Article


Nicola Lionetti 1 and Luigi Rigano 2,*

1 Rigano Laboratories S.r.l., 20125 Milano, Italy; lionetti@thecosmetologist.com
2 ISPE, Institute of Skin and Product Evaluation, 20125 Milano, Italy
* Correspondence: rigano@thecosmetologist.com

Academic Editors: Marisanna Centini and Cecilia Anselmi
Received: 27 March 2017; Accepted: 9 May 2017; Published: 16 May 2017

Abstract: The sun-and-skin interactions have controversial sides. Besides important beneficial effects, we need to take into consideration also some serious harmful results. In particular, these are connected to the portion of the solar spectrum traditionally identified as ultraviolet type A and B. The topical application of sunscreens (and the avoidance of extreme exposure to sun rays) is worldwide recognized as the best strategy to avoid sunburn and oedema. Moreover, such strategy can efficiently prevent the onset of skin cancer. Therefore, the first aim of sunscreen products is to efficiently minimize all damage of sun exposure, while, at the same time, keeping good skin tolerability, avoiding safety problems and developing pleasant sensorial properties. Sunscreens, i.e., substances able to reflect and/or absorb, at a partial or complete extent, UV radiation are the key actors in skin protection. They are used to implement the level of primary photoprotection against UV rays. This means that when they absorb the radiation energy, their molecules pass to an excited state and successively re-emit energy in other forms (vibrational, rotational, infrared radiation) to come back to the ground state.

Keywords: Sunburn Protection Factor; formulation; filters stability; nanoparticles

1. Introduction

The role the UV rays play in inducing adverse effects at systemic, ocular and skin level is becoming more and more evident. In the past, as the UVB radiation was held responsible for immediate and evident skin damages, such as erythema or sunburns [1] the attention was mainly focused on UVB protection. However, some biological damages caused by UVB radiation on the DNA of keratinocytes and by the longer wavelength UVA radiation on the dermis, are asymptomatic. Their effects tend to accumulate over time and show their mischiefs after many years. The UVB radiation induces carcinogenesis too. After penetrating the dermis, the UVA radiation causes the release of free radicals which progressively damage the nuclear DNA, cell membranes, functional and structural protein of skin cells and causes the onset of elastosis as well as possible cancerous changes.

Moreover, the UVA radiation is the main concomitant cause of skin photosensitization and phototoxicity [2]. Considering that the incident radiation spectrum is constituted by approximately 95% of UVA radiation, we can easily work out how important is to arrange an appropriate skin protection strategy also from this thick slice of the solar spectrum, which is particularly dangerous as cannot be screened by either plastic or glass. As regards the UVC rays portion of the spectrum, they are extremely harmful but cannot reach the surface of the earth because of the screening action due to the ozone layer.
The efficient reduction of all harmful uncontrolled exposure to ultraviolet radiation effects is one of the current problems of the cosmetics industry. In some regions of the world that could be defined “at high risk”, this is supported by the actions of governments and their public health policy. Moreover, the formulation of sunscreen products has increased and widened their protection range, while the information to consumers has become more complete and clear.

The result of this increasing attention lead, in the last years, to the development of precise standards. These forced the industry to respect manufacturing criteria, for example, of sunglasses and eyeglasses, hats, clothing (children’s suits), umbrellas, shielding paints for automobile windows and tents. These standards also detail the methods of measurement the protection factors (UVB and UVA). The Australian Cancer Council, non-governmental organization for the prevention of cancer, has dedicated many pages of its website to illustrate a series of tips and tools to prevent harmful exposures [3]. In Australia, the strong insolation due to the latitude of the continent adds to the high solar sensitivity of the inhabitants, mostly light-skinned for their Anglo-Saxon origin.

Also in Europe, a growing interest in sun protection developed quickly. In 2006, the European Commission published the Recommendation 2006/647/EC on protective efficacy of sunscreen products and related indications of use [4]. This publication was intended to standardize and simplify, in Europe, the way how the effectiveness of sun protection products is verified and the clarity of the label of commercial products.

According to that Recommendation, the SPF (Sunburn Protection Factor) value must be written on the label and just eight numerical values could be claimed, as well as the relevant protection level. It is important to underline that the minimum suggested labelled SPF must be 6 and the maximum 50+ (corresponding to a measured SPF value ≥ 60). Furthermore, the SPF value must be followed by the qualitative description (low, medium, high or very high protection) (Table 1).

<table>
<thead>
<tr>
<th>Protection Level</th>
<th>SPF Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low protection</td>
<td>6, 10</td>
</tr>
<tr>
<td>Medium protection</td>
<td>15, 20, 25</td>
</tr>
<tr>
<td>High protection</td>
<td>30, 40</td>
</tr>
<tr>
<td>Very high protection</td>
<td>50+</td>
</tr>
</tbody>
</table>

Finally, the UVA protection value should keep a precise correlation with the UVB protection value mentioned on the label. The minimum UVA protection should be at least 1/3 of the UVB (e.g., a SPF 15 product in the UVB range shall have a UVA protection factor of at least 5).

Furthermore, the critical wavelength value must be, at least, equal to 370 nm. This means the limit wavelength at which the area of the section under the integrated optical density curve starting at 290 nm up to 370 nm equals 90% of the integrated section drawn between 290 nm to 400 nm. In other words, the product must be able to absorb enough UV radiation at longer wavelength (UVA). The compliance to both requirements is shown on the label by the circled acronym UVA (Figure 1):

![UVA](image)

**Figure 1.** Symbol used for products compliant with the requirement of UVA protection and minimum Critical Wavelength of 370 nm.

Reporting on the label the following warnings for the consumers is also recommended:
• Do not stay too long in the sun, even while using a sunscreen product.
• Keep babies and young children out of direct sunlight.
• Over-exposure to the sun is a serious health threat.
• Reducing the quantity of sunscreen product applied will significantly lower the level of protection.
• Apply (generously) sunscreen products before sun exposure.
• Reapply frequently to maintain protection, and especially after perspiration, swimming or towelling.

Based on several studies, the International Agency for Research on Cancer of the World Health Organisation [5] has emphasised the importance of the link between the correct application of sunscreen products and the efficacy of the sun protection factor claimed. In particular, the frequent re-application of sunscreen products is crucial. Moreover, in order to reach the protection level indicated by the sun protection factor, sunscreen products have to be applied in quantities similar to those used for testing, i.e., 2 mg/cm², which equals 6 teaspoons of lotion (approx. 36 g) for the body of one average adult person. This quantity is by far higher than that usually applied by the consumers. Applying a smaller quantity of sunscreen product leads to a disproportionate reduction in protection. For example, if the applied quantity is halved, protection may fall by as much as two-thirds. These considerations have led to a more cautious and controlled sun exposure and more detailed use recommendations.

The cosmetic industry, especially in the sunscreens field, and the health authorities, active in this area much more than in other cosmetic fields, quickly follows the evolutionary consumer needs. The concept of broad spectrum, lasting and safety protections leads in a relentless search for new technological formulae able to:

1. Ensure uniformity of skin application, resistance to water, sweat and lately, the abrasive action of the sand;
2. Be photo-stable, in order to preserve the UV filters from the decomposition induced by solar irradiation and, consequently, the loss of efficacy during the period of the consumer exposure;
3. Reach the right synergic combination targeted for normal skin, sensitive skin and babies consumers, able to avoid all skin sensitization or photosensitization;

2. Efficacy and Evaluation of UVB Sunburn Protection Factor (SPF)

The SPF is an index of the protection potential of the product from UVB rays. It was globally adopted and is today written on the labels of all sunscreen products, including also the cosmetic lines against skin photoaging. For years, in the international context, different methods have coexisted [6–10] (Table 2).

Table 2. SPF assessment methods before 1994.

<table>
<thead>
<tr>
<th>Country</th>
<th>SPF Method</th>
<th>ISSUE DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA *</td>
<td>FDA</td>
<td>1978 (’93)</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>AS/NZS</td>
<td>1983</td>
</tr>
<tr>
<td>Germany</td>
<td>DIN</td>
<td>1984</td>
</tr>
<tr>
<td>Japan</td>
<td>JCIA</td>
<td>1992</td>
</tr>
<tr>
<td>South Africa</td>
<td>SABS1557</td>
<td>1992</td>
</tr>
</tbody>
</table>

* First standard method.

(SPF) [13]. This method was adopted by Europe, Australia and New Zealand, India, Canada, South Africa, Mexico, Chile, Russia, Japan, Mercosur and Asean. Currently, in 2017, there are only two standard methods for the determination of the Sun Protection Factor: the ISO 24444:2010 (now under revision) and the US FDA 2011 [14].

The test is performed on subjects belonging to photo-type I, II or III according to the Fitzpatrick classification (Table 3), on the basis these skin types being more prone to sunburn. The skin colour is determined by the measurement of the Individual Typology Angle ITA° (>28°).

Table 3. Classification of skin types according to Fitzpatrick.

<table>
<thead>
<tr>
<th>Photo-Type</th>
<th>Fitzpatrick Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>always burns, never tans</td>
</tr>
<tr>
<td>Type 2</td>
<td>usually burns, tans with difficulty</td>
</tr>
<tr>
<td>Type 3</td>
<td>sometimes burns, sometimes tans</td>
</tr>
<tr>
<td>Type 4</td>
<td>burns minimally, always tans</td>
</tr>
<tr>
<td>Type 5</td>
<td>rarely burns, tans profusely</td>
</tr>
<tr>
<td>Type 6</td>
<td>never burns, deeply tans</td>
</tr>
</tbody>
</table>

3. Evaluation of the Sun Product Water Resistance

In December 2005, Colipa published the guidelines for determining the water resistance of a sunscreen product [15] (Colipa Guidelines for evaluating Sun Product Water Resistance 2005) and, on the next year, the Colipa recommendation n. 16 on “Water Resistance labelling, 2006” [16]. These suggest how to evaluate the SPF (using the method ISO 24444:2010) before and after water immersion of the skin site where the sunscreen product has been applied.

For this purpose, a spa-pool fitted with a water recirculation device is utilised. This contains water at constant temperature between 27 °C and 31 °C.

For sunscreen products claiming to be ‘water resistant’, the SPF is measured after two 20 min immersions (40 min immersion in total). While, if they claim to be ‘very water resistant’, four 20 min each immersions will be required (80 min in total). A sunscreen product can claim to be ‘water resistant’ or ‘very water resistant’ if the SPF value after immersion is equal to more than 50% of the value found before immersion (90% lower unilateral confidence limit for the mean percentage of water resistance retention ≥ 50%).

To give an example, a 30 SPF product can claim ‘water resistant’ if it keeps its SPF value higher than 15 after immersion in water.

4. In Vitro Determination of UVA Photoprotection

In 2007 Colipa issued an in vitro evaluation method of the UVA protection factor and the critical wavelength [17]. After two subsequent revisions, in 2009 [18] and in 2011 [19], the Colipa method was substituted by the ISO 24443:2012 method [20]. This is based on the transmittance through a layer of sunscreen product applied on a standard substrate (PPMA polymethylmethacrylate Plexiglas TM), before and after controlled UV exposure. The sunscreen sample is exposed to an irradiation dose proportional to the initial UVA protection factor UVAPF0, calculated from the adjusted absorbance data of the non-exposed sample.

This method permits to determine the UVA protection factor (UVAPF) of the sunscreen product, the ratio between the labelled SPF protection factor (which was determined by the above-described in vivo test), the UVAPF and the critical wavelength.

5. Further In Vitro/In-Vivo Methods

Further testing methods are used for the determination of SPF and UVA protection. The SPF can be also measured by an in vitro test, which cannot be considered as an alternative to the in vivo
method. The reason is that there is poor correspondence between the in vivo and in vitro SPF values, especially for high SPF values and at high content of inorganic filters.

In the past, in order to determine the UVA protection factor, the PPD (persistent pigment darkening) in vivo test was employed [21]. The method currently used is the ISO 24442:2011 [22].

The drawbacks of the in vivo UVA test are, first of all the poor reproducibility, because of the difficulty of reading of the induced skin pigmentation. Secondly, the subjects need to be exposed to UVA rays for very long times and this is not considered ethically correct, while being uncomfortable for the volunteers.

6. FDA 2011 Final Rule

The FDA (1978) was the first in vivo method created for the evaluation of SPF on informed human volunteers. It was revised in 1993, 1999 and 2011. The last revision issued on June 17th 2011 by the Federal Register is very similar to the ISO 24444:2010 method. In fact, both are grounded on the International Sun Protection Factor (SPF) test method, Colipa, 2006.

The slight differences between the ISO and FDA methods have no influence on the results. Therefore, the SPF values obtained with the two methods are comparable.

The main differences between the methods are the following:

- the calibration times of the UV source (each 12 months for the FDA, each 18 months for the ISO);
- the reference sunscreen products (P2 for the FDA and P2, P3 or P7 for the ISO);
- progressions of exposure times used.

Furthermore, as regards the labeling of the products, the FDA method establishes that the maximum SPF value to be reported on the label is 50+.

A “Broad Spectrum” UVA protection can be indicated on the label only for sunscreens having SPF $\geq 15$ and a critical wavelength of at least 370 nm.

The water resistance claims allowed on the label are the following:

- 40 min water resistance followed by the SPF value measured after the immersion
- 80 min water resistance followed by the SPF value measured after the immersion

Lastly, in USA the sunscreen products are not considered cosmetic but over-the-counter (OTC) products.


Issued in 2012 [23], it indicates ISO 24444 and 24443 as methods for the determination of in vivo SPF and in vitro UVA protection factor.

Sunscreen products are classified in the following way:

1. Therapeutics sunscreens regulated by TGA (Therapeutic Goods Administration), i.e., sunscreen products with SPF $\geq 4$ having the primary function of protecting from UV rays and protective products such as insect repellent (SPF $\geq 4$) or skin care products with SPF $> 15$ having as secondary function the protection from UV rays.

2. Cosmetic sunscreens regulated by NICNAS (National Industrial Chemicals Notification & Assessment Scheme), i.e., protective products having the secondary function of protecting from UV rays (skin care products with SPF $\leq 15$ and size < 300 mL, lip balm and lip stick with solar filters, make-up products with solar filters).

The method AS/NZS 2604:2012 indicates 11 possible SPF values to be reported on the label:

- LOW protection: 4-6-8-10
- MEDIUM protection: 15-20-25
- HIGH protection: 30-40-50
VERY HIGH protection: 50+

All the products must have on the label the indication “broad spectrum” UVA protection, apart for colored products with SPF < 30.

The possible water resistance claims to report on the label are:

- SPF from 4 to 7: no water resistance properties
- SPF from 8 to 14: maximum 40-min water resistance properties
- SPF from 15 to 29: maximum 2-h water resistance properties
- SPF > 30: maximum 4-h water resistance properties

8. Formulation Solutions

A precise formulation strategy has to be set in order to match with all the described requirements (SPF, UVA, Critical wavelength, water resistance). Moreover, one should consider other variables, like the solubility and stability of some UV filters and, being cosmetic items, the sensorial aspects.

Particularly for the high SPF values, the best starting point is the selection of the right combination of UVB and UVA filters, able to reach the right broad spectrum protection and the best possible stability. In this phase, the use of a well-known, already tested, formula, the suggestions of the suppliers and/or the use of a sunscreen simulator freely available online (https://www.sunscreensimulator.basf.com) are some possible starting approach. Usually, the blending of a high number of UV filters at low percentage is better than a combination of two or three of them at high percentage, both for safety concerns and also to achieve a synergic combination of effects. The ideal aim is the highest possible protection with the minimum possible amount of UV filters. Moreover, a high amount of sunscreen ingredients is often associated to a bad (greasy or waxy) final perception on the skin. Some good combinations could be:

- (a) Diethylamino Hydroxybenzoyl Hexyl Benzoate and Ethylhexyl Triazone in 3:1 ratio [24];
- (b) Octocrylene and Butyl Methoxydibenzoylmethane in a ratio of more or less 3:1 [25];
- (c) Octocrylene + Butyl Methoxydibenzoylmethane + Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine [26];
- (d) Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine (Bemotrizinol) + Diethylhexyl Butamido Triazone + Butyl Methoxydibenzoylmethane (based on our experience, unpublished data).

Moreover, the addition of small amount of inorganic UV filters helps to boost the SPF values, because solids are able to scatter the UV rays and increase their probability to hit and interfere with the molecules of ‘chemical’ UV filters.

The use of Butyl Methoxydibenzoylmethane (Avobenzone) is almost essential to reach high UVA protection, but it has to be adequately stabilized in order to avoid the undesired photo-ketonisation reaction (Figure 2):

The stabilization of Avobenzone could be reached by using different strategies [28,29]:

(1) The right stabilizers:

- Among other filters (Octocrylene, Polysilicone-15, Methylbenzylidene Camphor, Bemotrizinol, etc.);
- among antioxidants (Pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate, Diethylhexyl Syringilidenemalonate);

(2) Solubility: octocrylene, ethylhexyl and homomethyl salicylates, to avoid crystal formation;

(3) Avoiding the incompatibility with metal ions, by using chelating agents like Disodium EDTA

(4) Avoiding formaldehyde donors;

(5) The combinations of Avobenzone with inorganic UV filters (this is not allowed in the USA) can improve the stability of avobenzone by about 10–15% but the inorganic UV filters must be of the coated type;
(6) Use polar solvents to inhibit Norrish-Type-I cleavage of Avobenzone (Paraffin is bad, Ethanol is good);

This important phase requires also some considerations concerning:

(a) The type of final users. The use of Octocrylene, Ethylhexyl Methoxycinnamate and PABA derivatives is not suggested for consumers with sensitive skin or for baby products [30].

(b) The market: Europe, Japan, USA, etc., similarly to what happens for test methods, also the number of available sunscreen ingredients is different according to the different legislations. In USA (where sunscreen products are sold as OTC and not as cosmetic products) the available number of UV filters is extremely limited in comparison to Europe. Also their maximum allowed percentages are in many cases different (Ethylhexyl Methoxycinnamate allowed at 10% in Europe, at 20% in Japan);

(c) If a water resistant formula is requested, the use of hydrosoluble UV filters (Phenylbenzimidazol Sulfonic Acid) could be a bad idea;

Among filters, the selection of inorganic filters is an increasing trend for the request of ‘natural’ claims. Titanium dioxide and zinc oxide are the most widely used metal oxides as UV filters. They are efficient, almost photostable, absorb the UVB and UVA radiations and re-emit them mainly as visible fluorescence or heat. For their chemical-physical characteristics, the surface of the two pigments has to be coated with “inert” substances like silica, alumina, stearic acid or silicone compounds. If uncoated, TiO\textsubscript{2} surface, after UV absorption, emits excited electrons, which can generate free radicals, resulting in oxidative damages into the dermal layers. On the other side, ZnO, if uncoated, can modify the \( \text{pH} \) of the product as it tends to turn partially into Zn hydroxides, partially releasing \( \text{OH}^- \) ions in the system [31]. Moreover, the coating prevents the agglomeration of particles and keep the pigments well dispersed in the system, while improving the stability and UV protection efficacy of the sunscreen product.

![Irreversible Photoreactions](image)

**Figure 2.** Irreversible photoreactions of Avobenzone [27].

Titanium dioxide and zinc oxide are especially used in their ‘nano-sized’ form for many reasons. The nanosize dimension enhances the protection capacity [32]. Moreover, the smaller the particles, the higher the homogeneity of the layer onto the skin, the better the coverage of the epidermis. Finally, for particle size of about 35 nm, nanoparticles are big enough to absorb, scatter and reflect short-wavelength UV radiation while they keep invisible to the longer-wavelength, visible light. In this way, the sunscreen formulation is transparent to the eyes. The optimum particle size for high UVB and UVA attenuation but good transparency is between 40 nm and 60 nm [33] (see Figure 3).
For all nanoparticles, the special range of dimensions can modify significantly their physicochemical properties. Such characteristics can increase the uptake and extend or even create new physico-chemical interactions with biological tissues. The potential toxicity risks are well described in a lot of studies: The main concern is the production of reactive oxygen species, including free radicals which will result in oxidative stress, inflammation, and consequent damage to proteins, membranes and DNA [34]. The access route for nanoparticles to enter the body are: ingestion, inhalation and through the skin. The oral exposure to nanoparticles as cosmetic ingredient in sunscreens is limited to accidental ingestion of small fractions of lip products and sun protection products and can be considered to be low [35].

![Figure 3.](image)

**Figure 3.** Effect of particle size on the UV attenuating properties of titanium dioxide. Reduction of particle size moves the peak of UV attenuation to shorter wavelengths, while improving transparency (Slighty modified from [36], with permission from Allured.

As far as titanium dioxide and zinc oxide are concerned, the Department of Dermatology, Venereology and Allergology of the University of Berlin states that zinc oxide nanoparticles penetrate only into the outermost layers of stratum corneum, furrows and into the orifices of the hair follicles but do not reach the viable epidermis [37]. Moreover, the United States Food and Drug Administration indicated that nano-scale titanium dioxide may have better efficacy than other filters while lacking toxicity. Finally, the scientific European committee has emitted in 2012 and 2013 two opinions concerning the 2 nano-size UV filters [24,38]. SCCS stated that the use of these ingredients in the nano-form remains safe for the human health.

At the moment, the only lack of confidence concerns the possibility of introducing these nano-ingredients in cosmetics applied in spray form. This is because of the possible risks of inhalation during the application onto the body, high dose and long residence time of the nanoparticles in the vital organs can lead to their dysfunction, and the limited toxicological data given by producers.

The second step is the solubilisation of sparing soluble solid UV filters like Avobenzone, Ethylhexyl Triazone, etc. This aspect is often neglected during the formulation process, with the consequence that, during its shelf life, the product slowly decreases its protective capacity due to the precipitation of filters. The problem is also magnified by the complexity of the system (presence of solid stabilizer, polymers, emulsifiers, etc.) and by the poor, and in some cases not correct, information available on the solubility of the filters. Therefore, this step asks for the selection of different polar oils (usually esters like Ethylhexyl Benzoate, Dibutyl Adipate, Diisopropyl Sebacate are good solubilizers) able to keep well dissolved the filters. A suggestion could be to prepare the oil phase of the formula (without waxy ingredients) and put it in the fridge in order to verify the stability of such solutions.
Among all the above reported requirements, the resistance to water-immersion is today a key parameter. In general, the main ways for obtaining water or very water resistant effects are the follows:

- Preparing a fully anhydrous formulation with the addition of film forming polymers;
- Creating w/o emulsions;
- Obtaining a meta-stable o/w emulsion with a low level of emulsifiers, adding, also in this case, good film forming polymers;

In the first case, the absence of emulsifiers avoids a driver of subtraction of the oil layer from the skin. Moreover, sunscreens are generally soluble in many (polar) oils and do not reach their limit of solubility because of the high amount of solvent materials. This formula can be with (25–50%) alcohol or without it. Nevertheless, all-oil formulae are not the most popular cosmetic form for sun protection, mainly for sensorial (and cost) reasons.

Water in oil emulsions have the advantage of the difficult removal from the skin surface. When water has evaporated from (or has been absorbed by) the skin, the emulsifier gets homogeneously dispersed in the oil phase and there is not enough energy available in the oil + emulsifier layer to incorporate again water droplets from the environment. Moreover, these systems show a good compatibility with the skin physiology and allow a normal evaporation of sweat.

One dilemma could be the request of a sprayable emulsion with water resistant efficacy; this is not easily practicable with w/o emulsion. One possible solution is the stabilization of the emulsion using a little amount of emulsifiers helped by the introduction of stabilizing polymers (like Acrylates derivatives). The choice of O/W formula requires, also, the introduction of film formers.

9. Conclusions

The formulation of efficient, up to date, internationally marketed sunscreens is a real challenge for the formulators. The formulation strategy, even if some guidelines exist in the literature and in suppliers’ documents, still requires thorough testing and adjustments. Stability of the obtained performances during time and shelf life and at extreme climates is contemporarily a matter of efficacy and of consumers’ safety. The objectives of this category of products are challenging and continuously refined with the progression of medical, physical and chemical knowledge. Indeed, a jungle even for the expert scientists!

Author Contributions: Nicola Lionetti and Luigi Rigano conceived and designed the lay-out of this paper and carried out the bibliographic research; Nicola Lionetti and Luigi Rigano analyzed critically the data; Nicola Lionetti wrote the paper; Luigi Rigano revised it.

Conflicts of Interest: The authors declare no conflict of interest.

References


35. SCCS (Scientific Committee on Consumer Safety). Opinion on Zinc Oxide (Nano form); SCCS: Brussels, Belgium, 2012.
38. Scientific Committee on Consumer Safety (SCCS). Opinion on Titanium Dioxide (Nano Form); SCCS: Brussels, Belgium, 2013.

© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).