Two Decades of Advancements in Sun Protection Factors Determination: A Comprehensive Review and Anticipation of Future Developments in Photoprotection Methods.

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COTY - Discovery & Innovation R&D – MONACO

Abstract

Despite global preventive efforts and warnings from dermatologists and health organizations, the incidence of skin cancers continues to surge annually. In 2021, K. Urban published an article revealing that skin cancers attributed to sun overexposure approached 8 million. Alongside protective clothing, increasingly potent topical sunscreens contribute to bolstering defense against these risks. It is imperative to possess standardized methods for consistently measuring these protective factors. Over two decades of research and collaboration have resulted in evolved and standardized international methodologies for determining protection factors.

Experts from diverse working groups and authorities, including the European Commission, the ongoing ISO standardization process and the possible systematic reviews, along with recommendations from Cosmetics Europe, and valuable input from consumers, contribute to improve, update and establish safeguards. However, it is not easy to have a comprehensive and straightforward understanding of the current situation.

Based on a comprehensive historical overview, this review will explain:

- The objectives and the work carried out by the different working groups

- The advantages and drawbacks of the standardized methods,

- The very latest developments expected this year at ISO level,

- Finally, the methods that will likely be proposed as candidates for standardization in the near future.

Introduction:

Despite global preventive efforts and warnings from dermatologists and health organizations, the incidence of skin cancers continues to surge annually. In 2021, K. Urban [1] published an article revealing that skin cancers attributed to sun overexposure approached 8 million. Alongside protective clothing, increasingly potent topical sunscreens contribute to bolstering defense against these risks. It is imperative to possess standardized methods for consistently measuring these protective factors. Over two decades of research and collaboration have resulted in evolved and standardized international methodologies for determining protection factors. This review comprehensively explores this 20-year journey, current advancements, and prospects in photoprotection methods.

Discussion

In September 2006, the European Commission published its recommendations regarding the effectiveness of sun care products [2]. These recommendations noted that “preference should be given to *in vitro* testing methods delivering equivalent results.

Industry should increase efforts to develop *in vitro* testing methods for the protection against both UVB and UVA radiation.

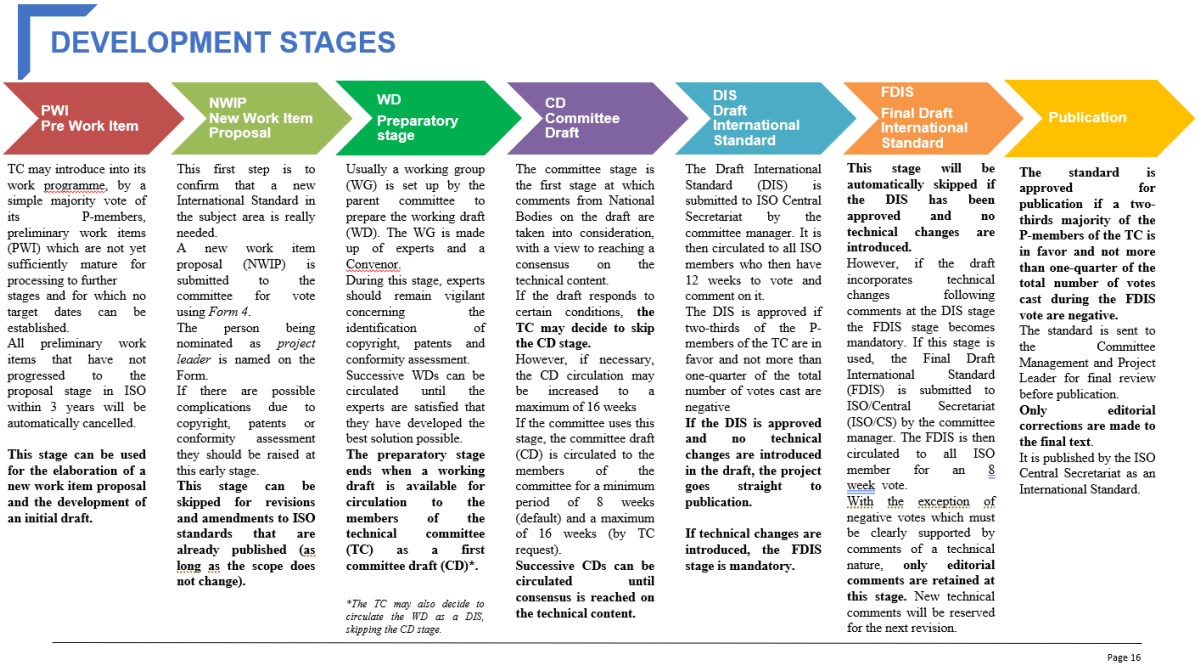
(17) While these testing methods should be used as reference methods, preference should be given to *in vitro* testing methods delivering equivalent results, as *in vivo* methods raise ethical concerns. Industry should increase efforts to develop *in vitro* testing methods for the protection against both UVB and UVA radiation.

This is what has been done as it is now well-recognized and widely accepted that *in vivo* SPF testing methods presents several major issues:

- It raises ethical concerns, as it involves the use of human volunteers for testing.
- In terms of inclusivity, this method is limited because it primarily validates only Caucasian skin types.
- Economically, these tests are relatively expensive, and the process is lengthy, typically taking between 3 to 4 weeks to complete.
- Additionally, conducting these tests is particularly challenging during the summer season because volunteers may have tan lines, which compromise the reliability of the results.

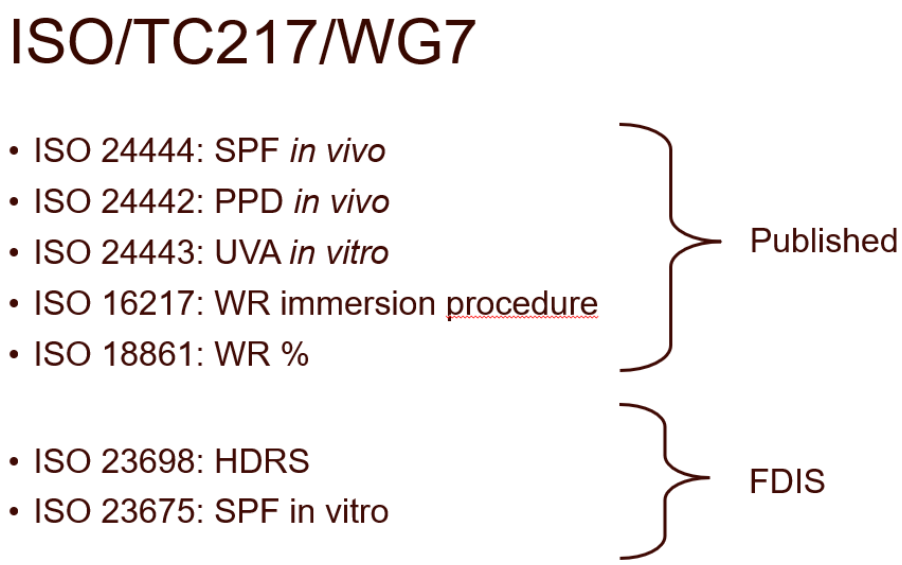
There are several ways for a method to be recognized internationally. The first is to publish it, but its acceptance and global deployment can take years. The second is to publish it through the International Organization for Standardization (ISO). This is the preferred route because ISO is recognized worldwide and has already published no fewer than 30,000 widely accepted standards [3].

There are several validation steps during the development of a standard. It starts with a Preliminary Work Item and ends with the publication of the International Standard.



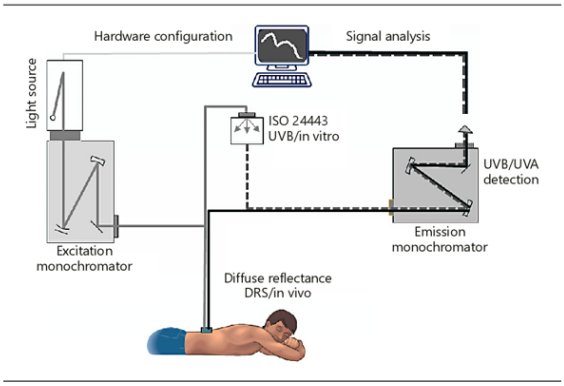
The intermediate steps gradually evolve the method through technical improvements provided by various experts in the ISO group. These experts for Working Group 7 come from around 40 countries representing all parts of the world. These experts may come from the industrial sector, academia, non-governmental organizations, public health organizations, or be independent experts. This allows ISO to propose standards based on multidisciplinary scientific consensus. This process generally takes 3 to 5 years.

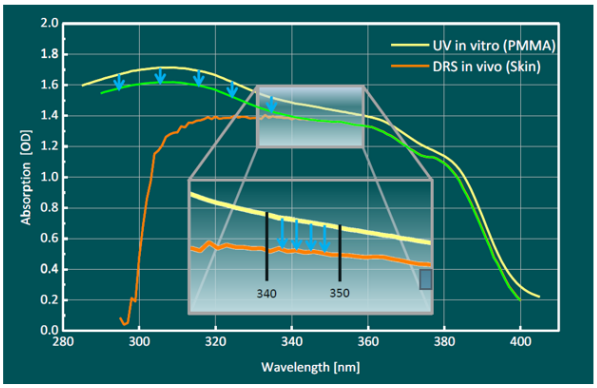
Working Group 7 is currently studying 7 standards: *in vivo* SPF, *in vivo* and *in vitro* UVA protection factor, *in vivo* water resistance, and two alternative methods to *in vivo* SPF, which are the Hybrid Diffuse Reflectance Spectroscopy (HDRS) and double plate *in vitro* SPF. The *in vivo* methods for SPF, UVA, and water resistance, as well as the *in vitro* UVA method, are well-known and will not be revisited here.



One of the proposed alternative methods is the Hybrid Diffuse Reflectance Spectroscopy (HDRS) [4-6]. This method is based on the hybridization of two parts: one performed on a human volunteer (application of the cream) and the other on a plastic substrate (obtaining the shape of the curve). The curve shape obtained from the *in vitro* part is adjusted to the absorption intensity obtained from the *in vivo* part. This method also includes irradiation to account for any potential photo-instability of the cream.

Methode HDRS



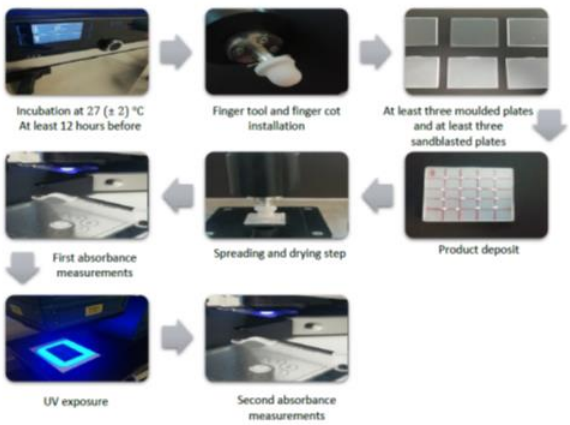


Courtesy of Schrader Institute

This method has the significant advantage of being non-invasive (the dose received by the volunteer is less than 1/10 of the minimal erythemal dose) but has the drawbacks of using human volunteers, who must also have a phototype not exceeding III.

Due to these limitations, several research groups, including Colipa, have focused more on another principle of alternative methods, this time 100% *in vitro*. At the end of the 90s the working group of COLIPA (now known as Cosmetics Europe) began developing an initial version of an *in vitro* method using PMMA plates [7]. In 2018, after a decade of development, during which all factors influencing the method were analyzed and controlled, a robust *in vitro* method for measuring SPF *in vivo* with high precision, repeatability, and reproducibility was proposed by Cosmetics Europe to ISO. This method is based on the use of two types of PMMA plates, UV irradiation proportional to SPF, and robotic spreading [8-11].

Background in vitro double plates method



1. Preparation of products and materials
2. Application of the product on substrates and automatic robotic spreading
3. Measurement of initial absorbance on two types of plates (from 290 nm to 400 nm)
4. Calculation of the initial in vitro SPF.
5. Calculation of the radiation dose (based on the initial in vitro SPF).
6. Irradiation with calculated dose.
7. Measurement of the final absorbance post-irradiation on both types of plates (from 290 nm to 400 nm).
8. Calculation of the final in vitro SPF

Courtesy of L'Oréal

Various optimizations and adjustments have led to a robust method this year, which will be submitted for a final approval vote. The results will be known by the end of September 2024, and there is no doubt it will be positive. Following some editorial adjustments, this method will likely be published in early 2025.

There will therefore be three coexisting methods for determining SPF for a while:

- a 100% *in vivo* method, which is the current gold standard (ISO24444)
- a 100% *in vitro* method (ISO23675)
- and a hybrid method using both *in vivo* and *in vitro* parts. (ISO23698)

Undoubtedly, the market will make its choice among these different methods.

The current issue is not really whether there is a difference in protection for the consumer between SPF 30 and SPF 50, but rather whether we can measure with precision, repeatability, and reproducibility an SPF 30 and an SPF 50. In other words, can we measure an SPF 30 and an SPF 50 and be sure they are statistically different?

And what does science demand? The same thing. The relevance of the choice, scientifically speaking, will also depend on the criteria of repeatability and reproducibility. In this regard, the double plate *in vitro* method is perfectly positioned. Moreover, it meets the expectations of consumers, regulatory bodies, ethics, and inclusivity concerns.

Conclusion:

In this review, we have discussed the research, improvements, publications, and standardizations carried out over almost 20 years.

Science takes time—time to read, time to make mistakes, time to learn from those mistakes, time to dialogue, exchange, and contradict one another, and finally to advance and reach a consensus. The alternative methods proposed are the result of over 20 years of research and development. They are proposed today not by chance or opportunism, but because they are ready to be used.

In 2025, we will have the possibility to use *in vivo* SPF and UVA methods for countries or regions that do not yet accept alternative methods, the HDRS for those who are not yet convinced by *in vitro* methods, and the *in vitro* double plate UVA and SPF methods, which are the only purely *in vitro* methods. These methods are economically advantageous, ethical, and inclusive.

The work is not finished but the wishes of the European Commission and many countries, organizations, or experts are therefore on the verge of being realized: enabling the testing of all sun protection factors *in vitro.*

Keywords: SPF – ISO- European Commission – Review

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