Application Note 48

Photo-Biological Testing With UV Solar Simulators

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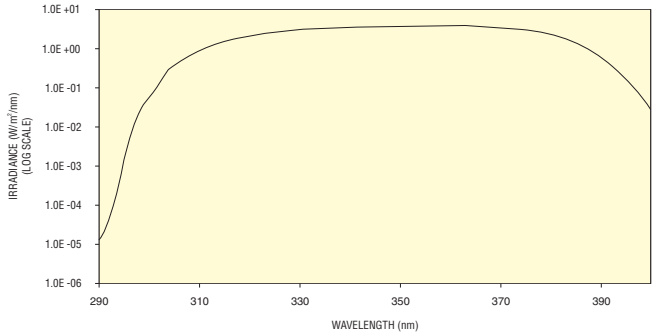
Photo-biology is the study of the effect of UVA and/or UVB, visible, and IR radiation upon living systems. The first law of photochemistry (Grotthaus-Draper Law) states that light must be absorbed for a photochemical event to occur. Chromophores in drug products and DNA in dermal tissue are targets for photochemical reactions. Photoirritation and/or photoallergy occur when a photoactive chemical enters the skin by dermal penetration or systemic circulation and becomes excited by appropriate UV or visible light photons.

Photo safety testing is suggested for any chemicals that absorb light in the range from 290-700nm for any substance that may be applied topically or can reach the skin and/or eyes by systemic exposure (oral or intravenous). There are four basic results or endpoints that photo-safety testing address. These are:

- **Photo-toxicity** sometimes referred to in literature as photo-irritation is described as an acute light-induced skin response to a photo-reactive chemical.
- **Photo-allergy** is described as an immune reaction to a chemical initiated by the formation of photo-products. This can be a byproduct of exposure to an antigen.
- **Photo-genotoxicity** is described as a genotoxic response after exposure to a chemical which is photo-activated by UV or VIS light.
- **Photo-carcinogenicity** is described as the potential for a chemical to promote skin tumor formation in combination with exposure to UV light.

For pharmaceuticals or cosmetic components, basic photo-safety testing is done to determine if any of the endpoints are produced on exposure by in-vivo or in-vitro testing of animals or cell cultures when exposed to UV radiation compared to comparable samples without ultraviolet radiation exposure, and to controls without the chemical exposed to the same dose of UV light. Many diverse classes of drugs (including antimicrobials, NSAIDs, antidepressants, anticonvulsants, diuretics, and antihypertensives) have been reported to cause photoirritation in humans.

The majority of methods call out for an irradiation spectrum which approximates the solar spectrum using appropriate filters to remove the UVC component but pass the UVA and UVB. Most methods do not provide specific further guidance and the variation in the intensity within the UVA and UVB can differ significantly depending on the light source used. Sol-UV Series Solar Simulators provide a defined spectral output certified to be compliant to FDA CFR Part 201.327, ISO 24444:2010(e) First Edition, and the International; l SPF Test Method (CTFASA/COLIPA/JCIA/CTFA: May 2006 for Spectral Match.



Colipa Irradiance Response Curve

ISO: 24444:2010(e), First edition 2010-11-15, Sun protection test methods - In vivo determination of the sun protection factor (SPF), Annex B, Definition of UV solar simulator output. Specifically section B.2.5 Solar simulator and filtration and section B.3.1 UV solar simulator acceptance limits.

	Measured % RCEE	
Spectral Range (nm)	**Lower Limit**	**Upper Limit**
<290		<0.1
290-300	1	8.0
290-310	49.0	65.0
290-320	85.0	90.0
290-330	91.5	95.5
290-340	94.0	97.0
290-400	99.0	100.0
UVA II (320-340)	≥ 20.0	
UVA I (340-400)	≥ 60.0	

The use of a standardized light source will facilitate easier comparison of experimental data by eliminating the variables associated with using various undocumented light sources with vastly differing spectral profiles in the UV. Besides spectral consistency, irradiance uniformity over the work area is maintained; this is critical since so called hot spots can lead to errors in delivered dosage. The Oriel Sol-UV Simulator's spatial uniformity performance standard is designed to deliver less than 5% non uniformity across the entire work area. Temporal stability is also important in minimizing dosage errors. Newport's experience in designing ultra stable power supplies and feedback controllers deliver the best short and long term stability and assures output light is stable over time

to minimize impact on the desired dosage.

The Sol-UV Series allows for varying the dosage using an integrated variable aperture and can be bundled with an optional light intensity control system to deliver specific dosages as a function of exposure time.

Photo-toxicity

For photo-toxicity testing the in vitro 3T3 NRU phototoxicity test is used to identify the phototoxic potential of a test substance induced by the excited chemical after exposure to light. The test evaluates photo-cytotoxicity by the relative reduction in viability of cells exposed to the chemical in the presence versus absence of light. Substances identified by this test are likely to be phototoxic in vivo, following systemic application and distribution to the skin. The reliability and relevance of the in vitro 3T3 NRU phototoxicity test was recently evaluated (1)(2). The in vitro 3T3 NRU phototoxicity test was shown to be predictive of acute phototoxicity effects in animals and humans in vivo. The test is not designed to predict other adverse effects that may arise from combined action of a chemical and light, for example, it does not address photogenotoxicity, photoallergy, or photocarcinogenicity, nor does it allow an assessment of phototoxic potency.

The 3t3 method suggests that simulation of sunlight with solar simulators is considered the optimal artificial light source. The irradiation power distribution of the filtered solar simulator should be close to that of outdoor daylight. They further state that xenon based solar simulators emit significant quantities of UVB and should be suitably filtered to attenuate the highly cytotoxic UVB wavelengths. The Sol-UV has filters available to suppress UVB. The method also states that irrespective of measures taken to attenuate parts of the spectrum by filtering or by unavoidable filter effects of the equipment the spectrum recorded below these filters should not deviate from standardized outdoor daylight. The COLIPA compliant output of the Sol-UV solar simulators meets these requirements.

Photo-Allergy

Photo-allergy testing is done in-vivo as it requires measuring an immune response to photo-products generated upon exposure to UV or VIS light. Sol-UV can be used to expose the animal to UV light typical of the wavelength range used in sunscreen protection factor (SPF) as described in the COLIPA monograph.

Photo-Genotoxicity

Photo-genotoxicity testing attempts to assess the potential of a compound to turn into a genotoxic product on exposure and activation by UV or VIS light. The photo-genotoxic response can also be inferred by damage to DNA (mutagensis) like strand breaks, or inhibition of the normal DNA repair mechanisms.

Photo-Carcinogenicity

Photo-Carcinogenicity is typically evaluated using in-vivo testing of albino hairless mice to evaluate the effect of UV light on promoting skin cancers of all types. The mechanisms may be photo-genotoxicity, immunosuppression, or photo induced by-products that display either mechanism. These studies typically use light sources whose output mimic the UV output of the sun, similar to the COLIPA standard and may involve accelerated dosages.

Sol-UV Performance Specification

Simulator Model	SOL-UV-2	SOL-UV-4	SOL-UV-6
Collimation Angle	(half angle) <±4	(half angle) <±4	(half angle) <±3
Output Power Adjustment Range	10 - 100% of Maximum	10 - 100% of Maximum	10 - 100% of Maximum
Output Power Adjustment Method	Manual	Manual	Manual
Uniformity Classification	<5% non-uniformity	<5% non-uniformity	<5% non-uniformity
Typical time to reach SED (Standard Erythemal Dose) @ Max Output Power	26 seconds	26 seconds	59 seconds
Working Distance	4 inches (50mm)	4 inches (50mm)	6 inches (150mm)

Resources

(1) Spielmann, H., Balls, M., Döring, B., Holzhütter, H.G., Kalweit, S., Klecak, G., L'Eplattenier, H., Liebsch, M., Lovell, W.W., Maurer, T., Moldenhauer. F. Moore. L., Pape, W., Pfannbecker, U., Potthast, J., De Silva, O., Steiling, W., and Willshaw, A. (1994). EEC/COLIPA project on in vitro phototoxicity testing: First results obtained with a Balb/c 3T3 cell phototoxicity assay. Toxic. In Vitro 8, 793-796.

(2) Anon (1998). Statement on the scientific validity of the 3T3 NRU PT test (an in vitro test for phototoxicity), European Commission, Joint Research Centre: ECVAM and DGXI/E/2, 3 November 1997, ATLA, 26, 7-8.

(3) www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm079252.pdf.

Newport Corporation

Worldwide Headquarters
1791 Deere Avenue
Irvine, CA 92606

(In U.S.): 800-222-6440
Tel: 949-863-3144
Fax: 949-253-1680

Email: sales@newport.com

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Visit Newport Online at: **www.newport.com**

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