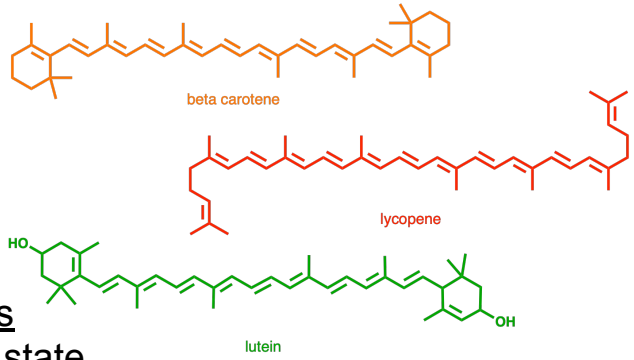
chromoplasts
make and store
carotenoids

photoreceptors
detect light

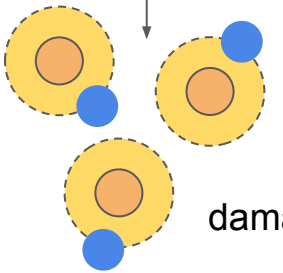
Carotenoid antioxidants quench reactive species



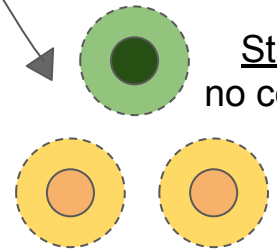
‘Excited state’ chlorophyll
damaging to plant cells +
can produce other ROSs



Carotenoids
quench excited state species to prevent cellular damage



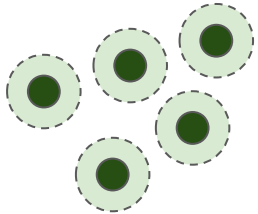
ROSs
damaging to plant cells



Stable species
no cellular damage

Dual-prong approach to prevent acute effects of sunburn and downstream cellular damage

Plants

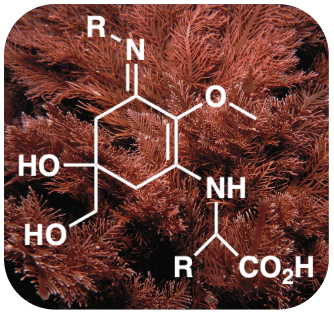


chlorophyll converts UVA/UVB light energy to sugars

UVA/UVB Absorbers

Sunscreen

Colorless carotenoids



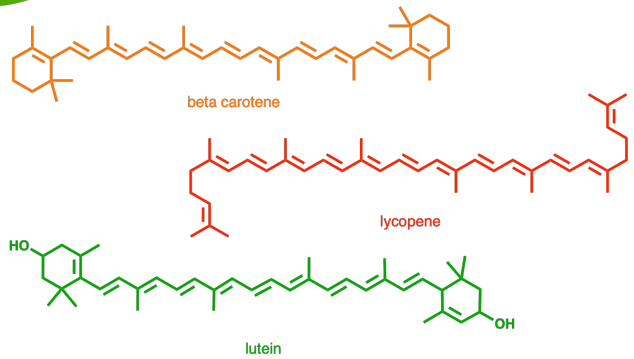
Mycosporine-like amino acids (MAAs)

Bio-derived compounds to absorb UVA/UVB rays and prevent cellular damage

Dual-prong approach to prevent acute effects of sunburn and downstream cellular damage

Antioxidants-ROS Quenchers

Plants



carotenoids quench reactive species

Sunscreen

vitamins

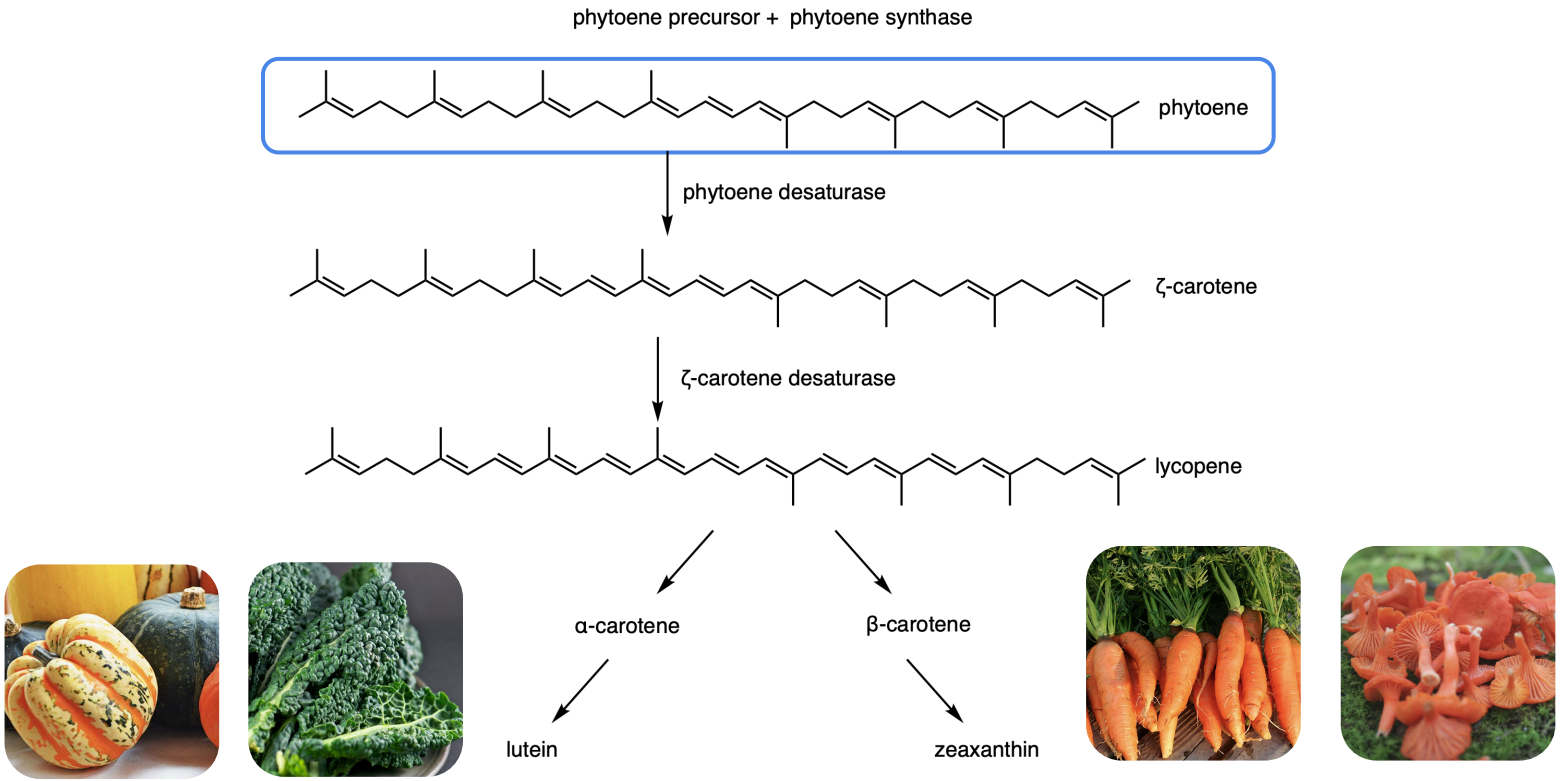
flavonoids

potent, plant-derived antioxidants to quench reactive species

Carotenoids

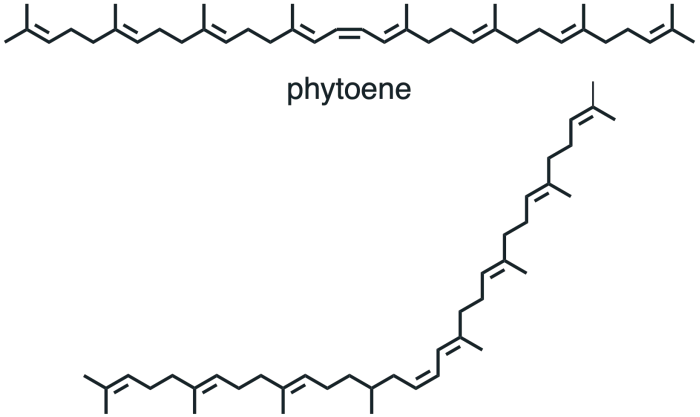



Carotenoid biosynthesis



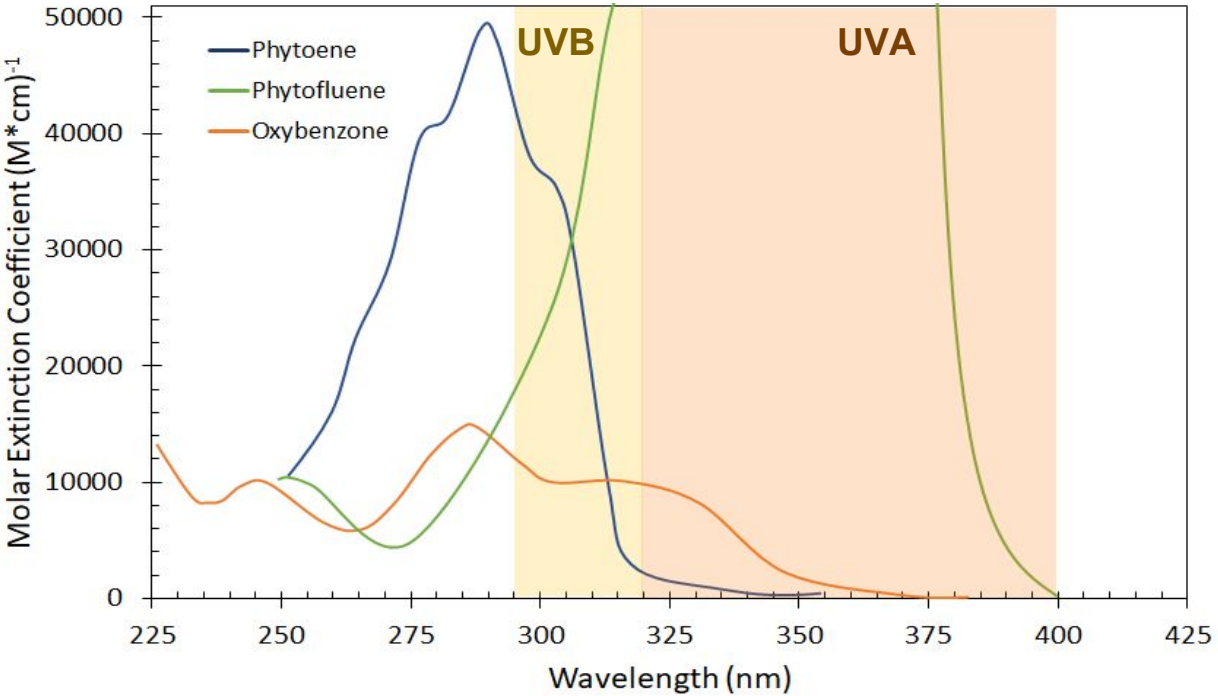
Colorless carotenoids provide multiple attractive properties

- **Broad UV-absorption** spectrum suggesting effective UVA/UVB absorption
- Do NOT absorb in the visible range
- **Potent antioxidants** protecting cells against further radical damage
- **Ubiquitous in nature**



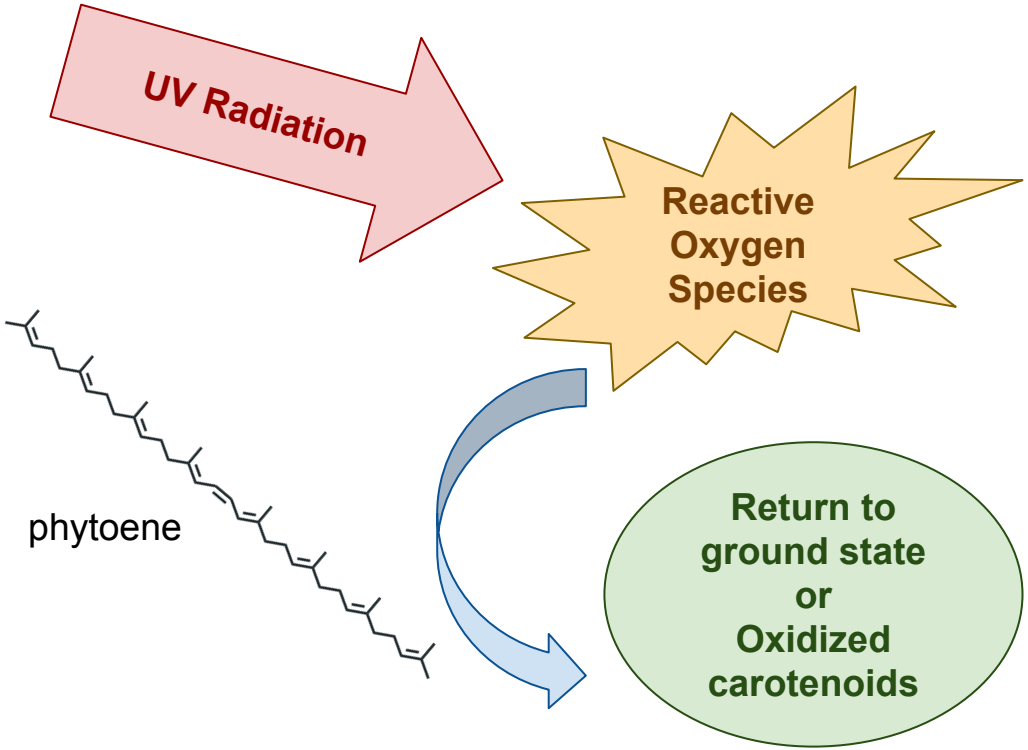
Colorless carotenoids are more effective UVB blockers than oxybenzone

How much light a chemical absorbs normalized by pathlength and concentration



Data plotted from: CDC, 2008; Shath, 2017 and Rahman Abid, 2017

Conjugated double bonds promote antioxidant characteristics



Pros:

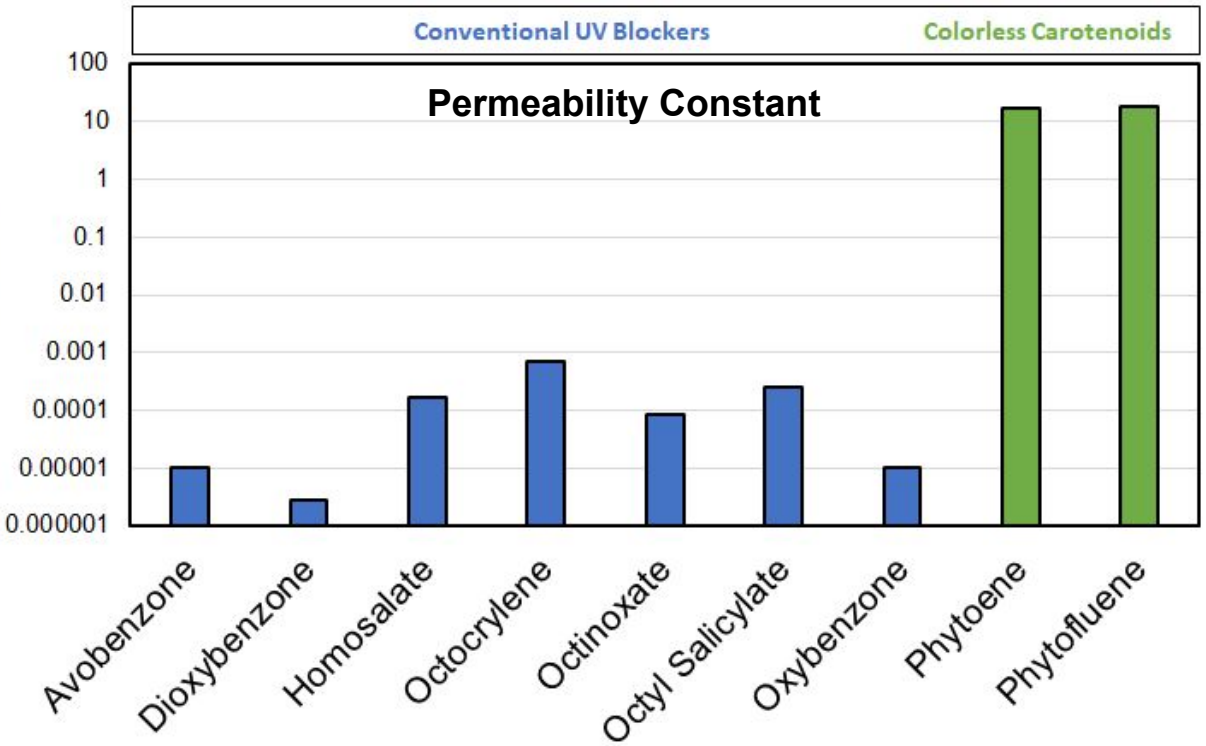
- Prevents skin damage from free radicals
- Stabilizes other active ingredients

Cons:

- Absorbance properties may be altered or lost
- Products of unknown toxicity

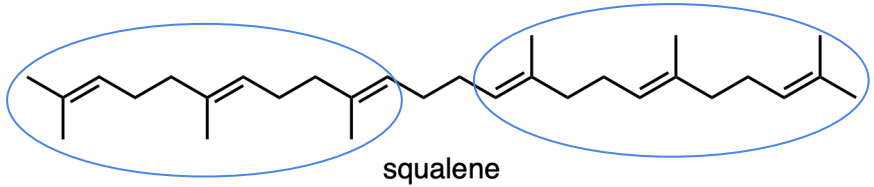
Colorless carotenoids are likely to penetrate human skin

Empirically calculated: LogKow, MW

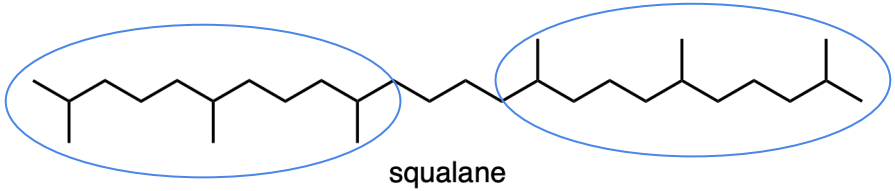


Phytoene and phytofluene are structurally similar to natural emollients

Triterpenoid Structure
Unsaturated (top)
Saturated (bottom)

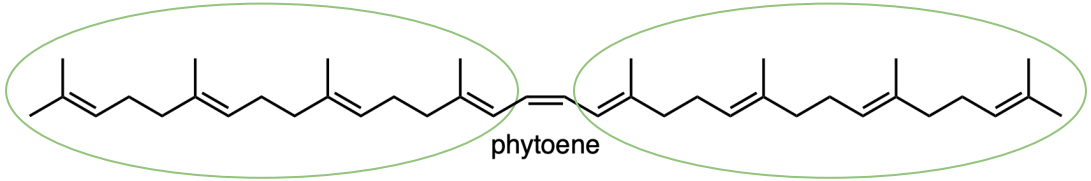


squalene



squalane

Tetraterpenoid Structure



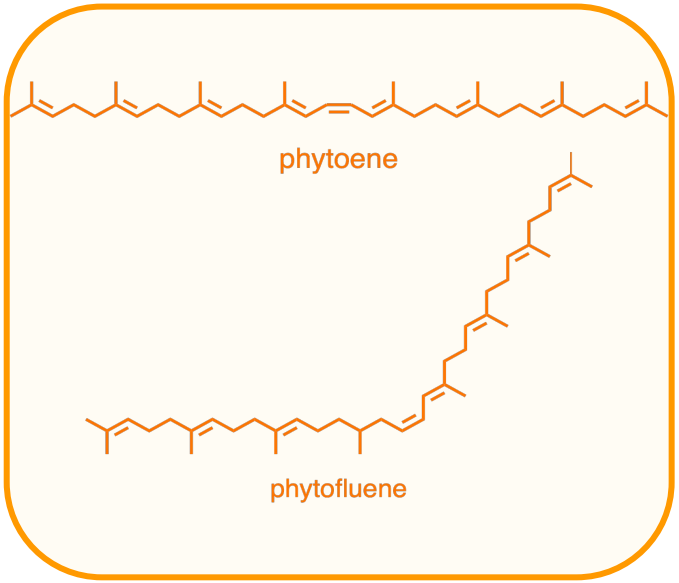
phytoene

Carotenoids are already present in our diets

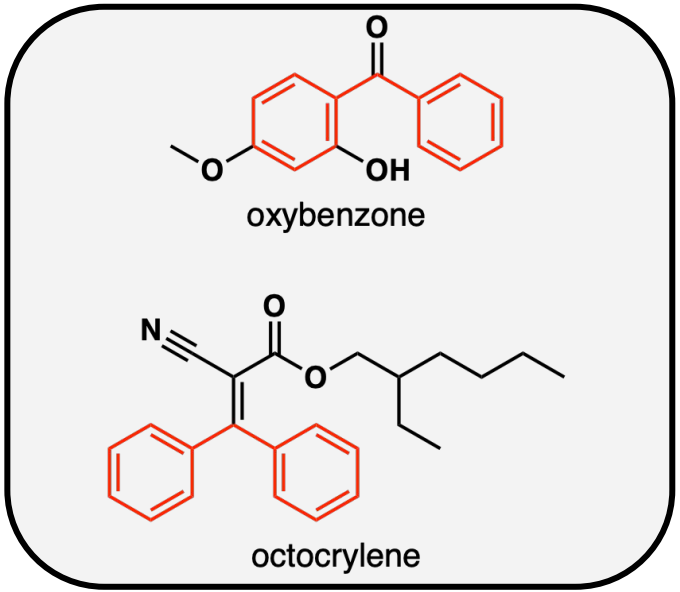
Source	Phytoene (mg/kg fresh weight)	Phytofluene (mg/kg fresh weight)
apricots	2.76	0.95
carrots	1.34	0.57
red pepper	1.69	0.51
grapefruit	1.25	0.51
tomatoes	1.86	0.82

Antonio J. Meléndez-Martínez et al. Archives of Biochemistry and Biophysics. (2015)

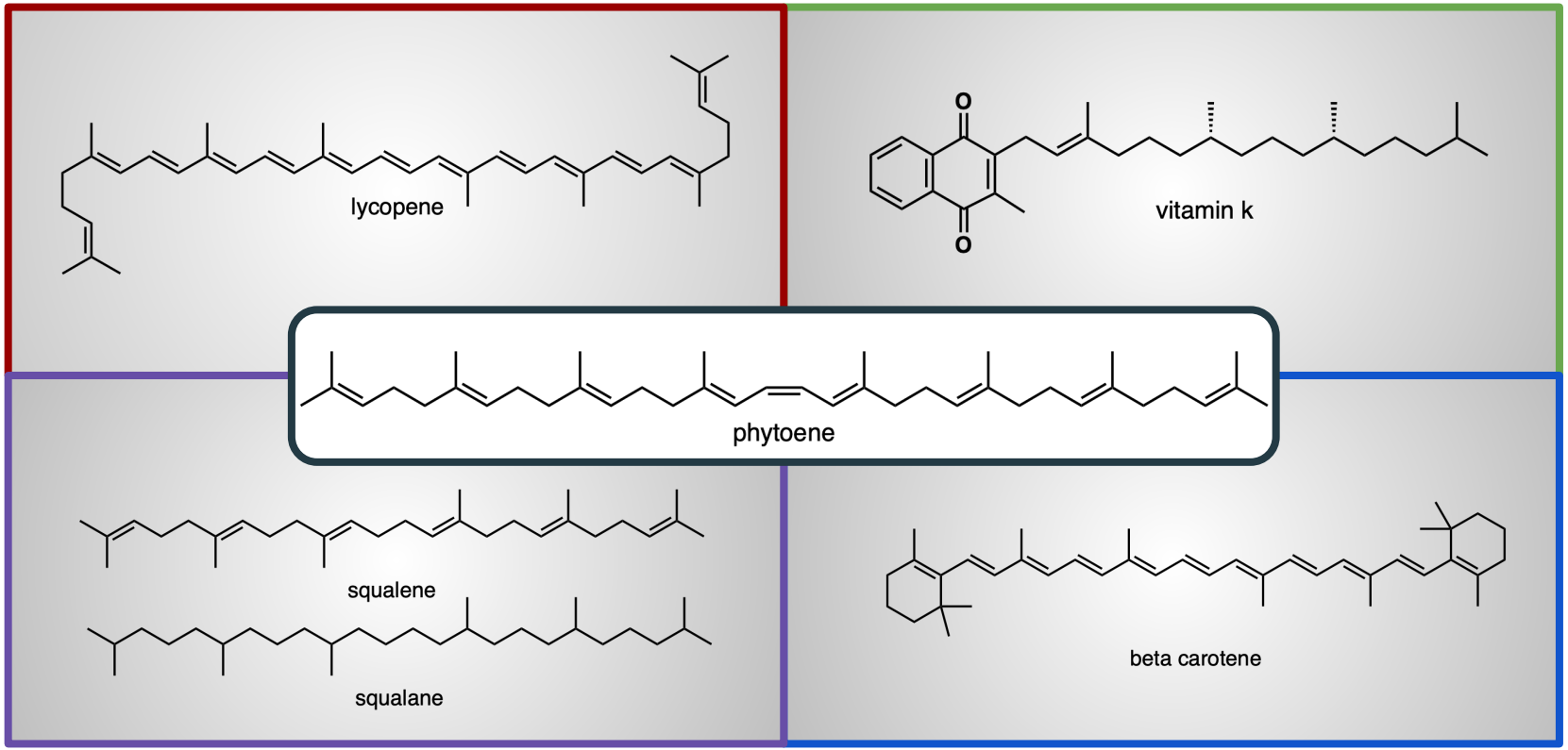
Colorless carotenoids lack benzophenone group linked to endocrine disruption



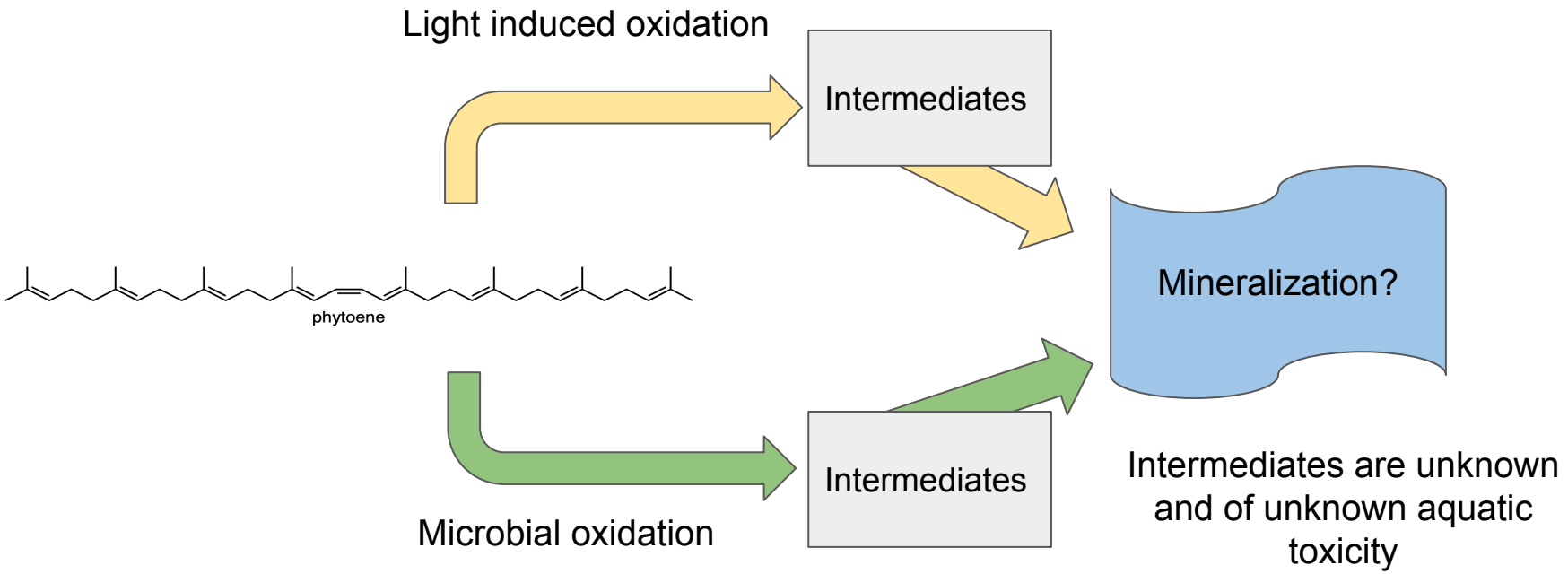
VS.



Toxicological analysis of structural “safe” analogs



Colorless carotenoids should not persist in the environment

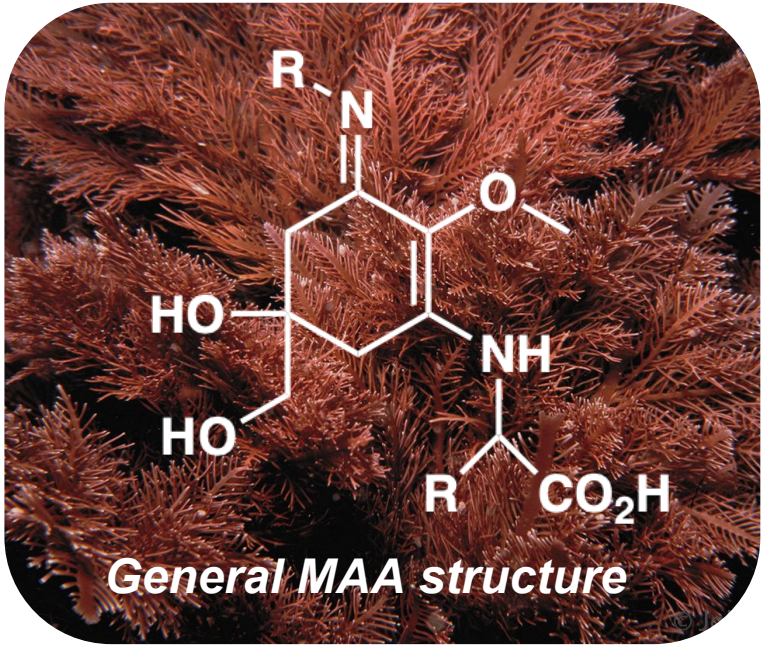


Mycosporine-like **A**mino **A**cid**s** are UV protectors in marine organisms

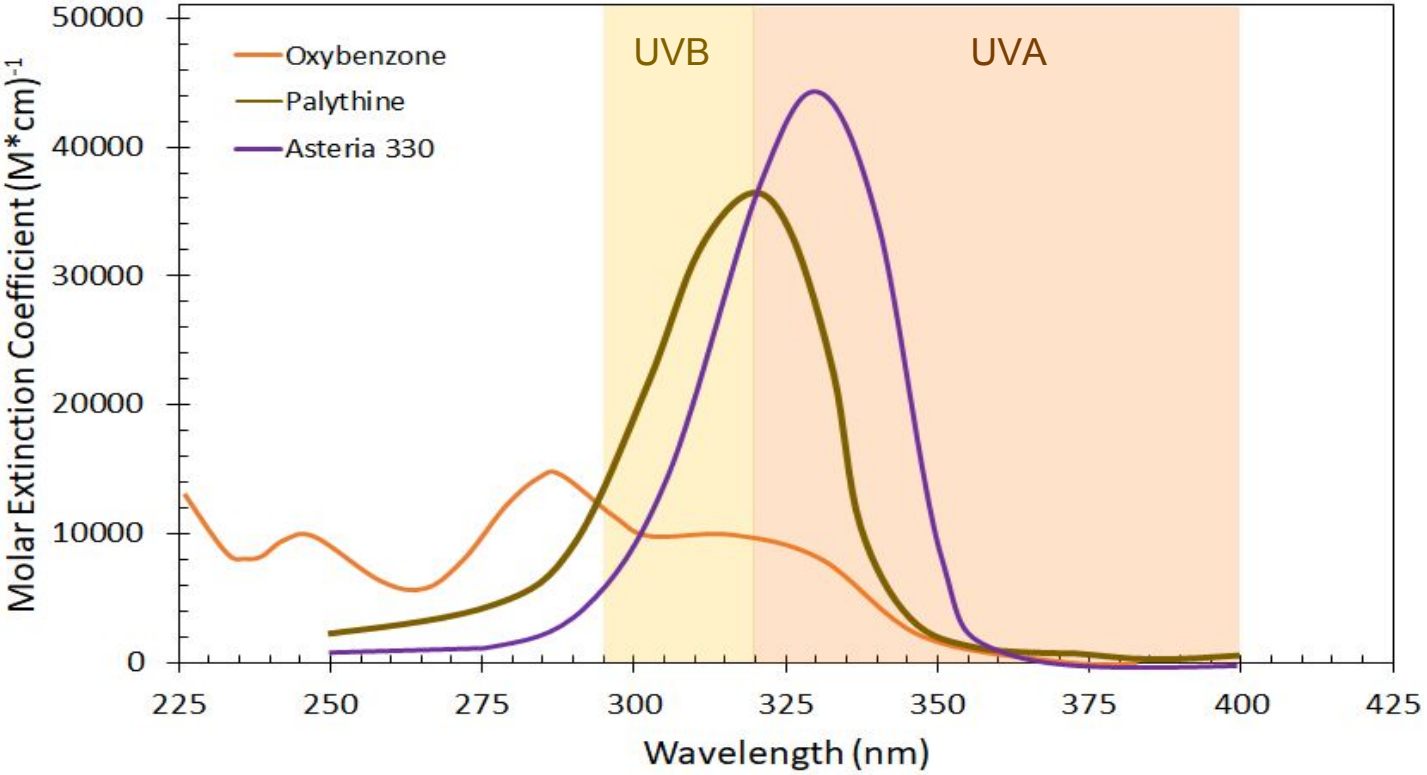


MAAs have many beneficial characteristics

- **Broad UV-absorption**
- **Potent antioxidants** protecting cells against further radical damage
- **Found in aquatic organisms**
- **Polar** - not skin permeable or bioaccumulative



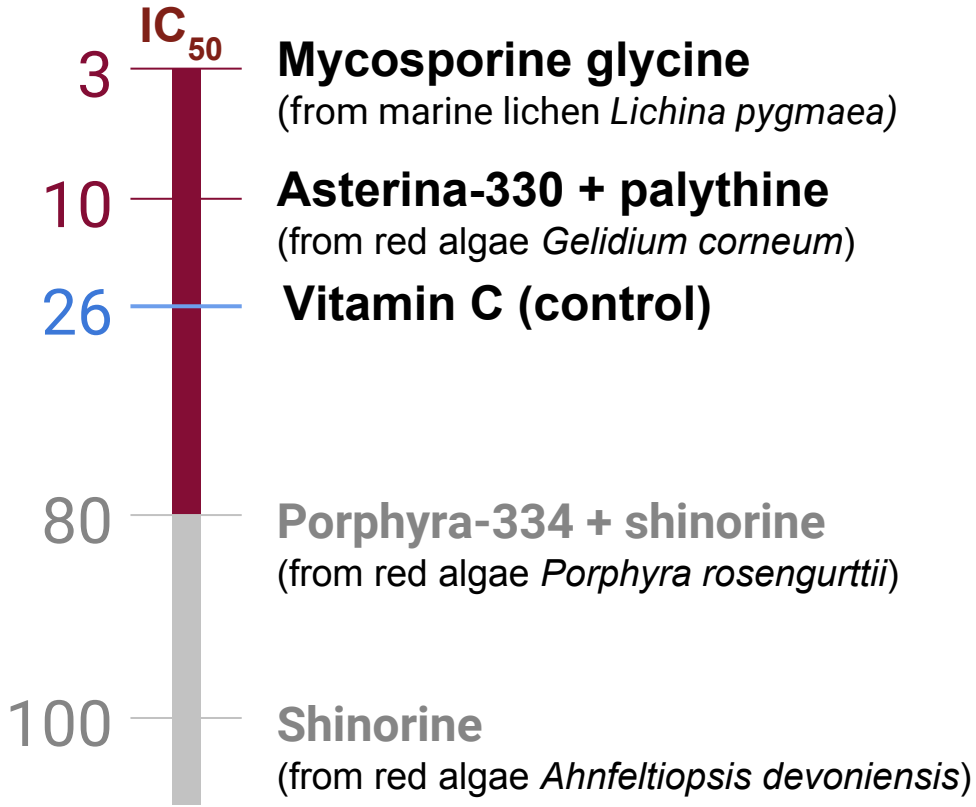
Some MAAs are more effective UV blockers



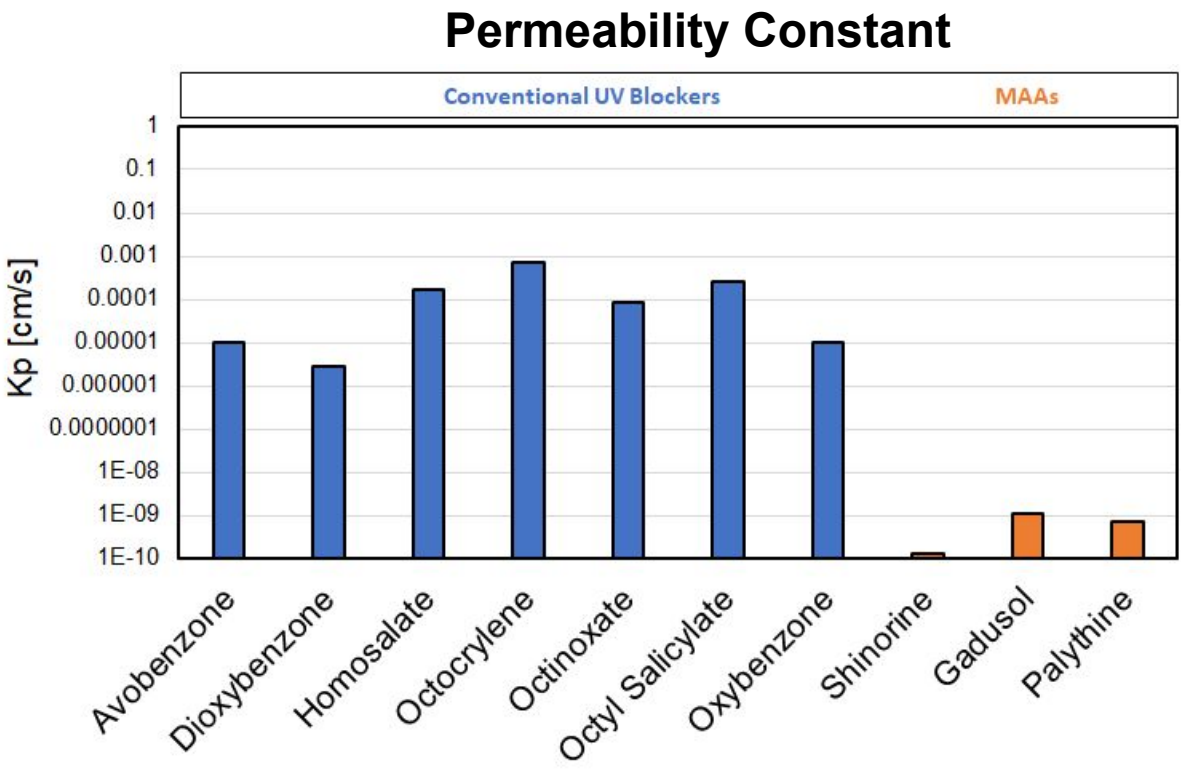
Comparing antioxidant capacity of MAAs

IC_{50}

Concentration (uM) to inhibit 50% of reaction with radical indicator



MAAs are not likely to penetrate skin

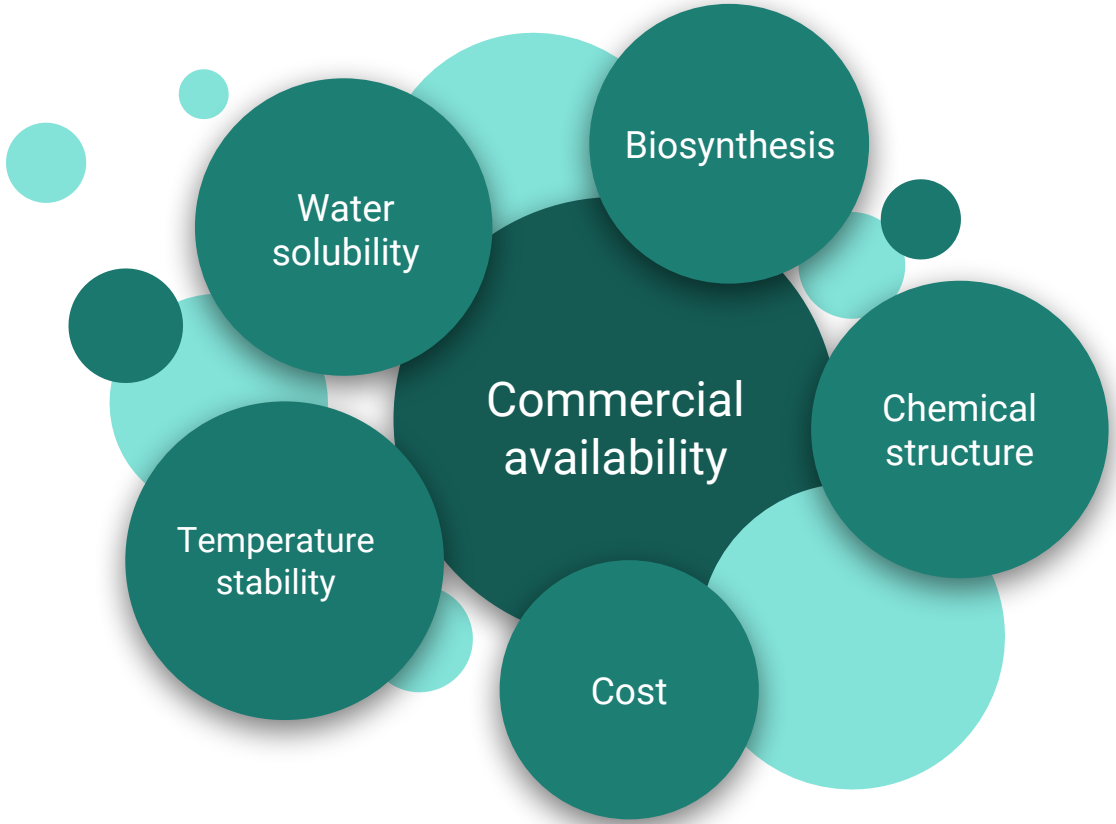


Hydrophilic

Mid-range molecular weight

One MAA product has reached the market as a sunscreen

MAAs are not commonly found commercially

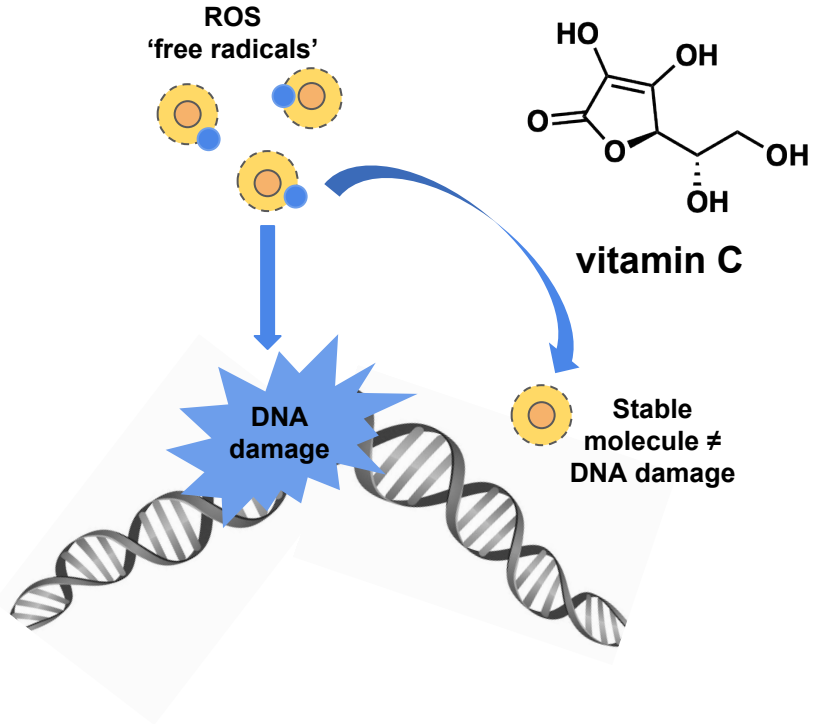


Antioxidant Additives

vitamins

flavonoids

Vitamin C protects against UVA-induced cell damage

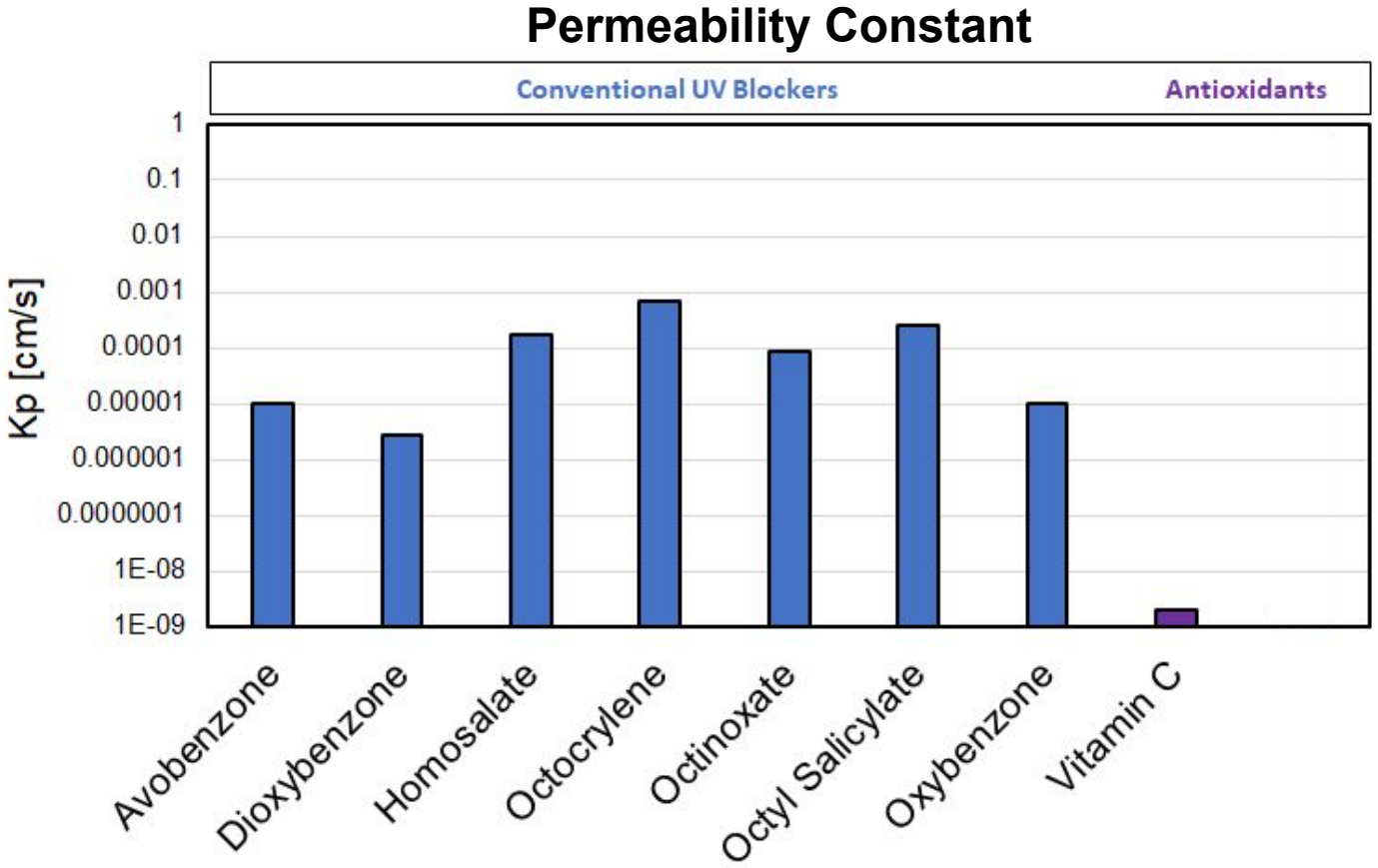


vitamin C

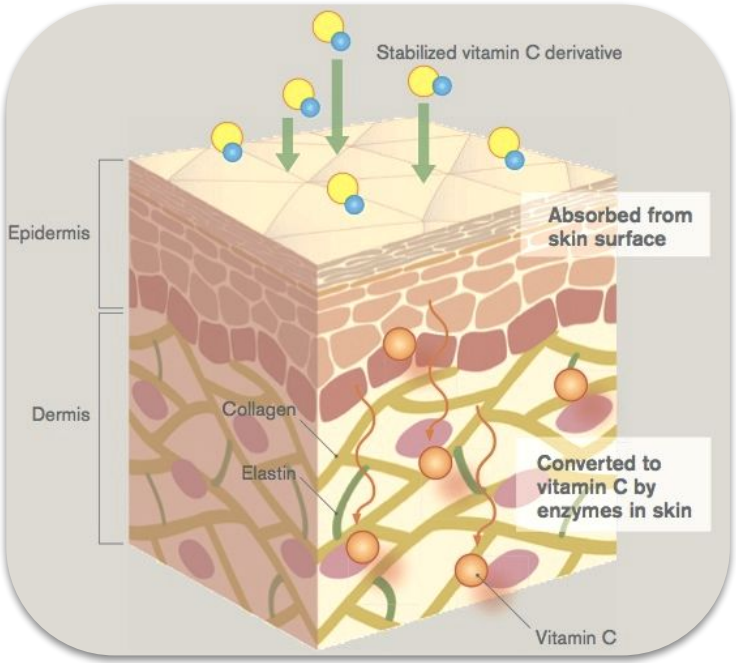
Quenches free radicals, preventing cellular damage associated with:

- Collagen degradation
- Immunosuppression
- Gene mutations leading to cell death

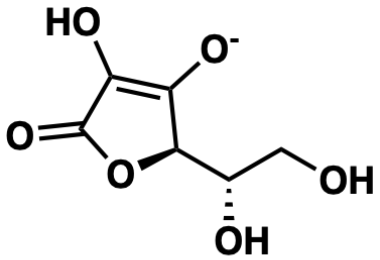
Vitamin C does not easily penetrate skin



Formulation requirements for topical vitamin C treatment



Telang, P.S. Ind Derm J. (2013)



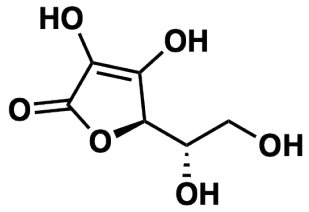
vitamin C

Water soluble and **charged** in a neutral formulation.

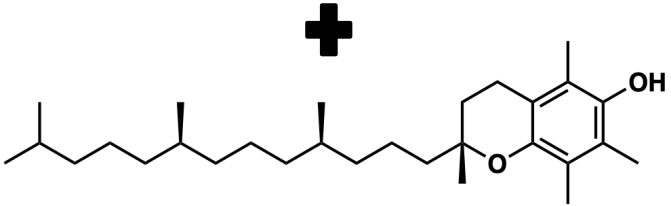
For **optimal dermal absorption**:

- **Acidic formulation**: uncharged form of vitamin C more effective at crossing skin barrier
- **Esterified forms**: more fat soluble so better at crossing cell membranes, and more stable

Vitamin E & Vitamin C have synergistic UVA/UVB protection properties

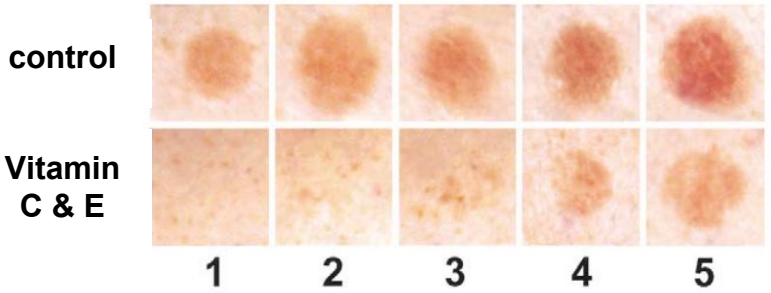


vitamin C



vitamin E

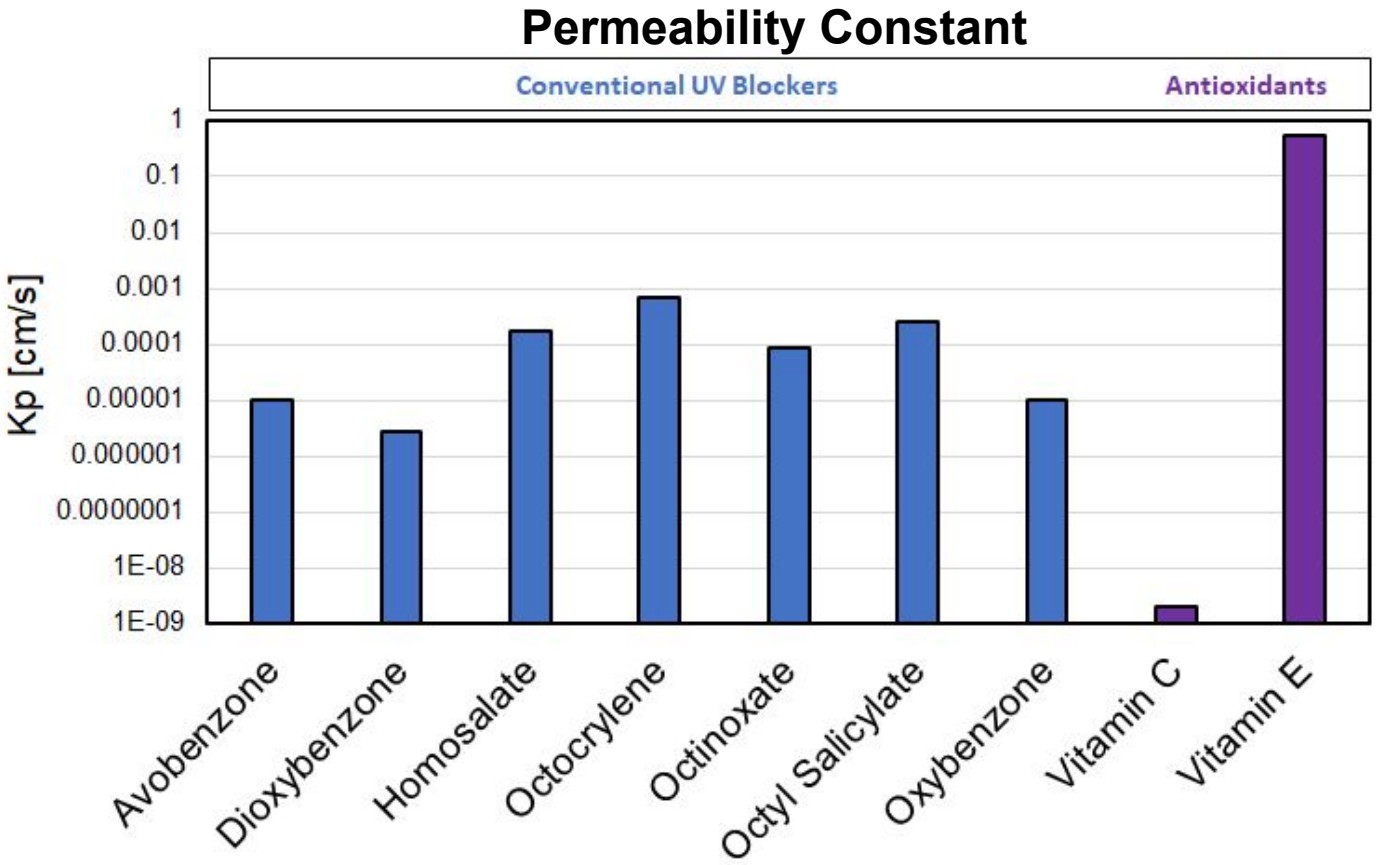
Lin et al. J Am Acad Dermatol. (2008)



# of UV exposures

- Vitamin E is a fat soluble antioxidant
- Combination of vitamin E and vitamin C
  - 4-fold protection against burn inflammation
  - Prevents thymine dimer formation, which damages DNA

Vitamin E is easily absorbed into skin



Plant-derived flavonoids are chemopreventive, could they also be effective in topical formulations?

epigallocatechin gallate (EGCG)

Forester, S.C. Mol. Nut. Food Res. (2011)

Induces cell death in certain cancer cell lines

anthocyanins

Shih, P.H. J. Ag. Food Chem. (2007)

Help body detoxify and excrete carcinogens

Several antioxidants have widespread health benefits

flavonoids

Anti-cancer, antihistamine, antimicrobial

β-carotene

Vision and skin health

resveratrol

Brain health & lower blood pressure

isothiocyanates

Anti-cancer, anti-inflammatory

vitamin C

Immunity, collagen formation, inflammation

Several antioxidants have minimal adverse health effects

Vitamin E Derivatives

- High doses increase risk of prostate cancer
- Maximum daily intake LESS than seen for adverse effects
- α-tocopherol: *in vitro* endocrine disruptor

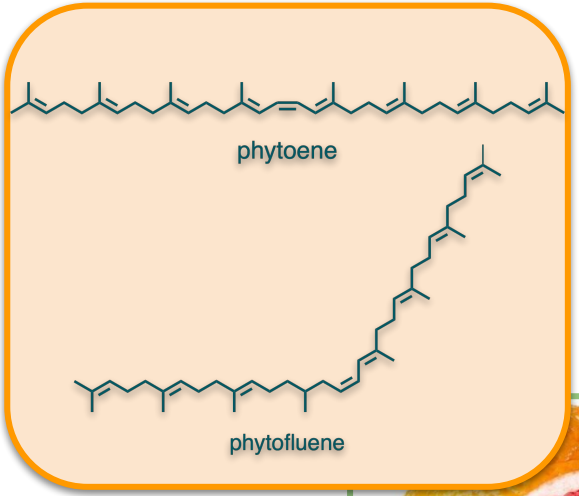
Vitamin C

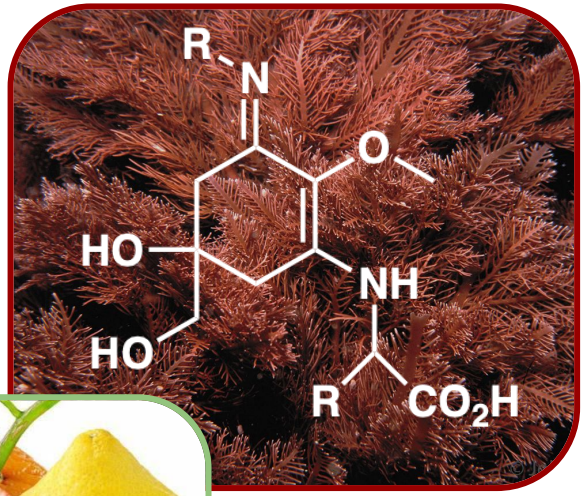
- Pro-oxidant in presence of heavy metals
- No data for skin or eye irritation

Flavonoids

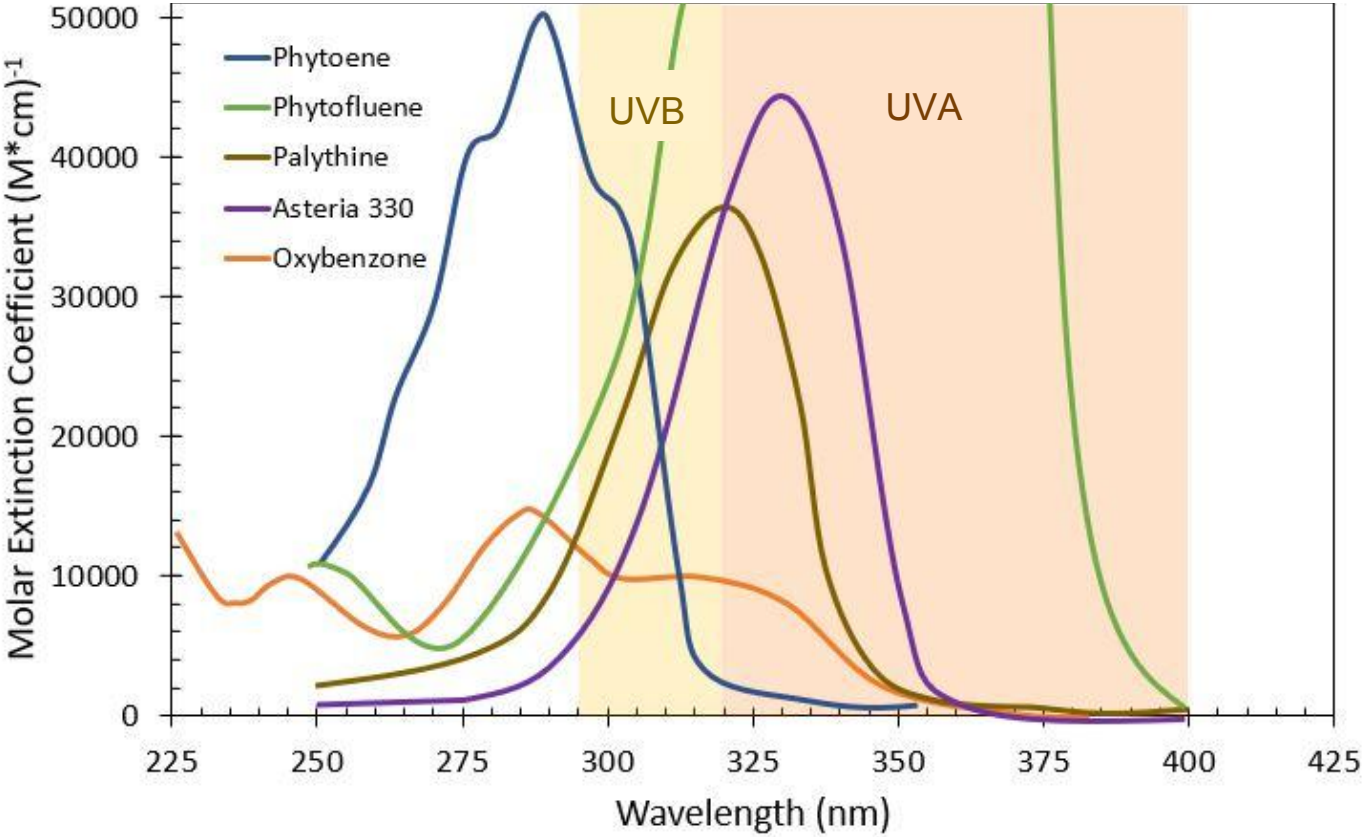
- Pro-oxidant in presence of heavy metals
- Rodent models associated with liver damage
- Toxicological profile is poorly understood

Findings & Recommendations



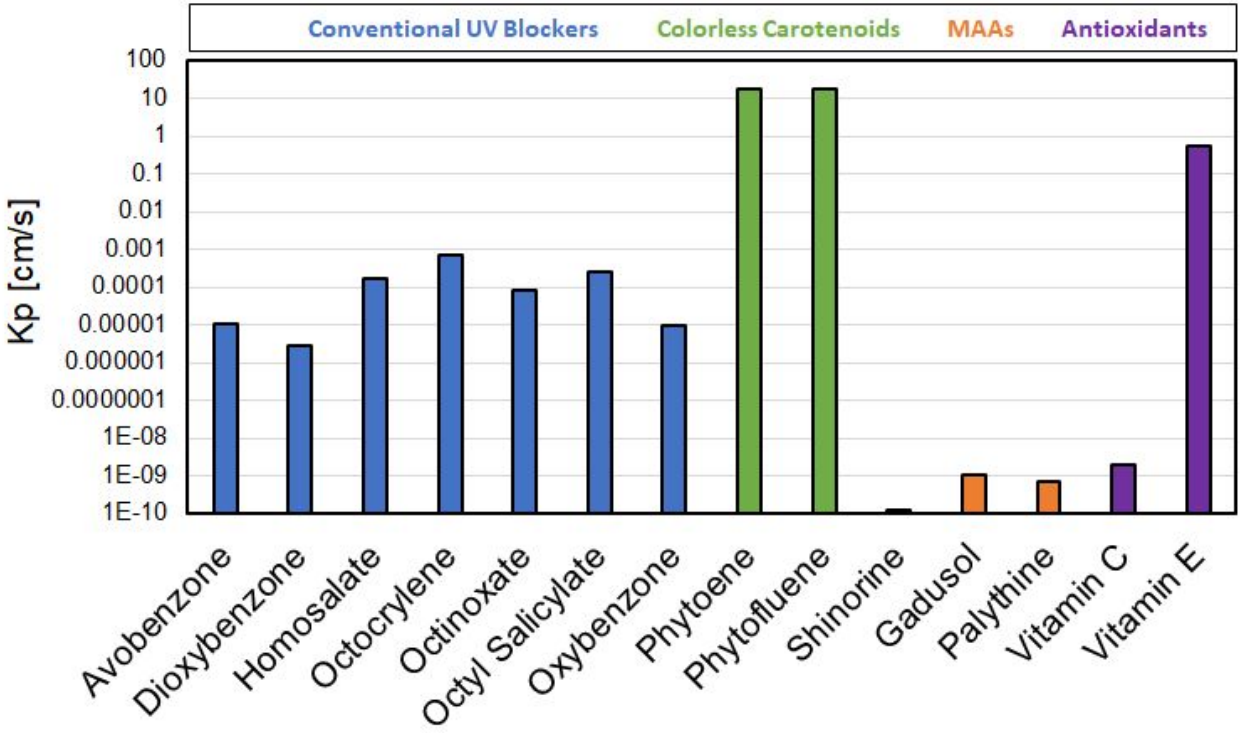


UV-Blocking of alternatives outperforms oxybenzone

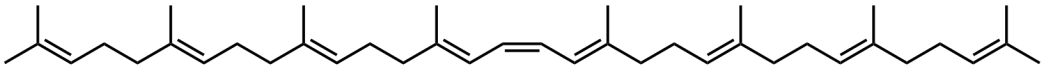
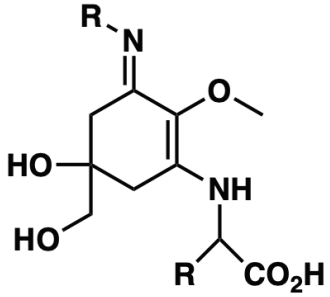
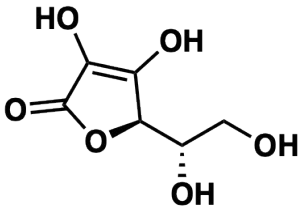
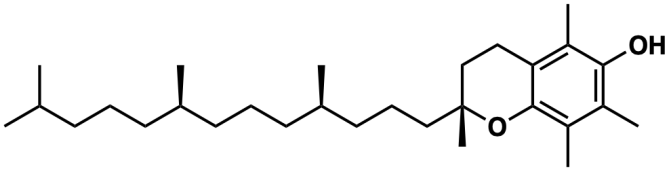


Carotenoids may penetrate skin while MAAs may wash off

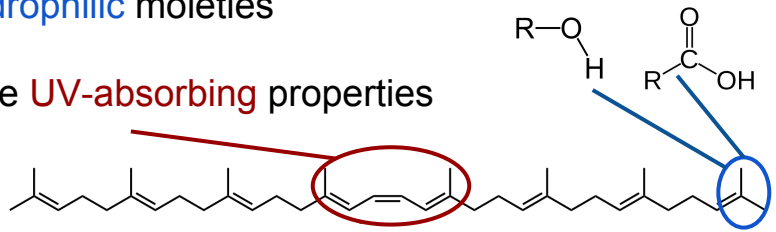
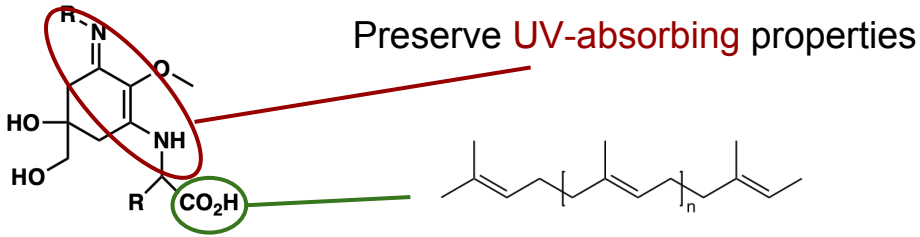
Permeability Constant



Proposed Solution 1: Direct use of alternatives as multipurpose additives

	Functional Use
Colorless Carotenoids 	1. **Emollient** 2. Chemical Stabilizer/Antioxidant 3. UV Absorber
 Mycosporine-like Amino Acids	1. **Chemical Stabilizer/Antioxidant** 2. **Antimicrobial** 3. UV Absorber
 Antioxidants 	1. **Chemical Stabilizer/Antioxidant** 2. **Skin Conditioner** 3. **Antimicrobial** 4. Indirect UV Absorber

Proposed Solution 2 (Long term): Use synthetic variants that improve performance criteria

Strategy	Issue	Resolution
Colorless Carotenoids	Skin permeability is too high due to **high hydrophobicity**	Add hydrophilic moieties Preserve UV-absorbing properties 
Mycosporine-like Amino Acids	Will easily wash off of skin due to **low hydrophobicity**	Replace hydrophilic moieties with hydrophobic groups Preserve UV-absorbing properties 

Remaining knowledge gaps

Technical Information

- Rates of dermal absorption of colorless carotenoids?
- Persistence of MAAs on skin?
- Thermal & photo stability of formulations
- Formulation benefits of antioxidants?

Safety Data

- Generally limited toxicological data
- How do colorless carotenoids influence dermal penetration of other ingredients?
- Workplace hazards associated with scale-up manufacturing?

Further Research

- Toxicity testing
- Sourcing of raw materials
- Cost feasibility

Thank you to Method & our Greener Solutions course leaders!

Kaj Johnson

Meg Schwarzman

Billy Hart-Cooper,

David Faulkner

Tom McKeag

& our Greener Solutions Cohort