Journal of Food and Drug Analysis, Vol. 10, No. 4, 2002, Pages 252-257 藥物食品分析 第十卷 第四期

Phototoxicology and Photocarcinogenesis at the U.S. Food and Drug Administration's National Center for Toxicological Research

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(Received: October 3, 2002; Accepted: November 11, 2002)

ABSTRACT

Ultraviolet radiation (UVR) causes skin cancer in humans and can induce skin cancer in test animals. The interaction of UVR with many drugs has been reported, however, there is a paucity of data concerning the carcinogenesis of cosmetic ingredients and environmental contaminants in combination with UVR. A research center has been developed at the U.S. Food and Drug Administration's National Center for Toxicological Research to quantify the potential carcinogenicity of combined exposure to chemicals and UVR. The chemicals tested in this facility are nominated to, and approved by, the National Toxicology Program.

In this paper we describe the nomination of chemicals, test animals, source of UVR, dosimetry, and test paradigm that are used. This unique test facility is being used to protect public health through quantifying the photocarcinogenicity of chemicals to which the public is exposed.

Key words: Phototoxicology, photocarcinogenesis, simulated solar light, SKH-1 hairless mice

INTRODUCTION & BACKGROUND

The U.S. Food and Drug Administration (FDA) was established to protect the health of U.S. citizens by ensuring the safety of drugs, cosmetics, medical devices, food, and food additives, contaminants, and preparation methods. As part of this responsibility, the FDA has an interest in determining whether exposure of drugs to sunlight *(ex vivo* or *in vivo)* can create toxic derivatives of the drugs and has for many years compelled drug manufacturers to determine the possible phototoxicity or photocarcinogenicity of some drugs. The FDA's Center for Drug Evaluation and Research (CDER) recently published a guideline describing when drugs should be tested for phototoxicity or photocarcinogenicity[(1)]. This guideline emphasizes a "decision-tree" approach where *in vivo* phototoxicity or photocarcinogenesis studies are suggested only if the chemical absorbs ultraviolet or visible light and has shown some evidence for phototoxicity *in vitro*. Of particular interest at the FDA's National Center for Toxicological Research (NCTR) are the chemicals that have phototoxic potential and either do not require premarket safety testing (*e.g.* some cosmetic ingredients) or are contaminants that are ubiquitous to the environment (*e.g.* polycyclic aromatic hydrocarbons, psoralens).

There has been continued interest by agencies in the U.S. Government to quantify the toxicological risk of environmental chemicals. NCTR, one of the six Centers of the FDA, has a mission to provide toxicological data, from both *in vitro* and *in vivo* assays, to assist the FDA in making science-based regulatory decisions. The National Toxicology Program (NTP), located at the National Institute for Environmental Health Sciences (NIEHS), was established to determine and quantify the toxicological and carcinogenic risk to man of chemicals in the environment. The NTP funds *in vitro* and *in vivo* toxicological studies including many 2-year rodent carcinogenicity assays and reports the findings to government agencies and the U.S. Congress (*e.g.* NTP[2,3]). These reports serve as comprehensive reviews of the toxic and carcinogenic potential of specific chemicals.

The nomination of chemicals to the NTP begins when a scientist or clinician notices human cases of toxicity or carcinogenicity following exposure to a particular chemical, or suspects a chemical might have toxic properties based on structural similarity to known toxicants. In the case of each of the FDA Centers, these nominations are forwarded to Chemical Selection Working Groups (CSWG) who evaluate the validity of the concern. All chemical nominations are forwarded to the FDA CSWG where the nomination is evaluated for scientific merit and potential impact on public health. Nominations with sufficient scientific concern and public health impact are then forwarded to, and evaluated

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by, the NTP Interagency Chemical Coordination and Evaluation Committee, which receives nominations from all U.S. government agencies. The nominations are evaluated by similar criteria (scientific merit, public health impact) and prioritized with recommendations for the type of testing (*e.g. in vitro* only, or *in vivo* carcinogenesis bioassay). Successful nominations are forwarded by this committee to the NTP for prioritization and funding.

At times, both the FDA and NTP are interested in quantifying the toxicological and carcinogenic potential of the same chemical. In 1992, these two agencies developed an Interagency Agreement (IAG) to cooperate and share expertise and resources concerning chemicals of mutual interest. This IAG has been highly successful, resulting in the completion of toxicological studies (*e.g.* mechanistic-based studies, sub-chronic studies, 2-year carcinogenesis bioassays) on chloral hydrate, fumonisin B1, urethane (with ethanol), malachite green, and endocrine disrupters (ethinyl estradiol, genestein, vinclozolin).

The alpha-hydroxy acids were nominated by the FDA to the NTP in 1998. These chemicals are included in cosmetic products as chemical-exfoliants and have been used to remove skin affected by ichthyosis, acne, xerosis, actinic keratosis, seborrheic keratosis, warts, and psoriasis[4,5]; however, one of the primary uses of alpha-hydroxy acid containing creams is correction of photoaged skin[6-11]. Since these products are used to correct sunlight-aged skin, there is the distinct possibility that these products could be used immediately before or after exposure to sunlight. Since treatment with glycolic acid would result in increase epidermal thickness through proliferation, and since the sunlight exposure would result in DNA damage, there exists the likelihood that increased mutations and skin cancer could occur in humans as a result of continued sun exposure during use of alpha-hydroxy acids. It became apparent that the best system for modeling human use of these cosmetics would be phototoxicology and photocarcinogenesis studies where animals are treated with cosmetic products and exposed to light containing ultraviolet radiation (UVR). This nomination became the basis for developing the Phototoxicology Center at NCTR.

I. *Animal model*

There have been several species of animals utilized to serve as surrogate models for human response to topically applied chemicals and solar light. These include South American opossum *Monodelphis domestica*, hairless rats or guinea pigs, and shaved conventional or transgenic animals[12-15]; however, the albino hairless SKH-1 mouse is the most widely accepted animal model for carcinogenesis studies involving UVR and topically applied chemicals ([13,14,16]; Figure 1). A comparison of the sensitivity of this and eight other hairless mouse strains to ultraviolet radiation (UVR) was reported[12], where it was demonstrated that squamous cell carcinoma development was dependent on the dose of UVR.

II. *Light source*

There have been numerous light sources used to determine the biological impact of various regions of the electromagnetic radiation spectrum. Some of these light sources produce proportionally more light in the ultraviolet region of the spectrum and are excellent sources for studying the biological impact of UVR; however, these electromagnetic radiation sources are dissimilar to terrestrial sunlight, the largest source of human exposure to UVR. Since light sources with a wide range of emission spectra are available, the biological effectiveness of photons of light needs to be considered before choosing a light source. Spectral action curves are mathematical representations of the effectiveness of photons in causing a biological response. As examples, the relationship of photon energy (*i.e.* wavelength) to induction of erythemal in the skin of humans[17] and retinal thermal hazards has been determined[18]. UVR at 270-290 nm is the most effective at inducing erythema in humans, while light at 430-450 nm is the most effective at inducing blue-light photochemical and retinal thermal damage. Therefore, if one were to conduct a study of the effect of a protective drug for blue-light photochemical damage, one would not want to select a radiation source which principally emitted between 280 nm and 400 nm, even though this would be an excellent source to study UVR-induced erythema.

Studies at our facility are designed to determine the effects of topically applied chemicals on the induction of sunlight-induced skin cancer in the SKH-1 mouse and the effect of the light on the toxicity of the topically applied chemicals. The spectral action curves have been determined for the induction of skin cancer in the SKH-1 mouse. The SCUP (Skin Cancer Utrecht-Philadelphia) skin cancer action spectrum[19] combines the skin carcinogenesis data from multiple studies of P.D. Forbes and F. Urbach and colleagues[20,21] at the Temple University and Argus Research Laboratories, Pennsylvania USA, and F.R. de Gruijl and J.C. van der Leun and colleagues at University of Utrecht, Netherlands (Figure 2). In this mathematical model, the wavelength-dependent relationship of skin cancer induction is maximum at 293 nm, and the effectiveness decreases by 10^{-4} between 300 nm and 340 nm. The relationship between

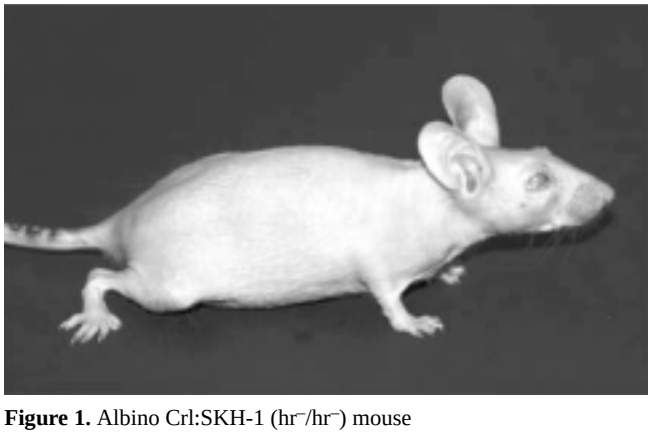

Figure 1. Albino Crl:SKH-1 (hr^{-}/hr^{-}) mouse

the human erythemal action spectrum and SCUP action spectrum bears particular comment. The dose- and wavelength-dependence of erythema in human skin has been recognized since the late 1920's. A spectral action curve for this response has been proposed by the Commission Interationale de l'Eclairage (CIE, [17,22]) and is shown in Figure 2. There is considerable similarity in the SCUP skin cancer action spectrum and CIE erythemal action spectrum, where the biological impact of electromagnetic radiation at 295 nm is approximately 10^4 greater than that at 340 nm. These similar spectral action curves suggest that underlying mechanisms of action (*i.e.* interaction of photon of light with biological matrix) are similar for these two biological processes.

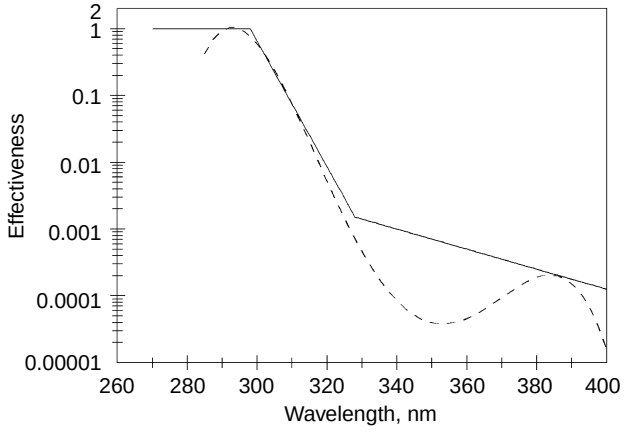

Figure 2. The SCUP action spectrum[19] for the induction of skin cancer in SKH-1 hairless mice (dashed line), and the CIE erythemal action spectrum[17,22] (solid line).

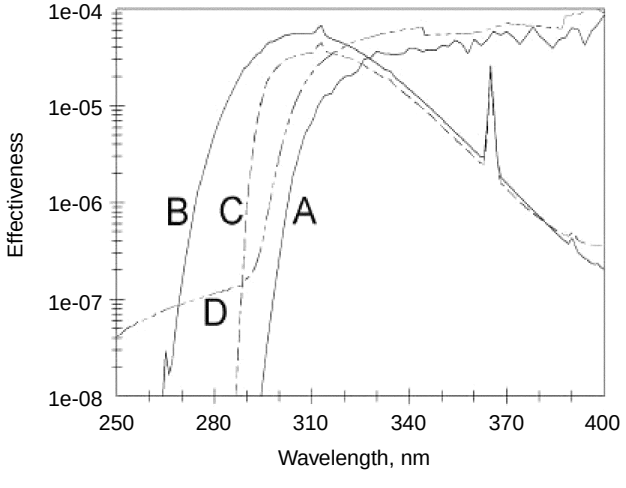

Figure 3. The spectra of the following were obtained using an Optronics OL-754 spectroradiometer: A (solid line), sunlight at 1130 hrs on 17 July 2001 in Jefferson, Arkansas USA; B (solid line), FS (fluorescent sunlamp, high output, National Biologics, Twinsburg, Ohio USA) at a distance of 15 cm; C (dashed line), FS filtered through cellulose triacetate (Kodacel®, Eastman Kodak) at distance of 15 cm; D (dot-dash-dot), simulated solar light (SSL) from 6.5 kW xenon-arc lamp filtered through Schott WG320 filter (Schott Glass Technologies, Duryea, PA USA), at a distance of 50 cm.

There are several sources that could be used to provide UVR for *in vivo* animal studies. The most commonly used source of UVR are fluorescent lamps which can produce intense levels of radiation in the UVB (280-315 nn) or UVA (315-400 nm) range, as shown in Figure 3. The fluorescent sunlamps (FS) emit considerable amounts of UVR below 290 nm, which are not present in sunlight (Figure 3). As a result, if one were attempting to mimic the exposure of humans to the UVR in sunlight, the FS would expose the test object to wavelengths to which humans are not normally exposed. In an effort to reduce these lower wavelengths of UVR, the FS emissions are typically filtered through cellulose triacetate as shown in Figure 3; however, even with the filtering, there is considerable amount of UVR between 285 nm and 300 nm when compared to sunlight. In addition, the ratio of UVB to UVA in filtered FS radiation is approximately 1:1, which is considerably higher than that of natural sunlight (approximately 1:20 or greater depending on the latitude, season, and environmental conditions). This ratio of UVB to UVA can become a critical factor in a study if there is synergism between the biological effects of UVB and UVA, or if the stability and toxicity of a chemical are different in UVA and UVB.

We have chosen to use filtered radiation from a long-arc xenon arc lamp for our studies using SKH-1 hairless mice. The use of this lamp in biological studies has been described[12,21,23]. The output from this lamp strongly resembles extraterrestrial solar radiation, and the UVR component is attenuated using long-pass glass filters (Schott Glass Technologies, Duryea, Pennsylvania USA). The spectrum of light we have achieved (Figure 3) has a UVB to UVA ratio of approximately 1:21, and can be modified depending on the needs of the study. At present, the intensity of the simulated solar light at 2 meters is approximately 25% the intensity of summer sunlight at 34˚N latitude.

III. *Dosimetry*

There are various methods for measuring the dose of UVR in an animal study. A spectroradiometer is the most accurate device for measuring the spectral distribution and dose of radiation delivered to an animal[24]. Spectroradiometers can be calibrated against NIST-traceable standards and can provide the irradiance of a light source (*i.e.* watts/m^2). The biggest experimental limitation to using spectroradiometric measurements for each study is the time required for obtaining the measurement, where quantifying the irradiance between 280 nm and 450 nm can take several minutes with most instruments. This is not a practical solution to rapid determination of UVR.

Broad-band dosimeters have been used to measure the dose of particular areas of the electromagnetic radiation spectrum. These devices typically have a photon-sensitive device (*e.g.* photodiode) with a sensitivity to the wavelengths of interest. The spectral sensitivity of the instrument

is altered by filtering the light through a series of optical filters. These dosimeters are very reliable, and with proper calibration, can accurately measure the UVR from a light source. We have chosen to use the Robertson-Berger erythemally-weighted dosimeter for determining the dose of UVR delivered to mice on our studies[24-26]. The spectral responsiveness of the Robertson-Berger dosimeter closely matches the SCUP skin cancer action spectrum and CIE erythema action spectrum. The irradiance of the SSL is determined between 250 nm and 450 nm using a spectroradiometer. The irradiance ($W/m^2/nm$) is then multiplied times the CIE erythemal action spectrum to determine the weighted irradiance ($W \cdot CIE/m^2/nm$), which is converted to Standard Erythemal Doses [SED[27,28]; $1\ SED = 100\ J \cdot CIE/m^2$]. The Robertson-Berger dosimeters are then calibrated to the weighted irradiance of SSL. This method of calibrating the dosimeters is very reproducible and accurate, and relies on the similarity of the spectral responsiveness of the dosimeter and CIE erythemal action curve. This method would not be valid if the spectral responsiveness of the dosimeters was different. With this approach, we can frequently calibrate many dosimeters and measure the dose of UVR in SEDs.

STUDY PROTOCOL

There are numerous experimental designs for the delivery of UVR to animals. In our case, we have taken advantage of the study designs reported by P.D. Forbes and colleagues using SSL[13,16,20,21,29-31]. The mice are randomly assigned to dose groups and are exposed to UVR starting at 8 weeks of age. The size of the groups depends on the statistical power desired for the study, but is typically 18, 24, or 36 mice/group/sex. Mice are allocated to groups that receive either 0, 0.7, 1.4, or 2.1 SED/day of SSL. The mice are treated five days/week for 40 weeks, followed by an additional 12 weeks of no treatment to allow tumor development. A dose-response relationship can be established with this protocol, where one-half of the mice will have skin tumors greater than 1 mm in diameter at approximately 54 weeks, 35 weeks and 22 weeks when receiving 0.7, 1.4, or 2.1 SED/day SSL, respectively (Howard, unpublished). Additional groups of mice are treated with the test article alone, in the absence of light, to determine if the test article can induce skin damage or cancer. The effect of the test article is determined by treating groups of mice with test article and 0.7 or 1.4 SED/day of SSL. A photococarcinogenic test article will decrease the mean time to tumor of a given dose of SSL, while a photoprotective chemical will increase the mean time to tumor for the particular dose of SSL.

The timing of the application of the test article and the SSL can be critical and is dependent on the proposed mechanism of action of the test article. For instance, the test article would be applied on a daily basis before exposure to SSL if the hypothesis is the test article is photoactivated by SSL to a toxic and carcinogenic chemical. If, however, the test article is thought to stimulate the growth of photodamaged cells into hyperplastic foci, the test article would be applied following irradiation. As a result, the exact study design will depend on the hypothesized mechanism of action of the test article. In some studies, a mixed design has been used, where the test article is applied before irradiation on Mondays, Wednesdays, and Fridays, and applied after irradiation on Tuesdays and Thursdays[29].

The mice are monitored for tumor development on a weekly basis. The mice are examined by trained personnel, and the size of skin lesions are quantified using calipers[23]. The development of the skin lesions is subsequently followed, allowing the investigator to determine the mean time to tumor (that is, week where one-half of the mice have skin tumors) for each of the test groups. Statistical analyses are then used to compare the tumor development in the groups and determine if the test article affected the development of skin lesions with a particular dose of SSL.

CONCLUSIONS

The Center for Phototoxicology has been developed to quantify the effect of test chemicals on the carcinogenesis of SSL using an established animal model (*i.e.* SKH-1 hairless mouse). In addition to the one-year photocarcinogenesis studies, we are conducting studies to determine the phototoxicity of the test compound *in vivo*, and studies on the mechanism of action of each test article. This approach is being used to determine if there is risk to the public when using topically applied alpha- and beta-hydroxy acids, aloe vera, and retinyl palmitate in combination with SSL.

ACKNOWLEDGEMENTS

The authors would like to thank P.D. Forbes, A. Hoberman, D. Learn, and C. Sambucco for their invaluable input and advice on xenon arc light sources and photocarcinogenesis methods.

The work described in this manuscript was supported in part by an Interagency Agreement between the U.S. Food & Drug Administration and National Institute for Environmental Health Sciences (IAG 224-93-001). The contents of this manuscript do not necessarily reflect the views or policies of the U.S. Food and Drug Administration, or National Institute for Environmental Health Sciences. The mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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Journal of Food and Drug Analysis, Vol. 10, No. 4, 2002

美國藥物食品管理局，國家毒理研究中心對光毒性與光致癌性效應之研究

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（收稿：October 3, 2002；接受：November 11, 2002）

摘　要

紫外線輻射會引起人類及實驗動物皮膚癌，另已有文獻報導紫外線輻射會與許多藥物產生交互作用，然而化粧品成分及環境污染物中，哪些成分經紫外線照射會致癌之報導卻不多。因此，美國藥物食品管理局國家毒理研究中心開發可量化化合物經曝露於紫外線輻射之致癌性，該中心進行試驗之化合物係屬國家毒理研究計畫所指定與批准之化合物。本文將敘述這些化合物，及所採用之實驗動物、紫外線輻射源、劑量及試驗範例等。該試驗機構對大眾會曝露之化合物，透過量化其致光致癌性，以確保公眾健康。

關鍵詞：光毒性學，光致癌性，模擬太陽光，SKH-1裸鼠