

## Chapter 2

# Chemical and physical characteristics of sunscreen constituents

### Active ingredients

The active ingredients of sunscreens may be classified as organic or inorganic chemical absorbers. Table 3 and Appendix 1 show those ingredients that are approved for use in Australia, Europe, Japan and the USA.

### Organic chemical absorbers

The organic chemical absorbers are generally aromatic compounds conjugated with a carbonyl group. One classification of such UVR absorbers (Shaath, 1997b) is based on their chemical structure, as follows: cinnamates, *para*-aminobenzoate (PABA) derivatives, salicylates, benzophenones, camphor derivatives, dibenzoyl methanes, anthranilates (Fig. 14) and miscellaneous compounds. Cinnamates, PABA derivatives, salicylates and camphor derivatives are all principally UVB absorbers, while benzophenone derivatives, dibenzoyl methanes and anthranilates are principally UVA absorbers. In most organic chemical absorbers, an electron-releasing group (an amine or a methoxyl) is substituted in the *ortho* or *para* position of the aromatic ring. UVA absorbers are all *ortho*-substituted, allowing easier electron delocalization of the internal hydrogen bonding.

### Inorganic chemical absorbers

Inorganic chemical absorbers, such as titanium dioxide (TiO<sub>2</sub>) and zinc oxide (ZnO), absorb and scatter UVR, unlike organic chemicals which only absorb.

ZnO and TiO<sub>2</sub> were used relatively little in commercial sunscreens until micro-fine forms became available, providing formulators with the opportunity to produce an effective product that was cosmetically acceptable (Anderson *et al.*, 1997; Fairhurst & Mitchnick, 1997). Inorganic absorbers are generally used in conjunction with organic absorbers to achieve high SPFs.

### Historical perspective

Sunscreens appeared in commerce in the 1920s in the USA and in the 1930s in Europe. During the Second World War, red petrolatum was used by US armed forces. The varieties and uses of sunscreens proliferated after that time with changes in fashions, increased leisure time and greater awareness of health issues (Shaath, 1997a). PABA was a popular sunscreen in the 1950s and 1960s. It presents two extremely polar groups (amino and carboxylic acid moieties) with a *para* orientation on the benzene nucleus, which gives it certain characteristics that make its use difficult. These groups induce some hydrogen bonds either intermolecularly (giving rise to a crystalline physical state, unsuitable for cosmetic formulations) or with solvents (resulting in high water solubility and a dramatic solvent effect on absorption spectra). As doubts were raised about the safety of PABA with regard to the induction of contact sensitization (Kligman, 1966; Funk *et al.*, 1997), derivatives have been prepared, and

the two functional groups are now protected in several sunscreens, diminishing many of the problems associated with PABA itself, namely its physical aspect and water solubility. One of these compounds, ethylhexyldimethyl PABA, is one of the best UVB absorbers, with one of the highest extinction coefficients.

Salicylates were the first UVR filters used in sunscreen preparations. They are *ortho*-disubstituted compounds, which allows the formation of internal hydrogen bonds and thus decreases the ability of electrons to interact with other ingredients or solvent or biological substrates. Although they are relatively weak UVR absorbers, they have excellent safety records and, because they are easily incorporated into cosmetic formulations, some are used to solubilize other usually insoluble cosmetic ingredients, such as benzophenones. Of the salicylates on the market today, homosalate and ethylhexyl salicylate are the most widely used in sunscreen preparations.

Cinnamates have an extra unsaturation conjugated to both the aromatic ring and the carbonyl group portion of the carboxylic acid, thus allowing electron delocalization throughout the molecule. Cinnamates have been improved over the years. Ethylhexyl methoxycinnamate is currently the most popular sunscreen chemical, with good UVR absorption, safety, solubility in oils and insolubility in water, so that it is suitable for use in most waterproof sunscreen formulations.

Table 3. Chemical UVR absorbers approved for use in Australia, Europe, Japan and the USA

INCI nomenclature	CAS No.	COLIPA No.	Approved for use in			
			EU <sup>a</sup>	Japan <sup>b</sup>	USA <sup>c</sup>	Australia <sup>d</sup>
<b>ORGANIC CHEMICAL ABSORBERS</b>						
<b>UVB absorbers</b>						
<i>Cinnamates</i>						
- Cinoxate	104-28-9	S-29		Y	Y	Y
- DEA-methoxycinnamate	56265-46-4	S-24				Y
- Diisopropyl methyl cinnamate	32580-71-5	S-23		Y		
- Ethylhexyl methoxycinnamate	5466-77-3	S-28	Y	Y	Y	Y
- Ethyl methoxycinnamate	99880-64-5	–				Y
- Glyceryl ethylhexanoate dimethoxycinnamate	–			Y		
- Isoamyl- <i>para</i> -methoxycinnamate	71617-10-2	S-27	Y			Y
- Isopropyl- <i>para</i> -methoxycinnamate and diisopropylcinnamate mixture	–	–		Y		
<i>para</i> -Aminobenzoic acids (PABAs)						
- Amyl dimethyl PABA	14779-78-3	S-5		Y		Y
- Ethyl dihydroxypropyl PABA	58882-17-0	S-2				Y
- Ethylhexyl dimethyl PABA	21245-02-3	S-8	Y	Y	Y	Y
- Ethyl PABA	94-09-7	–		Y		
- Glyceryl PABA	136-44-7	S-6		Y		Y
- PABA	150-13-0	S-1	Y	Y	Y	Y
- PEG-25 PABA	116242-27-4	S-3	Y			
<i>Salicylates</i>						
- Dipropylene glycol salicylate	7491-14-7	–		Y		Y
- Ethylene glycol salicylate	87-28-5	–		Y		
- Ethylhexyl salicylate	118-60-5	S-13	Y	Y	Y	Y
- Homosalate	118-56-9	S-12	Y	Y	Y	Y
- Isopropylbenzyl salicylate	94134-93-7	S-16				Y
- Methyl salicylate	119-36-8	–		Y		
- Phenyl salicylate	118-55-8	S-14		Y		
- TEA salicylate	2174-16-5	S-9			Y	Y
<i>Camphor derivatives</i>						
- 3-Benzylidene camphor	15087-24-8	S-61	Y			
- Benzylidene camphor sulfonic acid	56039-58-8	S-59	Y			
- Camphor benzalkonium methosulfate	52793-97-2	S-57	Y			
- 4-Methylbenzylidene camphor	38102-62-4	S-60	Y			Y
- Polyacrylamidomethyl benzylidene camphor	113783-61-2	S-72	Y			
<i>Miscellaneous</i>						
- Diethylhexylbutamido triazone	154702-15-5	S-78	Y			
- Digalloyl trioleate	17048-39-4	S-55				Y
- Ethylhexyl triazone	88122-99-0	S-69	Y			Y
- 5-Methyl-2-phenylbenzoxazole	7420-86-2	S-47		Y		
- Octocrylene	6197-30-4	S-32	Y		Y	Y

Table 3. (contd)

INCI nomenclature	CAS No.	COLIPA No.	Approved for use in			
			EU <sup>a</sup>	Japan <sup>b</sup>	USA <sup>c</sup>	Australia <sup>d</sup>
– Phenylbenzimidazole sulfonic acid	27503-81-7	S-45	Y		Y	Y
– Urocanic acid	104-98-3	S-46				Y
<b>UVA absorbers</b>						
<i>Benzophenones</i>						
– Benzophenone-1	131-56-6	S-33		Y		
– Benzophenone-2	131-55-5	S-34		Y		Y
– Benzophenone-3	131-57-7	S-38	Y	Y	Y	Y
– Benzophenone-4	4065-45-6	S-40	Y	Y	Y	Y
– Benzophenone-5	6628-37-1	S-40	Y	Y		
– Benzophenone-6	131-54-4	S-35		Y		
– Benzophenone-8	131-53-3	–			Y	Y
– Benzophenone-9	76656-36-5	S-36		Y		
– Benzophenone-10	1641-17-4	S-39				Y
<i>Camphor derivative</i>						
– Terephthalylidene dicamphor sulfonic acid	90457-82-2	S-71	Y			Y
<i>Dibenzoylmethane</i>						
– Butyl methoxydibenzoylmethane	70356-09-1	S-66	Y	Y	Y	Y
<i>Anthranilate</i>						
– Menthyl anthranilate	134-09-8	–			Y	Y
<i>Miscellaneous</i>						
– Bisimidazylate (proposed INCI name)	180898-37-7	S-80	Y			
<b>UVA and UVB absorbers</b>						
<i>Miscellaneous</i>						
– Anisotriazine (proposed INCI name)	187393-00-6	S-81	Y			
– Drometrizole trisiloxane	155633-54-8	S-73	Y			
– Methylene-bis-benzotriazolyl tetramethylbutylphenol	103597-45-1-P	S-79	Y			
<b>INORGANIC CHEMICAL ABSORBERS</b>						
– Titanium dioxide (CI 77891)	13463-67-7	S-75	Y <sup>e</sup>	Y <sup>e</sup>	Y	Y
– Zinc oxide (CI 77947)	1314-13-2	S-76	Y <sup>e</sup>	Y <sup>e</sup>	Y	Y

INCI, International Nomenclature of Cosmetic Ingredients; CAS, Chemical Abstracts Service; COLIPA, European Cosmetic, Toiletry and Perfumery Association; EU, European Union

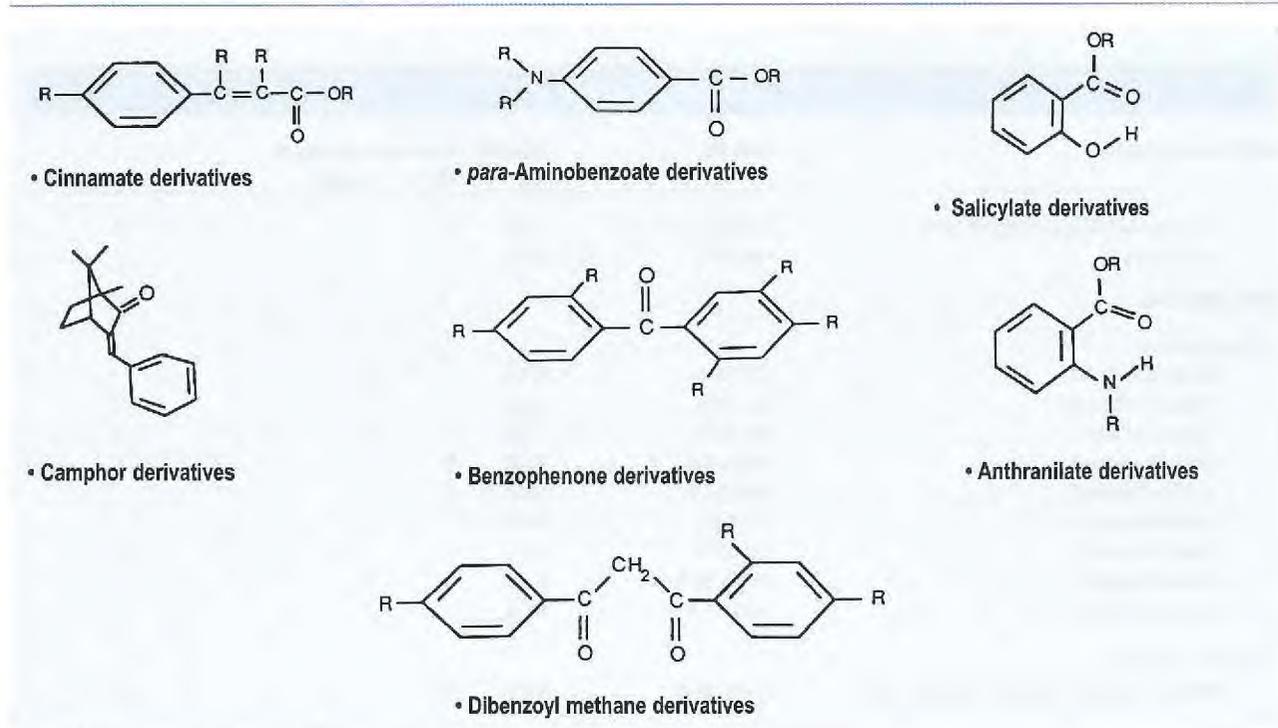
<sup>a</sup> From European Commission (2000)

<sup>b</sup> From Ministry of Health and Welfare (1999)

<sup>c</sup> From Food and Drug Administration (1999)

<sup>d</sup> The chemical UVR absorbers approved by the FDA (USA) and European Commission (EU) would be acceptable in Australia (Commonwealth Department of Human Services and Health, 1995)

<sup>e</sup> Approved as a cosmetic colourant



**Figure 14** The seven major groups of organic chemical sunscreen filters currently used in sunscreens

Benzophenones are dibenzoyl-methane derivatives that belong to the aromatic ketone category. They resonate easily, thus requiring a low quantum of energy; they therefore have a longer wavelength for electron transition. The main drawbacks to use of benzophenones as UVR filters are concern about their safety, as aromatic ketones are more difficult to detoxify than esters, and their solid state, which impairs their solubilization in cosmetic formulations. When high SPFs (20–30) are required, benzophenone-3 is usually used in combinations with solubilizers.

Camphor derivatives are bicyclic compounds with high extinction coefficients. With only one exception, they are solid. They are approved for use in Europe but not in the USA.

Anthranilates, such as menthyl anthranilate, are *ortho*-disubstituted aminobenzoates. This allows easy elec-

tron delocalization and a shift in the maximum absorption. Anthranilates, like salicylates, are stable and safe and have no significant solvent effects in cosmetic formulations.

Dibenzoylmethanes are substituted diketones with a keto–enol tautomerism which confers the characteristics of UVA filters (enol form). The keto form is responsible for high photoisomerization, resulting in a significant loss of protective power. These compounds have exceptionally high molar extinction coefficients but low photostability.

Of the miscellaneous compounds, phenylbenzimidazole sulfonic acid is a water-soluble sunscreen with effective dose-response relationships with SPFs. It has limited use in the USA.

TiO<sub>2</sub> became more popular after the introduction of micronized grades, but this product is still difficult to formulate. ZnO is used largely as a UVA absorber.

### Biological pigments

Melanin is the only natural pigment considered to be a sunscreen ingredient. It absorbs UVR and might provide both practical protection and the 'tanned' appearance desired by some people, but it is not available commercially (Chedekel & Zeise, 1997).

### Vehicles and formulations

pH and various solvents can profoundly influence the effectiveness of a sunscreen chemical because of shifts in absorption characteristics (Shaath, 1997b). In addition, the final formulation strongly influences the suspension, distribution, stability and retention of the sunscreen on the skin (Klein, 1997).

### Additional ingredients

At various times and under various circumstances, products containing sun-screening agents have also contained a

wide variety of other ingredients, including urocanic acid, antioxidants, stabilizers, vitamins, hormones, animal and plant extracts and preservatives. Whether and how these ingredients interact with the sunscreen chemical during use is not well documented.

Topically applied psoralens are known to enhance the induction of melanogenesis in skin exposed to UVR. For this reason, some sunscreen formulations were marketed with bergamot oil containing 5-methoxypsoralen. Since psoralens are known to enhance photocarcinogenesis (see IARC, 1987), they are no longer permitted in sunscreen formulations in Europe or the USA (Autier *et al.*, 1995, 1997a).

### Stability, photostability and reactivity

Analysis and quality control measures indicate that sunscreens stored under standard conditions meet or exceed the requirements for stability (Shaath, 1997c). Ideally, sunscreen molecules should absorb UV photons and then dissipate the excess energy through such processes as radiative decay (fluorescence and phosphorescence), self-quenching or internal conversion and vibrational relaxation (heat). In short, they should undergo little or no photochemistry. The following examples show that not all sunscreens meet this ideal.

Butyl methoxydibenzoylmethane was introduced in 1978 in Europe as a sunscreen ingredient that absorbed principally in the UVA region. The first formulation containing this ingredient that was marketed in the USA lost a significant amount of its effectiveness during use, reportedly because of photoreactions (Sayre & Dowdy, 1999).

The use of several esters of PABA has been reduced or discontinued

because of real or perceived cutaneous reactions, including irritation and contact sensitization (Funk *et al.*, 1997). One such ester (ethylhexyl dimethyl PABA) is reported to induce phototoxicity and photomutagenicity in budding yeast cells (Knowland *et al.*, 1993). Gulston and Knowland (1999) reported enhancement of DNA damage in human keratinocytes *in vitro* by a SPF-15 sunscreen formulation, and they attributed the effect to ethylhexyl dimethyl PABA.

Martincigh *et al.* (1997) catalogued the reported photochemical and photophysical characteristics of sunscreens, related compounds and their photoproducts. They also reviewed the evidence for photodimerization of DNA by sunscreens *in vitro*. They speculated that these events presage mutagenesis *in vitro* and, by extension, *in vivo*. They acknowledged that if such events occur only in the stratum corneum during use of sunscreens, little damage would be caused to viable cells.

### Analysis, verification and quality control

Analytical techniques of particular use in sunscreen chemistry have been reviewed (Shaath *et al.*, 1997a). The quality control procedures first involve physical and chemical analysis (Shaath, 1997c). The physical analysis includes tests for odour, colour, physical appearance, melting-point, refractive index, specific gravity, optical rotation, solubility, moisture, viscosity, pH and flash-point. The chemical analysis involves determination of saponification value, acid value, functional groups and metal content. Chromatographic and spectroscopic (UVR spectrum, infrared spectrum, nuclear magnetic resonance spectroscopy, mass spectrometry)

analyses are also performed (Klein, 1992; Shaath *et al.*, 1997b).

### New chemical absorbers

Several patents have been assigned for modifications of chemical UVR absorbers, including benzophenones, derivatives of dibenzoylmethane, ferulic acid amides, polyvalent metal salts of PABA, *para*-dimethyl PABA and 4-methoxycinnamic acid (Shaath, 1997a). Other derivatives (indoline derivatives, chalcone derivatives, benzylidene camphor) appear to be useful as chemical absorbers.

Natural and biosynthesized raw materials have also been described in patents and articles, including DL- $\alpha$ -tocopherol, thiamine or thiamine esters and genetically produced melanin incorporated in a polymer-based delivery system.

Several forms (microparticles and ultrafine powder) of the inorganic chemical absorbers TiO<sub>2</sub> and ZnO and other metal oxides have been shown to be superior to those available on the market. In addition, plastics, resin emulsions and particles have been studied for use as reflectors to block UVR

### Other properties of sunscreen ingredients

Sunlight generates active oxygen intermediates, including free radicals, in cells and tissues (Tyrrell, 1994), and these may damage cellular defence pathways. The free-radical scavenging antioxidant properties of the active components of sunscreens have not been investigated systematically. They will be relevant when sunscreens penetrate the cells and tissues in which active damaging intermediates are generated.