

Sun Protection Factor Testing: A Call for an In Vitro Method

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PRACTICE POINTS

- The methodology for determining sun protection factor (SPF) that currently is accepted by the US Food and Drug Administration is an expensive and imprecise in vivo test that exposes human participants to harmful UV radiation.
- In vitro tests for determining SPF may be viable alternatives to the current in vivo gold standard.
- Researchers and the sunscreen industry should actively develop these in vitro methodologies to adopt a more accurate and less harmful test for SPF.

The sun protection factor (SPF) value indicates to consumers the level of protection that a given sunscreen formulation provides against erythemally effective UV radiation (UVR).¹ In vivo SPF testing, the gold standard for determining SPF, yields highly variable results and can harm human test participants.² In vitro SPF testing methodologies have been under development for years but none have (yet) replaced the in vivo test required by national and international regulatory agencies.

Recent European studies have shown strong data to support a highly standardized in vitro method,¹ now under development by the International Organization for Standardization (ISO)—potentially to serve as a new SPF determination standard.^{1,3} Academia and industry should follow this example and actively take steps to develop and validate a suitable replacement for in vivo SPF testing.

In Vivo SPF Testing

The in vivo SPF test involves comparing doses of UVR necessary to induce erythema in human participants with and without sunscreen applied.² Although this method has long been the standard for SPF determination, it is associated with the following major disadvantages:

- Cost: The in vivo test is expensive.
- Variability: Results of the test are subject to high interlaboratory variability due to the inherent subjectivity of identifying erythema, the variable skin types of human participants, and other laboratory-dependent factors.² A study found that the average coefficient of variation for SPF values obtained from 3 or 4 laboratories to be 20%—with values exceeding 50% in some cases. With that level of variability, the same sunscreen may be labeled SPF 30, SPF 50, or SPF 50+, thereby posing a health risk to consumers who rely on the accuracy of such claims. In fact, Miksa et al² concluded that “the largest obstacle to a reliable SPF assessment for consumer health is the in vivo SPF test itself.”
- Ethical concerns: Human participants are intentionally exposed to harmful UVR until sunburn is achieved. For that reason, there have been calls to abandon the practice of in vivo testing.¹

Alternatives to In Vivo SPF Testing

There has been international interest in developing in silico and in vitro alternatives to the in vivo SPF test. These options are attractive because they are relatively inexpensive; avoid exposing human participants to harmful UVR; and have the potential to be more accurate and more reproducible than in vivo tests.

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In Vitro Protocols—Many such in vitro tests exist; all generally involve applying a layer of sunscreen to an artificial substrate, exposing it to UVR from a solar simulator, and measuring the UVR transmittance through the product and film by spectrophotometry.¹ Prior shortcomings of this method have included suboptimal reproducibility, lack of data on substrate and product properties, and lack of demonstrated equivalency to in vivo SPF testing.⁴

In Silico Protocols—These tests use data on the UV spectra of sunscreen filters, physical characteristics of sunscreen films on skin, and the unique photoinstability of filters to calculate expected UVR transmittance and SPF of sunscreens based on their ingredients.⁵ Reports have shown high correlation with in vivo values. Results are not subject to random error; reproducibility is theoretically perfect.⁵

Regulatory Agencies and In Vitro Testing

In the United States, sunscreens are regulated as over-the-counter drugs. In vivo testing is the only US Food and Drug Administration (FDA)–approved method for determining SPF for labeling purposes.¹ In a 2007 Proposed Rule and a 2011 Final Rule, the FDA stated that in vitro SPF tests were an inadequate alternative to in vivo tests because of their shortcomings.^{4,6}

Acknowledging the potential benefits of in vitro testing, the FDA wrote that it would consider in vitro alternatives if equivalency to the in vivo test could be proved.⁶ The agency has not published an official stance on in vitro SPF testing since those statements in 2007 and 2011. Of note, the FDA deems in vitro testing sufficient for making claims of broad-spectrum coverage.⁴

In contrast to the regulatory scenario in the United States, Europe regulates sunscreens as cosmetics, and the European Union (EU) has banned animal testing of cosmetics,⁷ which poses a problem for the development of new sunscreens. It is not surprising, therefore, that in 2006 the European Commission (the executive arm of the EU) published a mandate that in vitro SPF testing methods be actively developed due to ethical concerns associated with in vivo methods.⁸ In 2017, the International Organization for Standardization released specific validation criteria for proposed in vitro tests to facilitate the eventual approval of such methods.¹

Progress of In Vitro Methods

In recent years, advances in in vitro SPF testing methods have addressed shortcomings noted previously by the FDA, which has led to notably improved reproducibility of results and correlation with in vivo values, in large part due to strict standardization of protocols,¹ such as tight temperature control of samples, a multisubstrate approach, robotic product application to ensure even distribution, and pre-irradiation of sunscreen samples.

With these improvements, a 2018 study demonstrated an in vitro SPF testing methodology that exceeded

published ISO validation criteria for emulsion-type products.¹ This method was found to have low interlaboratory variability and high correlation with in vivo SPF values (Pearson $r=0.88$). Importantly, the authors noted that the consistency and reliability of in vitro SPF testing requires broad institution of a single unified method.¹

The method described in the 2018 study¹ has been accepted by the ISO Technical Committee and is undergoing further development³; it is expected to be approved by the European Committee for Standardization. After approval, adoption by member nations of the EU will require individual action, representing the next regulatory hurdle for in vitro SPF testing in Europe.

Final Thoughts and Future Steps

Recent data confirm the potential viability of in vitro testing as a primary method of determining SPF values.¹ Although ISO has moved forward with development of this method, the FDA has been quiet on in vitro SPF testing since 2011.⁴ The agency has, however, acknowledged the disadvantages of in vivo broad-spectrum testing, including exposure of human participants to harmful UVR and poor interlaboratory reproducibility.⁶

Given the technical developments and substantial potential benefits of in vitro testing, we believe that it is time for the FDA to revisit this matter. We propose that the FDA take 2 steps toward in vitro testing. First, publish specific validation criteria that would be deemed necessary for approval of such a test, similar to what ISO published in 2017. Second, thoroughly assess new data supporting the viability of available in vitro testing to determine if the FDA's stated position that in vitro testing is inadequate remains true.

Although these 2 steps will be important to the process, adoption of an in vitro standard will require more than statements from the FDA. Additional funding should be allocated to researchers who are studying in vitro methodologies, and companies that profit from the multibillion-dollar sunscreen industry should be encouraged to invest in the development of more accurate and more ethical alternatives to in vivo SPF testing.

In vitro SPF testing is inexpensive, avoids the moral quandary of intentionally sunburning human participants, and is more reliable than in vivo testing. It is time for the FDA to facilitate the efforts of academia and industry in taking concrete steps toward approval of an in vitro alternative to in vivo SPF testing.

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